# CARDIOGENIC SHOCK: BASIC AND CLINICAL CONSIDERATIONS

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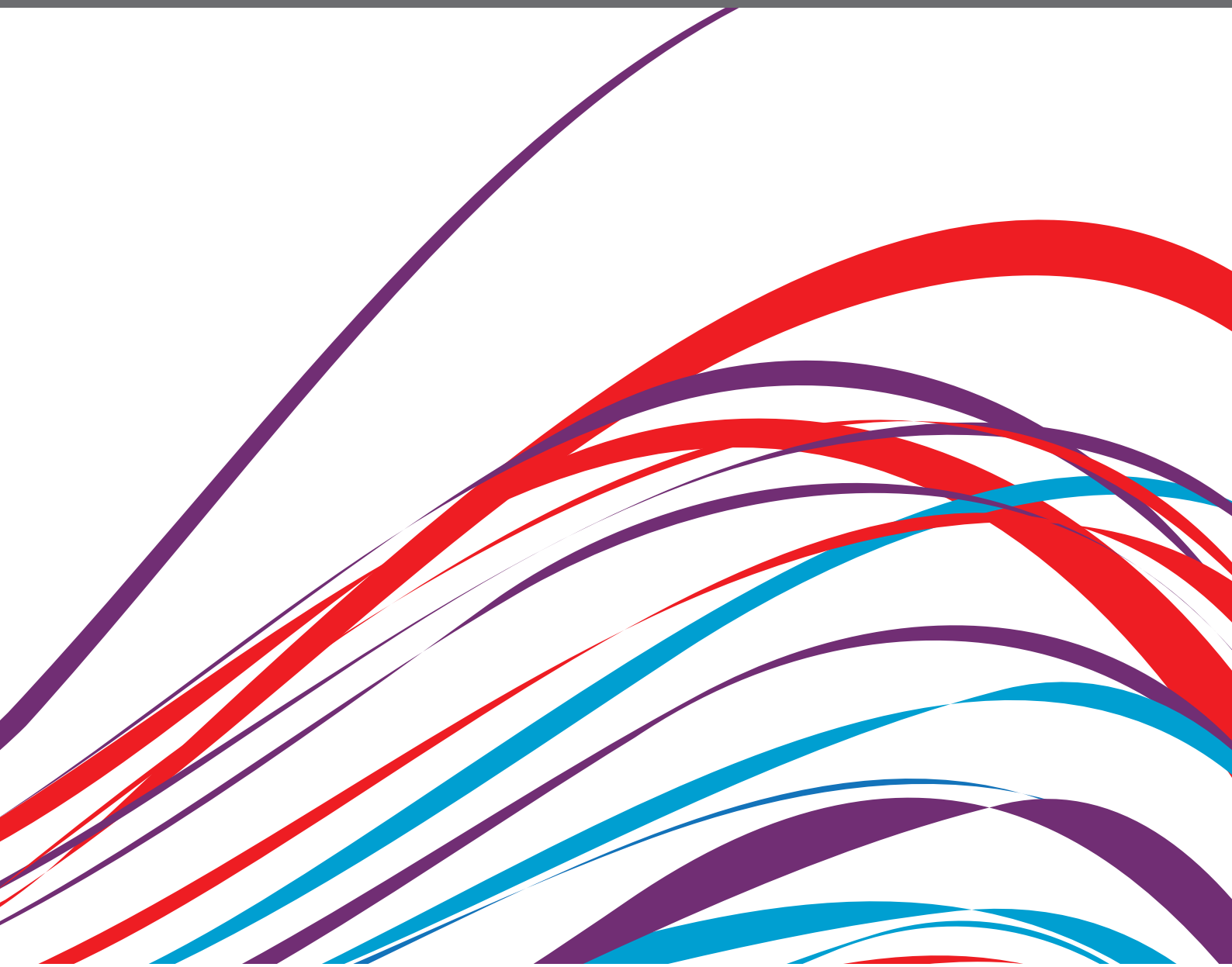

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# CARDIOGENIC SHOCK: BASIC AND CLINICAL CONSIDERATIONS

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EDITORIAL
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# Editorial: Cardiogenic Shock: Basic and Clinical Considerations

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**Keywords: cardiogenic shock, mechanical circulatory support, ECMO–extracorporeal membrane oxygenation, myocardial infarction, impella**

**Editorial on the Research Topic**

**Cardiogenic Shock: Basic and Clinical Considerations**

Cardiogenic shock (CS) remains a high morbidity/mortality condition despite advanced resource-intensive therapies. It is a heterogeneous illness requiring individualized therapies, leading to challenges in designing randomized clinical trials. A limited evidence base therefore informs treatments, and substantial gaps in knowledge persist.

In this Research Topic, leading investigators in the field address the spectrum of basic, translational, and clinical aspects of CS.

CS outcome, particularly in severe shock, depends on access to specialized capabilities to handle advanced stages of shock as well as durable support devices and transplantation. Villela et al. review systems of care in CS, including a "spoke and hub" and tiered models of care for management of patients with different stages of CS. They also discuss development of protocols with uniform definitions, management, and escalation of care in CS. Outcomes data from existing models are discussed, and barriers to creating systems of care are identified. Readers interested in understanding or creating structured, cost-effective, comprehensive CS systems of care will find this manuscript invaluable.

Long and Baran explore limitations of commonly used historical CS risk stratification scores, including limited applicability to non-ACS populations and inability to account for serial assessments. The authors discuss the intent and framework of the Society of Cardiovascular Angiography and Intervention (SCAI) CS classification that was developed to (a) risk stratify, prognosticate and classify patients in different stages of shock for appropriate intervention in a timely fashion, and (b) to design clinical trials that may allow hypothesis testing in a cohort of shock patients with less heterogeneity. Validation studies performed with the new SCAI classification are reviewed. They subsequently discuss future directions, including the need to account for heterogeneity of CS in management strategies and design of clinical trials.

Kanwar et al. review the impact of age on mortality in CS patients from the Cardiogenic Shock Work Group registry. This timely and relevant analysis, given increasing proportions of older patients with CS, finds that increasing age is associated with higher mortality across all SCAI stages, and provides insights into the role of temporary mechanical circulatory support (MCS) in older patients.

The inflammatory and metabolic effects of VA-ECMO are poorly understood, despite major clinical implications. Two manuscripts shed some light on this important topic. Siegel et al. find increased baseline monocyte activation and decreased stimulability in VA-ECMO patients, and changes in monocyte subtypes over time. Monocyte dysfunction may therefore be a marker of an immunoparalyzed state and higher mortality on ECMO. Mandigers et al. examine tissue perfusion and microcirculatory function in a porcine ECMO model. Skin mitochondrial partial oxygen pressure measurement was feasible and there was discrepancy between mean arterial



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pressure (MAP) and mitochondrial partial oxygen pressure, suggesting the role of using parameters such as mitochondrial partial oxygen pressure sensor in addition to MAP to assess adequacy of organ perfusion.

The role of MCS in high-risk surgical candidates is evolving, with limited high-quality data. The requirement for MCS, especially postoperatively, is a marker of higher risk. Hou et al. report on a cohort of patients with ascending aortic dissection who required VA-ECMO predominantly for failure to wean from cardiopulmonary bypass or postoperative CS and find sobering outcomes. The modality of support and optimal cannulation approach for post-CS is also not well-defined, with recent studies providing inconsistent results. Kalampokas et al. evaluate 86 patients who underwent VA ECMO for post-cardiotomy shock, and find no significant outcome differences between those undergoing central cannulation vs. peripheral cannulation.

Tsangaris et al. provide an expert review of VA ECMO in the management of CS. All major aspects of ECMO, including support indications, hemodynamics, venting, complications, and weaning strategies are thoroughly discussed. The role of VA-ECMO for COVID-associated CS is addressed. The authors also discuss their groundbreaking research on extracorporeal CPR from the Minnesota Resuscitation Consortium.

Schafer et al. examine the complex and still somewhat unresolved question of complete vs. incomplete revascularization in CS. After the CULPRIT-SHOCK trial there has been a general shift toward culprit vessel only initial revascularization. Most patients in CULPRIT-SHOCK, however, did not have hemodynamic support at the time of PCI. In this retrospective analysis from four high volume European centers, Impella-supported PCI with complete revascularization with low residual SYNTAX score was associated with lower mortality than Impella post-PCI or incomplete revascularization in a cohort of patients with profound CS and high incidence of cardiac arrest.

Finally, Sieweke et al. evaluate the role of microaxial-pumps in patients successfully resuscitated after an out of hospital cardiac arrest due to acute myocardial infarction (AMI) from the HACURE (Hannover Cardiac Unloading) Registry. It is important to note that the population studied was not extracorporeal CPR, rather post cardiac arrest CS. Fifteen patients from the Hanover Cardiac Unloading Registry who had out of hospital cardiac arrest (OHCA) + AMI + CS + Impella unloading were propensity matched to 15 patients from the Hanover Cooling Registry who had OHCA+AMI+CS without unloading. In this selected cohort, use of microaxial-pumps was associated with improved survival and neurological outcome. The role of VA-ECMO vs. microaxial pumps in this situation was not addressed here and remains unknown.

In conclusion, cardiogenic shock remains a major problem in cardiovascular medicine, but recent advances particularly in early recognition and systems of care approaches have had measurable impact in improving mortality. The challenge of translating these outcomes reported from established tertiary care academic centers to the overall population are, however, immense, and will need creation of many large-scale integrated regional systems of care, each with their individual resources, limitations, and geographic and other considerations. An improved appreciation of the heterogeneity of CS has highlighted the reasons for some of the failures of MCS trials in CS, and the evolving risk stratification models are enabling enhanced selection of patients with CS for clinical trials for specific therapies. The need for large, randomized trials to better understand the role and limitations of expensive and invasive MCS devices is now well-recognized and the trials are underway, albeit with substantial recruitment challenges. Although the clinical management of CS has achieved significant attention in recent years, the importance of the complex molecular biology of CS cannot be overstated, as paradigm changing approaches and dramatic improvements may not occur from optimization of currently available therapies but only rather after we understand the basic pathophysiology of CS in a much more sophisticated manner than we currently do. This Research Topic, with contributions from 80 expert authors worldwide, addresses aspects of each of these issues. We hope it will provide clinicians interested in learning about CS, those who manage patients with CS, and investigators who strive to expand the knowledge of CS with an overview and appreciation of cutting-edge issues in cardiogenic shock.

## AUTHOR CONTRIBUTIONS

DA: drafting manuscript. IR, KK, and DA: revision, editing, and final approval. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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# Veno-Arterial Extracorporeal Membrane Oxygenation for Patients Undergoing Acute Type A Aortic Dissection Surgery: A Six-Year Experience

*Jun-yi Hou[1†], Chun-sheng Wang[2†], Hao Lai[2†], Yong-xin Sun[2], Xin Li[2], Ji-li Zheng[3], Huan Wang[1], Jing-chao Luo[1], Guo-wei Tu[1*] and Zhe Luo[1,4*]*

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**Objectives:** Acute type A aortic dissection (aTAAD) is usually lethal without emergency surgery. Although veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is widely used in patients with cardiogenic shock following cardiac surgery, VA-ECMO support following aTAAD surgery has not been well-described. Based on our 6-year experience, we aimed to retrospectively analyze risk factors, application and timing of VA-ECMO, and outcomes in aTAAD patients.

**Methods:** In this retrospective, single-center study, we enrolled adult patients who underwent aTAAD surgery from January 2014 to December 2019 and were supported with VA-ECMO. Patients were divided into two groups according to whether or not they were successfully weaned from VA-ECMO. Preoperative, intraoperative and postoperative variables were assessed and analyzed. Outcomes of the patients were followed up until discharge.

**Results:** Twenty-seven patients who received aTAAD surgery with VA-ECMO support were included in the study. Nine patients (33.3%) were successfully weaned from VA-ECMO. The median VA-ECMO support time and length of hospital stay in the successfully weaned group were significantly longer than in the group could not be successfully weaned (192 [111–327] vs. 55 [23–95] h, $p < 0.01$; 29 [18–40] vs. 4 [3–8] days, $p < 0.01$). Overall in-hospital mortality was 81.5%. The main causes of death were bleeding (37%), neurological complications (15%), and multiple organ dysfunction syndrome (15%). Preoperative levels of creatine kinase-MB (CK-MB) were lower in patients who were successfully weaned from VA-ECMO than in the failed group (14 [6–30] vs. 55 [28–138] U/L, $p < 0.01$). Postoperative peak levels of CK-MB, cardiac troponin T, lactate dehydrogenase, and lactate were significantly lower in the successful group than in the failed group.

**Conclusion:** Postoperative VA-ECMO support was rarely used in aTAAD patients. Our study showed that VA-ECMO can be considered as a salvage treatment in aTAAD patients, despite the high rate of complications and mortality.

**Keywords: acute type A aortic dissection, veno-arterial extracorporeal membrane oxygenation, cardiogenic shock, aortic surgery, acute**

## INTRODUCTION

Acute type A aortic dissection (aTAAD) is a cardiovascular emergency associated with the formation of a false lumen in the media, caused by intimal weakness or tear. Blood surges through the false lumen and enlarges the tear at the proximal, distal, or both ends (1). Because of its high mortality rate, aTAAD is one of the most urgent surgical emergencies in cardiac surgical patients. Despite significant improvements in surgical techniques, cardiopulmonary bypass (CPB) practices, cerebral protection procedures, and perioperative management data published in the International Registry of Acute Aortic Dissection (IRAD) show that the mortality rate in aTAAD surgery is still ∼20% (2).

The heart is one of the organs most commonly affected by aTAAD, which can lead to cardiac tamponade, acute severe aortic regurgitation, and/or coronary artery involvement. Preoperative coronary artery dissection is usually associated with acute myocardial infarction and heart failure. A previous study showed that mortality associated with aTAAD involving the coronary artery was as high as 20% (3). Poor myocardial protection during surgery can also lead to myocardial ischemia or ischemia-reperfusion injury. Perioperative multiorgan malperfusion can also lead to uncorrectable acidosis and end organ dysfunction, which contribute to the extremely high mortality (4, 5).

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO), which provides temporary circulatory support for critically ill patients with refractory cardiogenic shock and cardiac arrest, can be used as a bridge to myocardial recovery in aTAAD patients (6, 7). Since ventricular assist devices are not yet available in China, our cardiovascular center has routinely used VA-ECMO to treat patients with CS. The use of VA-ECMO in aTAAD patients with cardiogenic shock has not, however, been well-documented although the prognosis of patients weaned from VA-ECMO support after aTAAD surgery is known to be poor. In the present study, we aimed to investigate the use and timing of VA-ECMO, risk factors and outcomes in aTAAD patients.

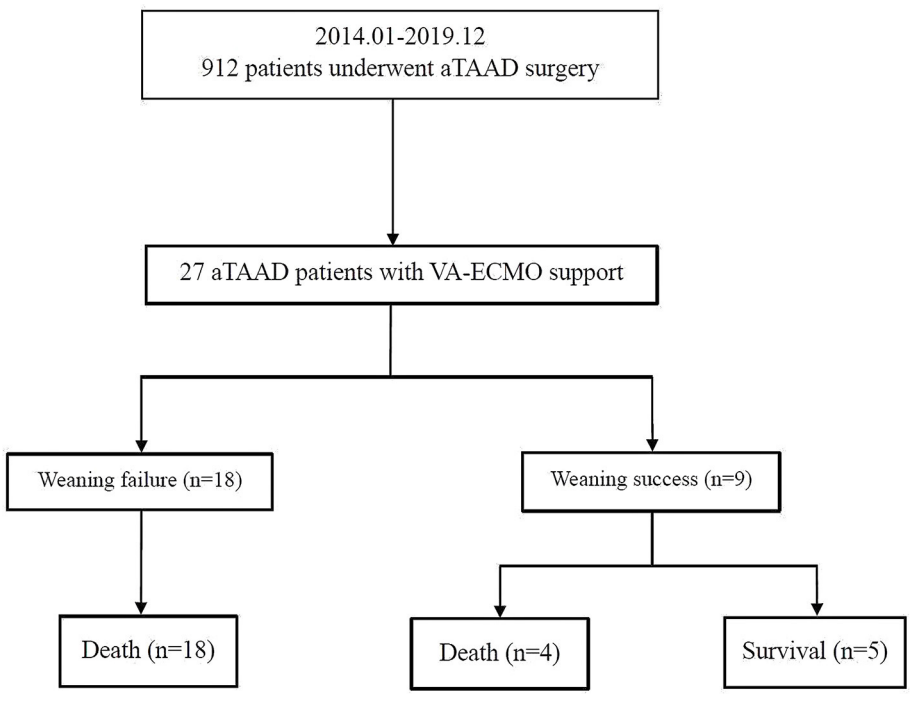


**FIGURE 1 |** Enrollment, allocation, and follow-up of aTAAD patients who received VA-ECMO. aTAAD, acute type A aortic dissection; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

# MATERIALS AND METHODS

## Patient and Study Design

In this retrospective, single-center study, we reviewed the records of adult patients who received VA-ECMO support after aTAAD surgery at Zhongshan Hospital, Fudan University (Shanghai, China) from January 2014 to December 2019. Exclusion criteria included: an age <18 years old or pregnancy. Zhongshan Hospital performs over 150 aTAAD surgeries per year, including ascending aortic and hemi- or total-arch replacement, with or without concomitant surgical treatment of the aortic root, as well as elephant trunk stent procedures for the descending aorta. The study was approved by the Ethics Committee of Zhongshan Hospital.

Patients were divided into two groups according to whether the VA-ECMO was successfully removed or not (patients were

**TABLE 1 |** Demographic and clinical characteristics of ECMO patients prior to surgery.

| Variables | Total ($n$ = 27) | Wean-from ECMO | | $p$-value |
|---|---|---|---|---|
| | | Success ($n$ = 9) | Failure ($n$ = 18) | |
| Age, year | 53 ± 14 | 45 ± 17 | 56 ± 12 | 0.06 |
| Male, *n* (%) | 22 (81) | 7 (78) | 15 (83) | 1.00 |
| BMI (kg/m$^2$) | 25.59 ± 3.49 | 25.45 ± 5.06 | 25.66 ± 2.58 | 0.91 |
| Comorbidities, *n* (%) | | | | |
| Hypertension | 24 (89) | 6 (67) | 18 (100) | 0.03 |
| Diabetes mellitus | 1 (4) | 0 (0) | 1 (6) | 1.00 |
| COPD | 5 (19) | 1 (11) | 4 (22) | 0.64 |
| Marfan syndrome | 1 (4) | 0 (0) | 1 (6) | 1.00 |
| Atrial fibrillation | 1 (4) | 0 (0) | 1 (6) | 1.00 |
| Clinical manifestation, *n* (%) | | | | |
| Coronary artery involvement | 11 (41) | 2 (22) | 9 (50) | 0.20 |
| Cardiac tamponade | 2 (7) | 0 (0) | 2 (11) | 0.54 |
| Aortic valve regurgitation | 3 (11) | 1 (11) | 2 (11) | 1.00 |
| Previous cardiac surgery, *n* (%) | 5 (19) | 1 (11) | 4 (22) | 0.64 |
| Laboratory tests | | | | |
| CK-MB level (U/L) | 38 (15, 61) | 14 (6, 30) | 55 (28, 138) | 0.01 |
| cTnT (ng/ml) | 0.60 (0.02, 3.45) | 0.03 (0.01, 0.68) | 0.97 (0.05, 4.57) | 0.09 |
| BNP (pg/ml) | 732 (262, 2,559) | 487 (196, 2,256) | 1,358 (306, 2,879) | 0.46 |
| Hb (g/L) | 131 ± 25 | 126 ± 19 | 134 ± 28 | 0.50 |
| PLT (×10$^9$/L) | 195 ± 67 | 226 ± 65 | 179 ± 63 | 0.09 |
| WBC (×10$^{12}$/L) | 13 ± 5 | 12 ± 5 | 13 ± 5 | 0.53 |
| Neutrophils (%) | 80 ± 11 | 75 ± 13 | 83 ± 9 | 0.09 |
| TBIL (μmol/L) | 21 ± 29 | 17 ± 8 | 24 ± 35 | 0.60 |
| DBIL (μmol/L) | 10 ± 25 | 5 ± 1 | 12 ± 30 | 0.49 |
| ALB (g/L) | 39 ± 4 | 39 ± 5 | 39 ± 4 | 0.83 |
| ALT (U/L) | 39 (24, 70) | 30 (14, 45) | 44 (25, 89) | 0.12 |
| AST (U/L) | 57 (23, 152) | 28 (20, 68) | 94 (27, 173) | 0.08 |
| LDH (U/L) | 302 (250, 520) | 253 (175, 399) | 355 (280, 579) | 0.06 |
| GFR (ml/min/1.73 m$^2$) | 72 ± 23 | 76 ± 31 | 69 ± 19 | 0.47 |
| Cr (μmol/L) | 132 ± 75 | 76 ± 37 | 160 ± 73 | 0.05 |
| BUN (mmol/L) | 8 (4, 10) | 5 (4, 9) | 9 (5, 10) | 0.18 |
| Lac (mmol/L) | 1.3 (1.0, 1.9) | 1.1 (1, 1.7) | 1.3 (1.1, 2.0) | 0.43 |
| EuroSCORE | 7 ± 3 | 6 ± 3 | 8 ± 3 | 0.10 |
| LVEF (%) | 60 ± 8 | 58 ± 8 | 62 ± 8 | 0.20 |
| Time from onset to hospital (h) | 11 ± 6 | 9 ± 6 | 11 ± 6 | 0.36 |
| Time from onset to operation (h) | 22 ± 14 | 22 ± 16 | 22 ± 13 | 0.93 |

*Continuous data are presented as the mean (SD) or median (IQR). Categorical data are presented as counts (%).*

*ECMO, extracorporeal membrane oxygenation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CK-MB, creatine kinase isoenzyme; cTnT, cardiac troponin T; BNP, brain natriuretic peptide; Hb, hemoglobin; PLT, platelet; WBC, white blood cell; TBIL, total bilirubin; DBIL, direct bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; GFR, Glomerular filtration rate; Cr, serum creatinine; BUN, blood urea nitrogen; Lac, lactate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction.*

defined as successfully weaned from VA-ECMO if they survived for longer than 48 h after VA-ECMO explantation) (8, 9). Baseline variables, which included age, gender, body mass index, comorbidities, laboratory tests, and operative characteristics, together with outcome variables, which included VA-ECMO support time, VA-ECMO weaning rate, mechanical ventilation time, length of stay in intensive care unit (ICU), length of hospital stay, complications, and in-hospital mortality, were compared between the two groups. All data were collected from the patients' hospital records by two residents (H-W and JY-H).

## Surgical Procedures

All aTAAD patients underwent emergency surgery, unless the patient refused surgery or had preoperative neurological complications. Surgical repair was performed under CPB and deep hypothermic circulatory arrest. In some patients, replacement of the ascending and proximal arch was sufficient, but when the intimal tear was in the aortic arch, total arch replacement was performed. We routinely used unilateral selective antegrade cerebral perfusion with deep hypothermic circulatory arrest as a cerebral protection strategy during emergent surgical repair of aTAAD. We used continuous cerebral near-infrared spectroscopy to monitor brain oxygenation during surgery.

## Timing of VA-ECMO Implantation

The decision to use VA-ECMO was made by the cardiac surgeon in the operating room or by the intensivist in the cardiac surgery ICU. Indications for VA-ECMO therapy included difficulty weaning from CPB or postoperative refractory cardiogenic shock despite adequate volumes and high doses of inotropes such as norepinephrine, dobutamine, epinephrine, and milrinone. A femoral venous cannula placed from the femoral vein to the right atrium was used as the VA-ECMO venous cannula. The femoral artery is most commonly used for arterial catheterization in adult patients, but this puts the aTAAD patients at risk of developing Harlequin syndrome. Because of this, we routinely used right axillary artery catheterization in aTAAD patients with refractory hypoxemia.

**TABLE 2 |** Intraoperative and postoperative clinical characteristics.

| Variables | Total ($n = 27$) | Wean-from ECMO | | $p$-value |
|---|---|---|---|---|
| | | Success ($n = 9$) | Failure ($n = 18$) | |
| Intraoperative conditions | | | | 1.0 |
| Ascending aorta+arch+ET (*n*) | 17 | 6 | 11 | |
| Bentall (*n*) | 4 | 1 | 3 | |
| Bentall+hemiarch (*n*) | 2 | 1 | 1 | |
| Bentall+arch+ET (*n*) | 4 | 1 | 3 | |
| Coronary artery bypass graft (*n*) | 10 | 4 | 6 | |
| Mitral valve surgery (*n*) | 1 | 0 | 1 | |
| Operation time (h) | 8.58 ± 2.25 | 8.50 ± 1.87 | 8.63 ± 2.47 | 0.90 |
| CPB time (min) | 271 ± 117 | 235 ± 83 | 290 ± 129 | 0.26 |
| Aortic cross clamp time (min) | 111 ± 40 | 94 ± 19 | 120 ± 46 | 0.12 |
| DHCA time (min) | 20 ± 9 | 22 ± 4 | 18 ± 11 | 0.29 |
| Post-ECMO support conditions | | | | |
| Perioperative blood transfusion (U) | 17 ± 5 | 20 ± 6 | 16 ± 4 | 0.37 |
| Peak CK-MB (U/L) | 244 ± 161 | 134 ± 92 | 300 ± 161 | 0.01 |
| Peak cTnT (ng/ml) | 7.7 (4.0, 21.8) | 4.0 (0.9, 7.1) | 19.5 (6.6, 29.9) | 0.01 |
| Peak BNP (pg/ml) | 3,400 (2,500, 7,845) | 3,400 (2,525, 7 500) | 3,429 (2,350, 8,671) | 0.71 |
| Peak lactate (mmol/L) | 18 ± 3 | 16 ± 4 | 19 ± 3 | 0.02 |
| Peak TBIL (μmol/L) | 41 (30, 58) | 38 (32, 58) | 44 (28, 63) | 0.78 |
| Peak DBIL (μmol/L) | 24 (19, 44) | 23 (14, 41) | 35 (19, 45) | 0.40 |
| Peak ALT (U/L) | 334 (163, 1,205) | 220 (179, 1,002) | 372 (106, 1,615) | 0.82 |
| Peak AST (U/L) | 584 (318, 1,720) | 340 (273, 1,694) | 959 (379, 2,624) | 0.28 |
| Peak LDH (U/L) | 2,038 ± 1,197 | 1,178 ± 669 | 2,468 ± 1,181 | 0.01 |
| Peak GFR (ml/min/1.73 $m^2$) | 22 (18, 30) | 24 (15, 61) | 22 (19, 26) | 0.67 |
| Peak BUN (mmol/L) | 19 ± 10 | 21 ± 4 | 18 ± 8 | 0.45 |
| Peak Cr (mmol/L) | 263 (185, 312) | 220 (129, 383) | 263 (192, 324) | 0.78 |
| Peak PCT (ng/ml) | 24 (14, 56) | 29 (13, 40) | 21 (15, 76) | 0.53 |

*ECMO, extracorporeal membrane oxygenation; ET, elephant trunk; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; CK-MB, creatine kinase isoenzyme; cTnT, cardiac troponin T; BNP, brain natriuretic peptide; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; GFR, glomerular filtration rate; Cr, serum creatinine; BUN, blood urea nitrogen; PCT, procalcitonin.*

## Management During VA-ECMO Support

In the initial stage of VA-ECMO, the target mean arterial pressure was maintained at ≥60 mmHg, thus, ensuring tissue perfusion without excessive increase of afterload. Serum lactate level was used as an indicator of tissue hypoperfusion and has been proved to predict outcomes of cardiogenic shock associated with organ failure (10). Cardiac structure and function, and hemodynamic conditions were routinely assessed by transesophageal and/or transthoracic echocardiography.

As soon as the VA-ECMO guidewire was implanted, heparin (1 mg/kg) was given intravenously. During VA-ECMO support, heparin was used as an anticoagulant. Active clotting time was maintained at 180–200 s or activated partial thromboplastin time was maintained at 50–80 s in patients with low bleeding risk. In patients with high bleeding risk, active clotting time was maintained at 160 s. Platelets were transfused when the patient's platelet count fell below $50 \times 10^9$/L (11).

A protective lung ventilation strategy was used, including an initial tidal volume of 6 mL/kg of ideal body weight, a positive end expiratory pressure of 5–10 cm $H_2O$, a respiratory rate of 10–12 times/min and fraction of inspired oxygen no more than 50%. All patients received remifentanil and midazolam to achieve target sedation and underwent daily awakening trials. We routinely monitored cerebral oxygen saturation and carried out a physical examination of the nervous system (12, 13).

When the primary disease was well-treated, the hemodynamics was stable and the tissue perfusion was satisfactory, the flow rate was gradually reduced to 1.5 L/min. Removal of ECMO was considered if echocardiography indicated that the left ventricular outflow tract velocity time integral was >10 cm, the lateral mitral annulus peak systolic velocity was >6 cm/s and the left ventricular ejection fraction was >25%(14).

## Statistical Analysis

Continuous data are expressed as mean ± standard deviation (SD), if normally distributed, or median (IQR), if not normally distributed. For continuous variables, the normality of distribution was evaluated using the Kolmogorov–Smirnov test. Categorical variables are summarized as percentages (%). Categorical variables were analyzed using the $\chi^2$ test or Fisher's exact methods and quantitative variables were analyzed using the Student's *t*-test or Mann–Whitney *U*-test as appropriate.

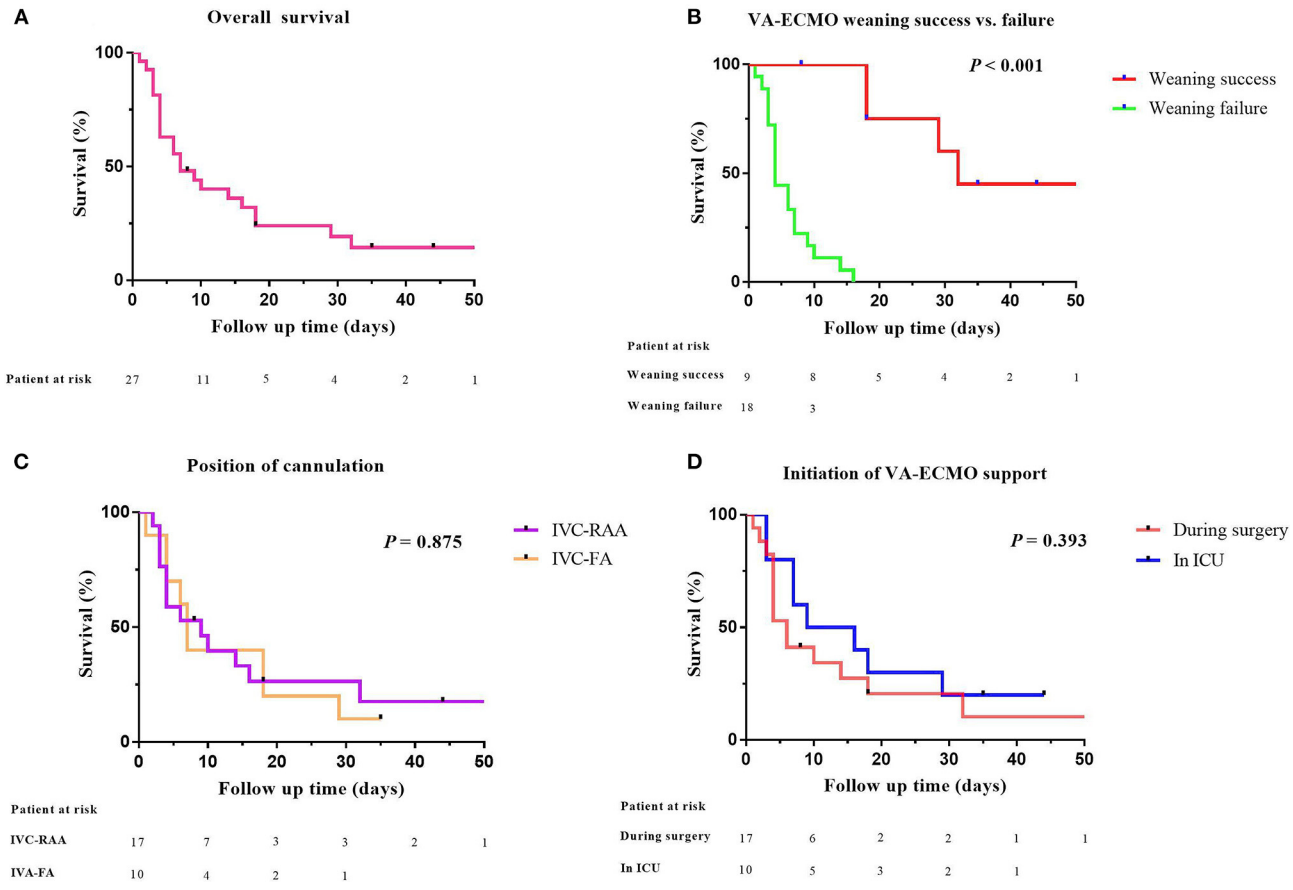


**FIGURE 2 |** Comparative survival in aTAAD patients after VA-ECMO support. **(A)** Kaplan–Meier analysis of overall survival in aTAAD patients supported by VA-ECMO from 2014 to 2019 ($n = 27$); **(B)** VA-ECMO weaning success or failure; **(C)** position of cannulation; **(D)** Initiation of VA-ECMO support (one patient in the successful weaning group was discharged after 96 days of follow-up. The abscissa was set to 50 days, one data point is outside the axis limits). aTAAD, acute type A aortic dissection; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

No adjustment was made for multiplicity. Log-rank testing and Kaplan–Meier survival curves were used to analyze survival. Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using SPSS software (version 19.0; SPSS, Inc., Chicago, IL, USA).

## RESULTS

Twenty-seven patients, who were supported with VA-ECMO following aTAAD surgery, were enrolled in the study between January 2014 and December 2019 (**Figure 1**). The mean age of the patients was 53 ± 14 years and 81% were male. Demographics, comorbidities, laboratory tests, and clinical manifestations of the successful group and failed weaning group are shown in **Table 1**. The preoperative CK-MB level in the failed group was significantly higher than that in successful group (14 [6–30] vs. 55 [28–138] U/L; $p < 0.01$). Age and preoperative cardiac troponin T (cTnT), lactate dehydrogenase (LDH), and creatinine (Cr) levels were higher in the failed group than in the successful group (45 ± 17 vs. 56 ± 12 years; 0.03 [0.01–0.68] vs. 0.97 [0.05–4.57] ng/mL; 253 [175–399] vs. 355 [280–579] U/L; 76 ± 37 vs. 160 ± 73 μmol/L), but the differences between the two groups were not statistically significant ($p > 0.05$).

Peri-operative details of the 27 patients who were supported with VA-ECMO are summarized in **Table 2**. Coronary artery bypass grafting was performed in ten patients because of poor cardiac function caused by coronary artery dissection. Although there were no significant difference in operation mode, operation time, CPB time, aortic cross clamp time, or deep hypothermic circulatory arrest time between the two groups, the CPB and aortic cross clamp times in the failed group were longer than those in the successful group (235 ± 83 vs. 290 ± 129 min; 94 ± 19 vs. 120 ± 46 min; $p > 0.05$). Postoperative peak CK-MB, cTnT, and LDH levels were all significantly higher in patients who failed withdrawal of VA-ECMO (134 ± 92 vs. 300 ± 161 U/L; 4.0 [0.9–7.1] vs. 19.5 [6.6–29.9] ng/mL; 1,178 ± 669 vs. 2,468 ± 1,181 U/L, respectively; $p < 0.01$). Postoperative peak lactate levels were also higher in the successful group than in the failed group (19 ± 3 vs. 16 ± 4 mmol/L; $p < 0.05$).

Seventeen patients received VA-ECMO support in the operating room because of difficulty in weaning from CPB, and ten patients had VA-ECMO initiated in the cardiac surgery ICU because of refractory postoperative cardiogenic shock. No progression of aortic dissection was observed during VA-ECMO support. After a median period of 192 h of support, nine patients (33%) were successfully weaned from VA-ECMO support and five patients (19%) survived to hospital discharge. One patient had residual right lower limb movement disorder. The in-hospital mortality rate was 81% (22 patients). The follow-up survival rate of aTAAD patients who required perioperative VA-ECMO support was relatively low (**Figure 2**).

Additionally, patients who were successfully weaned from VA-ECMO had a longer mechanical ventilation time (16 [8–31] vs. 3 [1–7] days; $p < 0.01$), a longer ICU stay (16 [11–35] vs. 3

**TABLE 3 |** ECMO implementation and clinical outcomes.

| Variables | Total ($n = 27$) | Wean-from ECMO | | $p$-value |
|---|---|---|---|---|
| | | Success ($n = 9$) | Failure ($n = 18$) | |
| Initiation of VA-ECMO support (*n*) | | | | 0.68 |
| During surgery | 17 | 5 | 12 | |
| In ICU | 10 | 4 | 6 | |
| Position of cannulation (*n*) | | | | 0.41 |
| IVC-FA | 11 | 5 | 6 | |
| IVC-RAA | 16 | 4 | 12 | |
| ECMO duration (h) | 82 (46, 192) | 192 (111, 327) | 55 (23, 95) | 0.01 |
| MV time (d) | 6 (2, 14) | 16 (8, 31) | 3 (1, 7) | 0.01 |
| CRRT, *n* (%) | 19 (70) | 6 (67) | 13 (72) | 0.77 |
| Major complications, *n* (%) | | | | |
| Bleeding | 10 (37) | 1 (11) | 9 (50) | 0.23 |
| Tamponade | 0 (0) | 0 (0) | 0 (0) | 1.00 |
| Neurological complications | 4 (15) | 2 (22) | 2 (11) | 0.58 |
| VT/VF | 3 (11) | 0 (0) | 3 (17) | 0.53 |
| Infection | 1 (4) | 1 (11) | 0 (0) | 1.00 |
| MODS | 4 (15) | 0 (0) | 4 (22) | 0.27 |
| ICU stay (d) | 6 (3, 14) | 16 (11, 35) | 3 (2, 5) | 0.01 |
| Hospital stay (d) | 7 (4, 18) | 29 (18, 40) | 4 (3, 8) | 0.01 |
| Mortality, *n* (%) | 22 (81) | 4 (44) | 18 (100) | 0.01 |

*VA-ECMO, veno-arterial extracorporeal membrane oxygenation; ICU, intensive care unit; IVC, inferior vena cava; FA, femoral artery; RAA, right axillary artery; MV, mechanical ventilation; CRRT, continuous renal replacement therapy; VT, ventricular tachycardia; VF, ventricular fibrillation; MODS, multiple organ dysfunction syndromes.*

**TABLE 4 |** Studies concerning the role of VA-ECMO in aTAAD patients.

| Reference | Study design | Sample size | Time of VA-ECMO implantation | Approach of cannulation | Wean from VA-ECMO | Mortality |
|---|---|---|---|---|---|---|
| Lin et al. (17) | Retrospective study | 20 | Postoperative | IVC-RAA is preferred | 65% | 65% |
| Sultan et al. (18) | Retrospective study | 35 (31 open surgery) | 27 during surgery<br>8 after surgery | No mention | No mention | 89.7% |
| Wang et al. (19) | Retrospective study | 7 | 6 during surgery<br>1 after surgery | IVC-FA | 100% | 14.3% |
| Mariscalco et al. (20) | Retrospective study | 62 | 46 during surgery | 19 central arterial cannulation | 37% | 74% |

*VA-ECMO, veno-arterial extracorporeal membrane oxygenation; aTAAD, acute type A aortic dissection; IVC, inferior vena cava; FA, femoral artery; RAA, right axillary artery.*

[2–5] days; $p < 0.01$) and a longer hospital stay (29 [18–40] vs. 4 [3–8] days; $p < 0.01$), compared with patients who failed weaning from VA-ECMO. No patient was lost to follow-up during this period. Details of VA-ECMO implementation and outcomes are presented in **Table 3**.

## DISCUSSION

In this single center study, 27 out of 912 aTAAD patients received VA-ECMO and achieved barely satisfactory results. An intra-aortic balloon pump cannot be used in aTAAD patients and VA-ECMO may be the only viable extracorporeal life support technique for aTAAD patients difficult to wean from CPB or with postoperative cardiogenic shock. Despite its higher in-hospital mortality and postoperative complications, VA-ECMO can be considered as salvage treatment in patients after aTAAD surgery.

aTAAD is not only a morphological abnormality of the aortic wall, but also involves hemodynamic changes that affect cardiac function and the blood supply of important organs, together with a systemic inflammatory reaction caused by dissection. Improvements in surgical, CPB and cerebral protection techniques, together with better perioperative management strategies (nitrogen oxide, continuous renal replacement therapy, and VA-ECMO), have led to a gradual decrease in the mortality rate of aTAAD, with mortality rates reported to be 15–30% (15, 16). VA-ECMO can provide temporary mechanical circulatory support and allow time for etiological treatment (6). Previous studies have shown that the in-hospital mortality of patients who receive VA-ECMO assistance after aTAAD surgery is still high (**Table 4**) (17–20). Nevertheless, there have been no randomized controlled studies. Additionally, successful weaning does not mean better survival, since 20–65% of patients weaned from VA-ECMO support do not survive to discharge (21). In our series, the successful weaning rate and mortality following VA-ECMO were 33.3 and 81.5%, respectively. The main causes of this difference may be associated with the onset time of aTAAD, the basic condition, surgical strategies, the indication of VA-ECMO, and cannulation strategies.

Several factors may be associated with VA-ECMO weaning failure. Younger age, lower preoperative CK-MB levels, reduced postoperative blood transfusion, higher antegrade cannulation rates, lower lactate levels, lower rates of continuous renal replacement therapy, and organ ischemia have all been shown to influence survival of aTAAD patients after VA-ECMO support (10, 17). We also found that preoperative CK-MB levels were significantly higher in the failed group than in the successful group. Although patients who failed weaning were older and had higher preoperative cTnT levels before CPB than the successfully weaned group, these differences were not statistically significant. Additionally, differences in perioperative blood transfusion, rate of antegrade cannulation, and rate of continuous renal replacement therapy did not reach statistical significance. Postoperative peak levels of cTnT, CK-MB, LDH, and blood lactate were, however, significantly higher in patients who failed weaning from VA-ECMO. CTnT and CK-MB are commonly used as indicators of acute myocardial infarction. Higher cTnT and CK-MB levels after 24–48 h of VA-ECMO support may be associated with poor prognosis. LDH, a key enzyme that regulates the conversion of pyruvate to lactic acid during anaerobic glycolysis, is widely distributed in the cytoplasm, and in mitochondria of the heart, liver, skeletal muscle, and other tissues and cells. When ischemic myocardial injury occurs, the damaged myocardial cell membranes rupture and LDH, which can also be used as a diagnostic marker of myocardial injury (22), is released into the blood serum. Failure to successfully wean from VA-ECMO may be attributable to more severe organ ischemia, including myocardial ischemia, liver and kidney injury, caused by aortic dissection before VA-ECMO was started.

In terms of cannulation strategies, peripheral cannulation is minimally invasive and is the routine pathway for most adult patients. Although femoral artery-femoral vein catheterization is easier and faster, we preferred to cannulate in the right axillary artery because of residual aortic dissection in aTAAD patients. Axillary artery cannulation is, however, technically more difficult than the femoral artery and there is also a risk of hyperperfusion of the ipsilateral arm and brain (23). We compared outcomes of patients who were subjected to the two different cannulation strategies and found there was no significant difference in prognosis between the two groups.

Complications of VA-ECMO support following aTAAD surgery include bleeding, cerebral dysfunction, malperfusion of vital organs, and infection. In our study, death usually occurred soon after surgery and major bleeding was the most common cause of death in patients who could not be successfully weaned from VA-ECMO. Causes of postoperative bleeding may be multifactorial (24–26). Systemic inflammatory reaction caused by dissection, longer CPB time, massive blood transfusion during surgery, hypothermia and postoperative VA-ECMO assistance all result in impaired postoperative coagulation and bleeding. Precise management and proper hemostasis, including bedside thromboelastography, reasonable infusion of fresh frozen plasma, platelets, fibrinogen, and prothrombin complex, are, therefore, very important during surgery.

Our study has several limitations. Firstly, the study was a single-center, retrospective study. Secondly, because of the rarity of aTAAD with VA-ECMO support, the sample size was too small and the follow-up time was relatively short, which meant that detailed analysis of risk factors was not possible. In the future, multicenter studies, with large patient populations, are needed to optimize management strategies and improve outcomes in this rare but complex cardiac emergency.

## CONCLUSIONS

This study showed that the use of VA-ECMO in aTAAD patients is a viable salvage strategy, despite the relatively high rate of complications and mortality. VA-ECMO could

provide a bridge-to-recovery for aTAAD patients with refractory cardiogenic shock.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## AUTHOR CONTRIBUTIONS

J-yH, G-wT, and ZL contributed to study design. Y-xS, J-yH, HW, HL, J-lZ, and Jc-L contributed to enrollment of participants. J-lZ and XL contributed to study management and data collection. J-yH and C-sW contributed to manuscript writing. G-wT and ZL contributed to data analyses and manuscript revision. All authors have read and approved the final manuscript.

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## REFERENCES

1. Bossone E, LaBounty TM, Eagle KA. Acute aortic syndromes: diagnosis and management, an update. *Eur Heart J.* (2018) 39:739–49. doi: 10.1093/eurheartj/ehx319
2. Evangelista A, Isselbacher EM, Bossone E, Gleason TG, Eusanio MD, Sechtem U, et al. Insights from the International Registry of Acute Aortic Dissection: a 20-Year Experience of Collaborative Clinical Research. *Circulation.* (2018) 137:1846–60. doi: 10.1161/CIRCULATIONAHA.117.031264
3. Chen YF, Chien TM, Yu CP, Ho KJ, Wen H, Li WY, et al. Acute aortic dissection type A with acute coronary involvement: a novel classification. *Int J Cardiol.* (2013) 168:4063–9. doi: 10.1016/j.ijcard.2013.07.031
4. Narayan P, Rogers CA, Benedetto U, Caputo M, Angelini GD, Bryan AJ. Malperfusion rather than merely timing of operative repair determines early and late outcome in type A aortic dissection. *J Thorac Cardiovasc Surg.* (2017) 154:81–6. doi: 10.1016/j.jtcvs.2017.03.041
5. Czerny M, Schoenhoff F, Etz C, Englberger L, Khaladj N, Zierer A, et al. The impact of pre-operative malperfusion on outcome in acute type A Aortic dissection: results from the GERAADA registry. *J Am Coll Cardiol.* (2015) 65:2628–35. doi: 10.1016/j.jacc.2015.04.030
6. Rao P, Khalpey Z, Smith R, Burkhoff D, Kociol RD. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest. *Circ Heart Fail.* (2018) 11:e004905. doi: 10.1161/CIRCHEARTFAILURE.118.004905
7. Keebler ME, Haddad EV, Choi CW, McGrane S, Zalawadiya S, Schlendorf KH, et al. Venoarterial extracorporeal membrane oxygenation in cardiogenic shock. *JACC Heart Fail.* (2018) 6:503–16. doi: 10.1016/j.jchf.2017.11.017
8. Mebazaa A, Combes A, van Diepen S, Hollinger A, Katz JN, Landoni G, et al. Management of cardiogenic shock complicating myocardial infarction. *Intensive Care Med.* (2018) 44:760–73. doi: 10.1007/s00134-018-5214-9
9. Rastan AJ, Dege A, Mohr M, Doll N, Falk V, Walther T, et al. Early and late outcomes of 517 consecutive adult patients treated with extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock. *J Thorac Cardiovasc Surg.* (2010) 139:302–11:11.e1. doi: 10.1016/j.jtcvs.2009.10.043
10. Zhong Z, Jiang C, Yang F, Hao X, Xing J, Wang H, et al. Veno-arterial extracorporeal membrane oxygenation support in patients undergoing aortic surgery. *Artif Organs.* (2017) 41:1113–20. doi: 10.1111/aor.12951
11. Balle CM, Jeppesen AN, Christensen S, Hvas AM. Platelet function during extracorporeal membrane oxygenation in adult patients. *Front Cardiovasc Med.* (2019) 6:114. doi: 10.3389/fcvm.2019.00114
12. Laimoud M, Ahmed W. Acute neurological complications in adult patients with cardiogenic shock on veno-arterial extracorporeal membrane oxygenation support. *Egypt Heart J.* (2020) 72:26. doi: 10.1186/s43044-020-00053-5
13. Bembea MM, Felling R, Anton B, Salorio CF, Johnston MV. Neuromonitoring during extracorporeal membrane oxygenation: a systematic review of the literature. *Pediatr Crit Care Med.* (2015) 16:558–64. doi: 10.1097/PCC.0000000000000415
14. Aissaoui N, Luyt CE, Leprince P, Trouillet JL, Leger P, Pavie A, et al. Predictors of successful extracorporeal membrane oxygenation (ECMO) weaning after assistance for refractory cardiogenic shock. *Intensive Care Med.* (2011) 37:1738–45. doi: 10.1007/s00134-011-2358-2
15. Ma GG, Hao GW, Lai H, Yang XM, Liu L, Wang CS, et al. Initial clinical impact of inhaled nitric oxide therapy for refractory hypoxemia following type A acute aortic dissection surgery. *J Thorac Dis.* (2019) 11:495–504. doi: 10.21037/jtd.2019.01.42
16. Andersen ND, Ganapathi AM, Hanna JM, Williams JB, Gaca JG, Hughes GC. Outcomes of acute type a dissection repair before and after implementation of a multidisciplinary thoracic aortic surgery program. *J Am Coll Cardiol.* (2014) 63:1796–803. doi: 10.1016/j.jacc.2013.10.085
17. Lin TW, Tsai MT, Hu YN, Lin WH, Wang WM, Luo CY, et al. Postoperative extracorporeal membrane oxygenation support for acute type A aortic dissection. *Ann Thorac Surg.* (2017) 104:827–33. doi: 10.1016/j.athoracsur.2017.01.059
18. Sultan I, Habertheuer A, Wallen T, Siki M, Szeto W, Bavaria JE, et al. The role of extracorporeal membrane oxygenator therapy in the setting of Type A aortic dissection. *J Card Surg.* (2017) 32:822–5. doi: 10.1111/jocs.13245
19. Wang Y, Piao H, Li B, Wang W, Huang M, Zhu Z, et al. Extracorporeal membrane oxygenation in stanford type A aortic dissection. *Int Heart J.* (2019) 60:845–8. doi: 10.1536/ihj.18-496
20. Mariscalco G, Fiore A, Ragnarsson S, El-Dean Z, Jonsson K, Dalen M, et al. Venoarterial extracorporeal membrane oxygenation after surgical repair of type A aortic dissection. *Am J Cardiol.* (2020) 125:1901–5. doi: 10.1016/j.amjcard.2020.03.012
21. Ortuno S, Delmas C, Diehl JL, Bailleul C, Lancelot A, Naili M, et al. Weaning from veno-arterial extra-corporeal membrane oxygenation: which strategy to use? *Ann Cardiothorac Surg.* (2019) 8:E1–E8. doi: 10.21037/acs.2018.08.05
22. Zeng J, Pan Y, Cui B, Zhai T, Gao S, Zhao Q, et al. Calciumsensing receptors in human peripheral T lymphocytes and AMI: cause and effect. *Int J Mol Med.* (2018) 42:3437–46. doi: 10.3892/ijmm.2018.3924
23. Frenckner B, Broman M, Broome M. Position of draining venous cannula in extracorporeal membrane oxygenation for respiratory and respiratory/circulatory support in adult patients. *Crit Care.* (2018) 22:163. doi: 10.1186/s13054-018-2083-0

24. Koerner MM, Harper MD, Gordon CK, Horstmanshof D, Long JW, Sasevich MJ, et al. Adult cardiac veno-arterial extracorporeal life support (VA-ECMO): prevention and management of acute complications. *Ann Cardiothorac Surg.* (2019) 8:66–75. doi: 10.21037/acs.2018.12.09
25. Koster A, Ljajikj E, Faraoni D. Traditional and non-traditional anticoagulation management during extracorporeal membrane oxygenation. *Ann Cardiothorac Surg.* (2019) 8:129–36. doi: 10.21037/acs.2018.07.03
26. Mazzeffi M, Strauss E, Meyer M, Hasan S, Judd M, Abuelkasem E, et al. Coagulation factor levels and underlying thrombin generation patterns in adult extracorporeal membrane oxygenation patients. *Anesth Analg.* (2019) 129:659–66. doi: 10.1213/ANE.0000000000004275

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REVIEW
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# Overview of Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO) Support for the Management of Cardiogenic Shock

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Cardiogenic shock accounts for ∼100,000 annual hospital admissions in the United States. Despite improvements in medical management strategies, in-hospital mortality remains unacceptably high. Multiple mechanical circulatory support devices have been developed with the aim to provide hemodynamic support and to improve outcomes in this population. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is the most advanced temporary life support system that is unique in that it provides immediate and complete hemodynamic support as well as concomitant gas exchange. In this review, we discuss the fundamental concepts and hemodynamic aspects of VA-ECMO support in patients with cardiogenic shock of various etiologies. In addition, we review the common indications, contraindications and complications associated with VA-ECMO use.

**Keywords: extracorporeal membrane oxygenation, cardiogenic shock, mechanical circulatory support, VA-ECMO indications, VA-ECMO complications**

## INTRODUCTION

The primary objective of this paper is to provide a comprehensive review of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) use in the management of adult patients with refractory cardiogenic shock (CS).

## THE EVOLVING DEFINITION OF CARDIOGENIC SHOCK

Cardiogenic shock is commonly defined as a state of low cardiac output that is inadequate to support the systemic perfusion requirements in the context of normal cardiac filling pressures. Organ hypoperfusion is a central feature of CS. The resultant tissue ischemia and reduced nutrient delivery, if persistent, may lead to multi-organ failure including altered mental status, oliguria with <30 cc/h urine output, narrow pulse pressure, and arterial lactic acid level exceeding 2 mmol/L (1, 2).

Historically, clinicians and investigators established the presence of CS by using a combination of select abnormal hemodynamic parameters and evidence of end-organ dysfunction. Consequently, various landmark clinical trials employed different definitions to diagnose CS

(**Table 1**). Most commonly using some combination of the following criteria: (I) profound hypotension with a systolic blood pressure (BP) <80–90 mmHg for at least 30 min, a drop in mean BP of 30 mmHg or more from baseline, the need for vasoactive medications to maintain a systolic BP above 90 mmHg despite adequate fluid resuscitation; (II) elevated biventricular filling pressures with central venous pressure (CVP) above 10 mmHg and pulmonary capillary wedge pressure (PCWP) exceeding 15 mmHg; (III) significantly reduced cardiac index (<1.8 L/min/$m^2$ or <2.2 L/min/$m^2$ with hemodynamic support); and (IV) low mixed venous blood oxygen saturation signaling increased peripheral oxygen extraction due to hypoperfusion (16). Systemic vascular resistance (SVR) is markedly elevated in most cases of CS. While calculating SVR is critical to establish the type of shock in routine clinical practice, it has not been included in the definition of CS used by landmark clinical trials as patients may initially present with normal or even low SVR. The presence of low SVR may signify end-stage CS as a result of inappropriate vasodilation despite hypotension, low cardiac output, and tissue hypoperfusion. Accordingly, it is associated with microvascular dysfunction, more severe systemic inflammatory response (cytokine storm) and, ultimately, worse clinical outcomes (22). Coronary perfusion pressure and, therefore, coronary blood flow may decrease significantly in CS owing to the severely elevated ventricular filling pressures and systemic hypotension. This will further worsen myocardial ischemia and contractility contributing to the vicious cycle of CS (8, 18).

Up until recently, the diagnosis of CS was binary (present or absent) and was established based on a combination of distinct hemodynamic parameters detailed above. However, it became increasingly clear that the clinical condition of patients meeting the minimum criteria of CS are extremely heterogenous. It may include outpatients with low cardiac output, those requiring a single inotrope infusion as well as end stage patients needing biventricular mechanical circulatory support (MCS). Recognizing the continuum of hemodynamic instability in this population, the Society for Cardiac Angiography and Intervention (SCAI) recently published an expert consensus statement defining five stages of CS ranging from at risk to extremis (35, 36). A combination of easily identifiable hemodynamic parameters, biochemical markers and physical examination findings define each stage. This simple and validated framework aims to facilitate targeted patient management by matching the intensity of medical therapy and the level of mechanical support to each individual's CS stage. In addition, physicians can quickly and frequently re-assess their patient's CS stage and adjust the management accordingly. Utilizing this strategy is expected to reduce complications, improve clinical outcomes, and survival.

## EPIDEMIOLOGY OF CARDIOGENIC SHOCK

Accurately pinpointing the prevalence of CS is challenging and varies based on the era the data was collected and the definition

**TABLE 1 |** The broad range of criteria utilized to define cardiogenic shock.

| Study | Definition |
|---|---|
| Aissaoui et al. USIK/UCIC/FAST-MI registries (3) | • SBP < 90 mmHg<br>• Oliguria or signs of peripheral hypoperfusion |
| Basir et al. The Detroit cardiogenic shock initiative (4) | • SBP < 90 mmHg or need for supportive measures to maintain SBP > 90 mmHg<br>• Signs of peripheral hypoperfusion or oliguria or elevated lactate<br>• Cardiac index <2.2 LPM/$m^2$ or PCWP ≥ 15 mmHg |
| Bisdas et al. (5) | • SBP < 90 mmHg<br>• Lactate ≥ 4 mmol/L<br>• Cardiac index <2.2 LPM/$m^2$ |
| Brechot et al. (6) | • LVEF < 25% or increased inotrope score or SBP < 90 mmHg despite inotrope use<br>• Cardiac index < 2.2 LPM/$m^2$ |
| Brechot et al. (7) | • LVEF < 35%<br>• Lactate ≥ 4 mmol/L<br>• Cardiac index < 3 LPM/$m^2$ |
| Califf et al. (8) | • SBP < 90 mmHg for more than 30 min or SBP drop >30 mmHg from baseline for 30 min<br>• Cardiac index <2.2 LPM/$m^2$ or PCWP ≥ 15 mmHg<br>• Oliguria, signs of peripheral hypoperfusion or $avO_2$ > 5.5 ml/dL |
| Chioncel et al. ESC heart failure long-term registry (9) | • SBP < 90 mmHg or drop > 30 mmHg from baseline for 30 min<br>• Oliguria or signs of peripheral hypoperfusion |
| Chung et al. (10) | • SBP < 90 mmHg and pulmonary edema or need for supportive measures to maintain SBP > 90 mmHg |
| De Roo et al. (11) | • MAP ≤ 60 mmHg<br>• Cardiac index < 2.2 LPM/$m^2$ with hemodynamic support |
| Goldberg et al. (12) | • SBP < 80 mmHg<br>• Signs of peripheral hypoperfusion or oliguria |
| Goldberg et al. (13) | • SBP < 80 mmHg<br>• Signs of peripheral hypoperfusion or oliguria |
| Harjola et al. CardShock study (14) | • SBP < 90 mmHg for more than 30 min or need for supportive measures to maintain SBP > 90 mmHg<br>• Signs of peripheral hypoperfusion or lactate ≥ 2 mmol/L |
| Helgestad et al. (15) | • SBP < 90 mmHg for more than 30 min or need for supportive measures to maintain SBP >90 mmHg<br>• Signs of peripheral hypoperfusion, oliguria or lactate ≥ 2.5 mmol/L |
| Hochman et al. SHOCK study (16) | • SBP < 90 mmHg for more than 30 min or need for supportive measures to maintain SBP > 90 mmHg<br>• Cardiac index <2.2 LPM/$m^2$ or PCWP ≥ 15 mmHg<br>• Oliguria or signs of peripheral hypoperfusion |
| Hochman et al. SHOCK study (17) | • SBP < 90 mmHg for more than 30 min or need for supportive measures to maintain SBP > 90 mmHg<br>• Signs of peripheral hypoperfusion or oliguria<br>• Cardiac index < 2.2 LPM/$m^2$ or PCWP ≥ 15 mmHg |

*(Continued)*

**TABLE 1 |** Continued

| Study | Definition |
|---|---|
| Hollenberg et al. (18) | • SBP < 90 mmHg for more than 30 min<br>• Cardiac index < 2.2 LPM/$m^2$ or PCWP ≥ 15 mmHg |
| Holmes et al. GUSTO-I (19) | • SBP < 90 mmHg for more than 60 min or need for supportive measures to maintain SBP > 90 mmHg<br>• PCWP ≥ 15 mmHg |
| Hulman et al. (20) | • Cardiac index <2 LPM/$m^2$ with support |
| Killip et al. (21) | • SBP < 90 mmHg<br>• Oliguria or signs of peripheral hypoperfusion |
| Kohsaka et al. SHOCK study (22) | • SBP < 90 mmHg for more than 30 min or need for supportive measures to maintain SBP > 90 mmHg<br>• Cardiac index < 2.2 LPM/$m^2$ or PCWP ≥ 15 mmHg<br>• Oliguria or signs of peripheral hypoperfusion |
| Lee et al. (23) | • SBP < 90 mmHg for more than 30 min or need for supportive measures to maintain SBP > 90 mmHg |
| Muller et al. ENCOURAGE derivation cohort (24) | • LVEF < 25% or SBP < 90 mmHg despite inotrope use<br>• Cardiac index < 2.2 LPM/$m^2$ |
| Ostadal et al. ECMO-CS (25) | • LVEF < 35% or LVEF 35–55% in combination with valvular disease or need for supportive measures to maintain MAP > 50 mmHg<br>• Cardiac index < 1.8 LPM/$m^2$ without support or central venous pressure >7 mmHg or PCWP ≥ 12 mmHg<br>• $SvO_2$ < 50% in two consecutive measurements |
| Ouweneel et al. (26) | • SBP < 90 mmHg for more than 30 min or need for supportive measures to maintain SBP > 90 mmHg |
| Pozzi et al. (27) | • SBP < 90 mmHg<br>• Signs of peripheral hypoperfusion or oliguria |
| Rihal et al. SCAI/ACC/HFSA/STS guidelines on MCS use for cardiogenic shock (28) | • SBP < 90 mmHg for more than 30 min or drop >30 mmHg from baseline for 30 min<br>• Cardiac index <2.2 LPM/$m^2$ with support or cardiac index <1.8 LPM/$m^2$ without support or PCWP ≥ 15 mmHg |
| Seyfarth et al. ISAR-SHOCK (29) | • SBP < 90 mmHg for more than 30 min or need for supportive measures to maintain SBP > 90 mmHg<br>• Signs of peripheral hypoperfusion or oliguria<br>• Cardiac index < 2.2 LPM/$m^2$ or PCWP ≥ 15 mmHg |
| Sheu et al. (30) | • SBP < 90 mmHg and pulmonary edema or need for supportive measures to maintain SBP > 90 mmHg |
| Thayer et al. Cardiogenic shock working group registry (31) | • SBP < 90 mmHg for more than 30 min<br>• Cardiac index <2.2 LPM/$m^2$ |
| Thiele et al. (32) | • SBP < 90 mmHg for more than 30 min or need for supportive measures to maintain SBP > 90 mmHg<br>• Oliguria<br>• Cardiac index <2.2 LPM/$m^2$ with support or cardiac index <1.8 LPM/$m^2$ without support or PCWP ≥ 18 mmHg |
| Tsao et al. (33) | • SBP < 90 mmHg and pulmonary edema or intervention required to maintain SBP > 75 mmHg |
| Wu et al. (34) | • Refractory ventricular tachycardia or need for supportive measures to maintain SBP > 90 mmHg |

*SBP, systolic blood pressure; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; LVEF, left ventricular ejection fraction; SvO2, mixed venous blood oxygen saturation; avO2, arteriovenous oxygen difference; SCAI, Society for Cardiovascular Angiography and Interventions; ACC, American College of Cardiology; HFSA, Heart Failure Society of America; STS, Society of Thoracic Surgeons; MCS, mechanical circulatory support; CS, cardiogenic shock.*

used (21, 35, 37, 38). CS is estimated to account for ∼100,000 annual hospitalizations in the United States alone (12, 13, 19, 32). Various studies and randomized clinical trials focusing on patients with myocardial infarction (MI) have reported a prevalence of 6–10%, with a slight increase over time (19, 39–42).

Acute coronary syndrome is the most frequent cause of CS, representing 80% of all cases (14). While more common in patients with ST-elevation myocardial infarction (STEMI), it may also complicate non-STEMI (43, 44). Prior to the advances in medical therapy and interventional strategies, in-hospital mortality of post-MI CS reached 80% with nearly half of these occurring within the first 24-h of presentation (9, 21). Although the emphasis on optimal medical therapy, MCS use and the widespread adoption of early revascularization strategies led to a significant decline in mortality rates, the mortality of CS associated with ACS remains high at 30–50% (3, 13, 45–47). Elderly patients (age >75 years), females, and those with underlying diabetes mellitus or prior myocardial injury are particularly at risk.

While the incidence of post-MI CS has declined over the past decades, there has been a concomitant increase in the incidence of CS caused by other etiologies (48). The most common causes include acute on chronic heart failure (HF), fulminant myocarditis, high-risk pulmonary embolism, stress-induced cardiomyopathy, severe valvular disease, sepsis, and hemodynamically unstable arrhythmias (2, 14). Among ∼8 million HF hospitalizations between 2005 and 2014 recorded in the National Inpatient Sample, the incidence rose from 4.1 to 15.6 per one thousand HF hospitalizations (48). For the same time period, a large registry analysis found that the proportion of patients admitted with post-MI CS has dropped significantly from 65.3 to 45.6% (49). The overall in-hospital mortality rate for this population initially was 42.4% but has decreased substantially to 27.1% (49).

## MECHANICAL CIRCULATORY SUPPORT STRATEGIES FOR THE MANAGEMENT OF CARDIOGENIC SHOCK

Multiple MCS devices have been developed over the past decades with the aim to provide various levels of hemodynamic support

to improve the devastating morbidity and mortality associated with CS. The fundamental assumption is that ventricular support and decompression leads to a reduction in myocardial wall stress and oxygen consumption, while concurrently augmenting end organ perfusion.

Several types of MCS devices are used in routine clinical practice. The intra-aortic balloon pump (IABP) was first developed in the 1960s and remains the most frequently utilized percutaneous temporary MCS device (50). While it only provides a modest increase in cardiac output, it augments diastolic coronary flow and reduces myocardial oxygen consumption (28). Newer percutaneous ventricular assist devices (pVAD) can provide significantly higher level of hemodynamic support and include the Tandemheart (LivaNova, London, UK) and the Impella family (Abiomed Inc., Danvers, MA, US). The increasingly utilized VA-ECMO systems (Centrimag, Abbott, Chicago, IL, US and Cardiohelp, Maquet, Rastatt, Germany) provide complete hemodynamic support and concomitant gas exchange. Randomized clinical trials directly comparing the efficacy and outcomes achieved with these devices are scarce and are limited by low enrollment, the predominance of post-MI patients and the highly variable definition of CS (26, 29, 51, 52) (**Table 1**).

## INTRODUCTION TO VA-ECMO

VA-ECMO is a temporary mechanical circulatory support system that enables complete and immediate cardiopulmonary support in the setting of cardiogenic shock and cardiac arrest (53). It consists of a centrifugal pump capable of propelling up to 8 L/min of blood and venous drainage and arterial return cannulas. A hollow fiber membrane oxygenator is spliced into the circuit that not only provides blood oxygenation but also carbon dioxide ($CO_2$) clearance via sweep gas flow. This latter function is a critical distinguishing feature from other MCS strategies, such as IABP and pVADs. VA-ECMO may also be placed surgically, especially in the post-cardiotomy setting, when oxygenated blood is returned directly into the ascending aorta (central cannulation technique). However, this review focuses primarily on the use of peripherally placed VA-ECMO as this is the most common type of support instituted by cardiologists in the setting of cardiac arrest or refractory CS.

The preferred approach for percutaneous VA-ECMO is femoral artery and vein cannulation. In an adult, the tip of an 18–28 Fr cannula draining deoxygenated venous blood is positioned in the mid right atrium (RA) or the superior vena cava-RA junction. After passing through the "membrane lung," oxygenated blood is returned to the systemic circulation via a 15–19 Fr arterial cannula with its tip typically positioned in the iliac artery. Selecting cannulas with appropriate diameters is critical not only to reduce the risk of vascular injury but also to avoid significant negative inflow (preferably <50 mmHg) and high outflow pressure (<300 mmHg). To mitigate the risk of distal limb ischemia, an 8 Fr distal reperfusion cannula is routinely inserted into the superficial femoral artery in our center and is spliced into the arterial limb of the circuit (2, 54).

Peripheral VA-ECMO is increasingly utilized as a short-term support strategy to manage patients presenting with cardiac arrest, severe biventricular HF and CS stages C-E, independent of etiology (48). It can be initiated safely in the cardiac catheterization laboratory by experienced interventional cardiologists with very short door to support time, even during ongoing cardiopulmonary resuscitation (CPR) (55, 56). Depending on local institutional policies and the specific clinical scenario, it may also be instituted in the field (mobile ECMO programs), at bedside in the ICU, or in the operating room (57). Full VA-ECMO support not only allows time to perform diagnostic and therapeutic interventions while maintaining appropriate hemodynamics and gas exchange, but also provides time for potential organ recovery. Multiple clinical trials are currently ongoing with the aim to address the potential clinical benefits of early VA-ECMO initiation in various patient populations (4, 25).

## HEMODYNAMIC ASPECTS OF VA-ECMO SUPPORT

VA-ECMO is used in the management of CS due to its capability to reduce myocardial work (pressure-volume area) while providing complete hemodynamic and respiratory support. Myocardial pressure-volume area can be thought of as the sum of myocardial potential energy and myocardial stroke work (58, 59). Both are thought to be increased profoundly in CS due to a vicious cycle of maladaptive neurohormonal and vascular mechanisms (8, 60).

In the typical VA-ECMO setup in CS, the venous inflow cannula drains blood directly from the vena cavae or the RA. This significantly decreases right ventricular (RV) preload, trans-pulmonary blood flow and, therefore, left ventricular end-diastolic volume (LVEDV) and pressure (LVEDP) (61–63). Thus, VA-ECMO likely promotes hemodynamic stabilization in the setting of CS and cardiac arrest via reduced LVEDV and LVEDP. It follows, then, that VA-ECMO has been shown to reduce stroke work in pre-clinical models of CS caused by acute myocardial infarction (64). The myocardial pressure-volume area and myocardial potential energy may be further reduced by the weaning of inotropic and vasopressor drugs once VA-ECMO support is instituted. These pharmacologic agents are known to increase myocardial oxygen consumption and left ventricular (LV) stroke work dramatically (59, 65).

The use of VA-ECMO also improves systemic perfusion. Typically, mean arterial blood pressure rises after VA-ECMO initiation while the high-volume venous displacement from the RA reduces central venous pressure. The systemic arterio-venous pressure gradient increases as a result, thereby enhancing systemic circulation. This may be particularly relevant to improving blood flow in organs with portal circulation, such as the liver and kidney (63). Fluid removal and relief of venous congestion can be further enhanced by splicing a continuous veno-venous hemodialysis machine (continuous renal replacement therapy; CVVHD) into the VA-ECMO circuit. By providing large volume oxygenated

blood flow, organ perfusion can be supported irrespective of the intrinsic cardiac function. Importantly, the native right ventricular function is not as critical to the provision of systemic perfusion (as is the case with IABP and some pVADs) due to the lessened reliance on transpulmonary flow with VA-ECMO.

Despite the acknowledged benefits of VA-ECMO, there are still several critical gaps in the literature regarding the hemodynamic implications of prolonged VA-ECMO usage. Most notably, there is an absence of data using invasive ventricular catheterization to define how myocardial work and overall pressure-volume area is affected in the clinical (human) setting. Currently, most published pressure-volume loop data demonstrating the effects of varying levels of VA-ECMO support are based on computer simulations or animal experiments, rather than actual patient data (59, 66–68). Many of these studies used at least one fixed parameter (e.g., LV contractile strength) when performing their analysis. Yet, in real-life, these variables are interdependent and contractile strength will vary based on the Frank-Starling equation. Moreover, it is unclear how the hemodynamic responses on VA-ECMO support differ between patients with normal and depressed baseline LV ejection fraction, normal and dilated LV cavity and/or right ventricular dysfunction. Presumably, there is a diverse array of hemodynamic mechanisms in these HF sub-types, all of which remain largely uncharacterized *in vivo*.

The effect of retrograde arterial flow on LVEDV/LVEDP and LV unloading remains controversial and deserves special mention. Some commentators argue that the retrograde blood flow increases LV afterload by increasing mean arterial BP. This is thought to raise LVEDP, decrease stroke volume, reduce native cardiac output, and render a deleterious effect on LV performance (66, 68, 69). It is likely that this phenomenon more pertinent to patients with the complete lack of or minimal cardiac contractility, as opposed to patients that have preservation of LV function (63). Nevertheless, it is increasingly common to utilize one of the "LV venting" strategies, such as an IABP or Impella, despite unclear universal benefit (70). The device choice is often dependent of the center's experience and the benefit of upgrading from one strategy to another remains unexplored.

The populations in which venting devices offer a clear benefit remain largely uncharacterized. The hemodynamics of patients with different HF phenotypes are likely to respond differently to VA-ECMO support, thus creating a differential risk-benefit ratio for the addition of an unloading strategy. Patients with acute CS in the setting of severe, pre-existing HF and elevated left atrial pressure may be best suited for unloading. Moreover, patients with biventricular shock in whom the RV recovers before the LV, may also benefit from unloading. Under these circumstances, the RV may provide increased trans-pulmonary flow prompting a rise in LV preload, despite ongoing VA-ECMO support. The combination of increased preload and afterload may lead to an increase in the LV's myocardial oxygen consumption, thereby supporting the need for an unloading strategy.

# COMMON INDICATIONS FOR VA-ECMO SUPPORT

## Cardiogenic Shock Complicating Acute Myocardial Infarction

Despite the widespread use of early revascularization strategies, 6–10% of patients with acute coronary syndrome will progress to develop CS, representing 60–80% of all CS cases (12, 14, 15, 71). Myocardial ischemia and necrosis may continue following the index injury as the infarct extends circumferentially and toward the subepicardial regions. This prompts a further decline in cardiac function, increase in filling pressures, and excess oxygen consumption of the healthy residual myocardium. These, combined with reduced coronary perfusion pressure, initiate a vicious cycle until ∼50% of the functional LV mass is lost and CS ensues. Initiating VA-ECMO early in this setting reduces cardiac work, myocardial oxygen consumption and improves coronary blood flow. Therefore, VA-ECMO may limit infarct extension and allow time for the hibernating myocardium to recover (72).

The in-hospital mortality of post-MI patients with CS approaches 70–80% with traditional management, including vasoactive agents and IABP (12, 16, 17). Several non-randomized trials have demonstrated a clear benefit of VA-ECMO support in this population. As a result, its use has increased over 5-fold between 2000 and 2010 in one report (73). In a single-center retrospective study of 98 patients with MI, early VA-ECMO cannulation was associated with an all-cause in-hospital mortality of 67.3%. Patients presenting with CS as well as cardiac arrest were included (74). In a single center, retrospective observational study, Pozzi et al. identified 56 post-MI patients who presented with evidence of CS and were supported with VA-ECMO for a mean of 8.7 days. Survival to hospital discharge reached 41.1 and 32.1% were alive after a mean follow-up of 38.0 ± 29.9 months (27). In another single center study from Korea, 20 patients with post-MI CS were initiated on VA-ECMO before proceeding with coronary revascularization. Although CPR was performed in 70% of the cohort before cannulation, the in-hospital survival rate reached 50% (75). Multiple other, relatively small studies from around the world have reported similar rates of successful VA-ECMO decannulation and hospital discharge in the setting of post-MI CS (10, 23, 24, 30, 33, 34, 76–78) (**Table 2**).

Ventricular septal rupture (VSR) is a rare but dreaded complication of acute STEMI. It typically develops within 1–5 days after the STEMI and confers ∼90% mortality (79) due to the rapid development CS. VA-ECMO may be an effective temporary hemodynamic support strategy to stabilize these patients. It can be instituted promptly and utilized as a bridge to definitive surgical management while allowing the friable myocardium surrounding the rupture site to mature (80, 81). A case series of three individuals with post myocardial infarction CS and VSR placed on VA-ECMO showed excellent results with decannulation achieved in all patients and 100% survival (82).

The timing of VA-ECMO cannulation is of paramount importance in this population. It should be initiated within 60 min of the recognition of refractory CS, especially if initial attempts at hemodynamic stabilization with fluid resuscitation

**TABLE 2 |** Outcomes of VA-ECMO support stratified by the initial cause of cardiogenic shock.

| Indication for VA-ECMO support | Reported survival (%) |
|---|---|
| Acute myocardial infarction | 33.8–66.7 |
| Cardiomyopathy | 35.7–57.0 |
| COVID-19 infection | 0–36.6 |
| eCPR | 8.8–54.0 |
| Fulminant myocarditis | 60.0–74.0 |
| Primary graft failure post heart transplantation | 50.0–84.2 |
| Massive pulmonary embolism | 38.5–53.1 |
| Cardiomyopathy in the setting of sepsis | 59.8–75.0 |

*eCPR, extracorporeal cardiopulmonary resuscitation.*

and pharmacological agents fail (83). Preferably, MCS support should be established prior to proceeding with coronary interventions (28). The increased and early utilization of VA-ECMO in patients with post-MI CS is expected to translate into further improved clinical outcomes.

## Cardiogenic Shock Caused by Acute Fulminant Myocarditis

Acute fulminant myocarditis is a relatively uncommon, but severe condition characterized by the sudden and profound inflammation of the myocardium. Although the exact pathogenesis often remains obscure, myocyte edema and necrosis develop in response to various infectious and non-infectious triggers. The ensuing hypotension may progress to refractory cardiogenic shock within 2 days to 2 weeks of the initial insult. Owing to the profound hemodynamic instability and biventricular failure, escalating doses of vasoactive medications and IABP are often insufficient to maintain sufficient organ perfusion. VA-ECMO is an invaluable asset in the management of these patients. It may limit ongoing myocardial damage by providing prompt and effective circulatory support until the inflammatory storm subsides. Although VA-ECMO may serve as a bridge to durable left ventricular assist device (LVAD) or heart transplantation, full cardiac recovery is common within seven to 10 days in patients with fulminant myocarditis. With the exception of giant cell myocarditis, disease recurrence is uncommon and medical management is effective.

The available data also reflect a relatively positive prognosis in this population. In a multicenter, retrospective study of 57 patient with fulminant myocarditis, the mean duration of VA-ECMO support was 9.9 $\pm$ 19 days. 71.9% of patients were successfully discharged from the hospital and 5-years survival rate reached 65.2% (84). Another small, single-center study performed in Japan between 1991 and 2001 enrolled 14 patients with fulminant myocarditis requiring percutaneous VA-ECMO support for an average of 6.25 days. 71% of the cohort was weaned successfully and all of these had full cardiac recovery within 6–12 months (85). A study utilizing the ELSO database from 1995 through 2011 included 147 patients with a diagnosis of acute myocarditis who underwent ECMO support and showed a survival to hospital discharge rate of 61% (86). Many other groups have reported similarly high weaning and hospital discharge rates, establishing VA-ECMO as an extremely effective strategy for the management of patients with fulminant myocarditis associated with hemodynamic collapse (87–100) (**Table 2**).

## Acute Pulmonary Embolism/Right Ventricular Failure

The rate of hospital admissions for acute pulmonary embolism (PE) continues to rise and it remains one of the leading causes of cardiovascular death in the US (101, 102). Mortality reaches 80% in patients needing mechanical ventilation, 77% in those who require CPR within the first 24 h of admission and 37% in patients with syncope (103). Once the diagnosis is established, immediate risk stratification is critical. High-risk (massive) PE is characterized by: (I) Sustained systemic hypotension (systolic BP $<$ 90 mmHg for at least 15 min or requiring inotropic support with no other identifiable underlying causes, such as arrhythmia, sepsis or hypovolemia); (II) Clinical evidence of shock; III) Pulselessness or profound bradycardia (heart rate $<$40 BPM) (104, 105). Obstruction of 30–50% of the pulmonary vasculature in combination with vasoconstriction caused by thromboxane $A_2$ and serotonin released from activated platelets lead to an acute increase in pulmonary vascular resistance (106, 107). As the unconditioned right ventricle (RV) is rarely able to generate a mean pulmonary artery (PA) pressure $>$40 mmHg in the acute setting, stroke volume decreases, the ventricle dilates and, ultimately, RV failure develops (108). The associated coronary hypoperfusion and myocardial ischemia lead to a further decline in RV function. These changes are critical as short-term mortality is driven primarily by the RV failure. In addition to the hemodynamic changes, respiratory failure is also common in patients with acute high-risk PE owing to the immediate development of ventilation-perfusion (V/Q) mismatch.

Most patients with massive PE and shock die within the first hour of presentation (109). Therefore, it is vital to initiate hemodynamic and respiratory support as early as possible after patient contact. Of the available MCS devices, peripheral VA-ECMO is the only system that can provide both and can be instituted within minutes in experienced centers. It allows rapid patient stabilization and therapeutic interventions to be performed, such as thrombolysis or thrombectomy. VA-ECMO removes blood from the RA in the veno-arterial configuration and, after oxygenation and $CO_2$ elimination, returns it to the arterial system bypassing the pulmonary circulation. Therefore, it reduces RV strain, stabilizes the PA pressure, increases systemic perfusion and normalizes gas exchange.

To date, only a limited number of studies are available on the use of VA-ECMO in the setting of massive PE. These are mostly case reports and case series (110, 111) and no randomized clinical trials have evaluated the safety and efficacy of this approach. Overall survival rates are highly variable and depend on the definitive interventions used to manage PE, such as thrombolysis, surgical thrombectomy or heparin administration. In some reports, survival reaches 70% with good neurological function at discharge (**Table 2**). Cardiac arrest prior to VA-ECMO initiation and a lactic acid level exceeding 6 mmol/L

was associated with worse outcomes (112–117). The recent European Society of Cardiology guidelines state that VA-ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in patients with PE and refractory circulatory collapse or cardiac arrest if appropriate expertise and resources are available (Class IIb, level of evidence: C) (118). Randomized controlled trials are needed to establish the clear benefit of VA-ECMO support in this population.

## VA-ECMO Use in the Setting of COVID-19-Associated Cardiogenic Shock

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization on March 11, 2020. The causative virus, SARS-CoV-2 is highly infectious with a case fatality rate approaching 5.94% in the United States (119, 120). Although relatively rare, the most severe complications include acute respiratory distress syndrome, acute coronary syndrome secondary to coronary thrombosis or microembolism and stress-induced cardiomyopathy (121–127). SARS-CoV-2 affects most, if not all organs in the human body and the heart is no exception. In a series of 138 patients admitted with COVID-19 infection, the rate of acute cardiac injury was 7.2% (128). Another, smaller study documented an even higher rate of 17% (129). In both series, cardiac injury was defined by elevation of cardiac biomarker levels >99th percentile or the presence of new abnormalities on electrocardiography or echocardiography.

Given the prior use of VA-ECMO in patients with H1N1-associated myocarditis, several centers implemented VA-ECMO support for COVID-19-related CS. Given the extreme number of infections and limited resources, the Extracorporeal Life Support Organization (ELSO) has released guidelines on the contraindications for VA-ECMO use in this population (126, 130). These include, but are not limited to: advanced age, presence of any terminal disease, severe central nervous system injury, significant underlying comorbidities (such a dementia, liver failure, metastatic malignancy), severe multiorgan failure, severe peripheral vascular disease, "do not resuscitate" status, clinical frailty scale category $\geq$3, contraindications to anticoagulation, inability to accept blood products and ongoing CPR. The decision to proceed with VA-ECMO initiation should be made on a case by case basis after discussion with family and using a multidisciplinary team approach (131).

Recent reports suggest that only 5% of ECMO-supported patients for COVID-19 infection required VA configuration, while the need for VAV cannulation was reported in 6% (132, 133). As the severity of CS improves more rapidly than the respiratory failure, most patients on VAV-ECMO were ultimately converted to VV support for ongoing ARDS. Literature on patient survival requiring VA-ECMO cannulation for COVID-19-associated hemodynamic collapse remains scarce (**Table 2**). Further studies, such as the ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease (ECMOCARD) are warranted in this population.

In the case of respiratory failure and severe right ventricular dysfunction with preserved LV function, a veno-venous cannulation strategy with an oxygenator spliced into the circuit may be considered (Protek Duo oxyRVAD; Tandemlife, Pittsburgh, PA). A retrospective study by Mustafa and colleagues showed a mortality rate of 15% in 40 patients with most achieving freedom from ventilator care and ECMO support (134). Further studies are needed using this system in patients with severe COVID-19 infection.

## Extracorporeal Cardiopulmonary Resuscitation

VA-ECMO is increasingly utilized as a support strategy in the setting of out-of-hospital and in-hospital cardiac arrest. The provision of early extracorporeal cardiopulmonary resuscitation (ECPR) can maintain vital organ perfusion during and immediately after the arrest. In addition, ECPR provides full hemodynamic and respiratory support while reversible causes of the cardiac arrest are addressed and allows time for patients to recover from multi-organ failure (61).

Data regarding this approach has been available in the literature for over a decade. Survival rates for out-of-hospital cardiac arrest with ECPR use have varied widely from 7 to 45% (135–149). The disparity in outcomes seen in observational data is likely attributable to the broad heterogeneity of the study protocols. Some of these sources of heterogeneity include (I) the type of rhythm (shockable vs. non-shockable), (II) cannulation site (field, emergency room, or cardiac catheterization laboratory), and (III) intensive care unit strategies used in the post-arrest period. Moreover, there is a steep learning curve for the rapid, efficient, and safe initiation of peripheral VA-ECMO in the setting of cardiac arrest, particularly when CPR is ongoing.

Several observational studies from the Minnesota Resuscitation Consortium (MRC) support the use of ECPR strategy for select patients. Early data from the group described the feasibility of community-wide implementation of an ECPR approach (55). It was demonstrated that, through close collaboration with community emergency medical services, it is possible to facilitate rapid patient transfer to an ECPR hub where immediate VA-ECMO initiation and coronary revascularization is feasible. Accordingly, 50% of the patients enrolled in this protocol demonstrated survival to discharge with good neurologic function despite presenting with refractory ventricular tachycardia/ventricular fibrillation (VT/VF) arrest and ongoing CPR. Subsequent data from the group validated these survival results and suggested that rapid coronary revascularization is fundamental to improving outcomes and achieving high survival rates to discharge, owing to the incidence of underlying severe coronary artery disease in this population (150). This was further corroborated by a retrospective cohort study from the MRC where the ECPR approach was associated with improved rates of neurologically favorable survival to discharge compared to a matched cohort from the ALPS trial receiving standard advanced cardiac life support (ACLS) (151). Again, this is likely due to the ability of VA-ECMO to mitigate the severe and progressive metabolic derangements that occur with prolonged CPR. Collectively, these data from the MRC suggest

that early VA-ECMO initiation combined with rapid coronary revascularization and an intensive care bundle promotes organ recovery, including cardiac function, following out-of-hospital cardiac arrest (152) (**Table 2**).

More recently, the MRC has published a single center randomized trial (Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation; ARREST) of 36 patients with out-of-hospital cardiac arrest due to refractory VT/VF. Patients were randomized to receive ECPR or standard ACLS on presentation. Patients in the VA-ECMO-facilitated resuscitation cohort had significantly higher in-hospital (43 vs. 7%) and post-discharge survival at 6-months (43 vs. 0%, $p = 0.0063$) (55). This was the first randomized clinical trial clearly demonstrating the benefits of a mature ECPR program. Several studies are currently planned or underway to invasively study the hemodynamic changes associated with VA-ECMO support (153–155).

## Other, Rare Indications for VA-ECMO Use in the Setting of Cardiogenic Shock

Other indications for VA-ECMO use include (I) *Sepsis in the setting of underlying cardiomyopathy*. Hemodynamic collapse may develop as the left ventricle is unable to augment cardiac output to counteract the severe vasodilation. Limited data has shown a benefit for VA-ECMO use in selected patients (6, 7, 156) (**Table 2**); (II) *Primary graft dysfunction following orthotopic heart transplantation*. Several studies have shown significantly improved outcomes when VA-ECMO is initiated early in this setting (11, 20, 157, 158) (**Table 2**); (III) *Obstructive shock*. Large intracardiac mass lesions, most commonly metastases, may limit blood flow across the cardiac valves. This may lead to severe hypotension and, ultimately, obstructive shock. Of the available MCS devices, VA-ECMO is the only option to support hemodynamics in this setting.

# COMPLICATIONS OF VA-ECMO SUPPORT

Although peripheral VA-ECMO is a promising strategy that provides life support to patients with refractory CS, its use may be associated with potentially devastating complications. Some of these are preventable. Here, we review some of the common complications encountered while initiating or managing patients on VA-ECMO.

## Hemocompatibility-Associated Complications: Bleeding and Thrombosis

Bleeding is the most common complication reported in patients supported with VA-ECMO. In addition to access site bleeding, the risk of systemic hemorrhage is inherently increased in this population. Upper and lower gastrointestinal bleeding, hemopericardium, hemothorax, intra- and retroperitoneal hemorrhage and intracranial bleeding are the most frequent. It may be attributed to a combination of factors: (I) Acquired coagulopathy owing to blood exposure to artificial MCS surfaces, (II) Anticoagulation strategies used to reduce the risk of *ex vivo* thrombus formation, (III) Shear stress-associated platelet activation, (IV) Consumptive coagulopathy, (V) Constant activation of the fibrinolytic system, (VI) Systemic inflammatory response in the setting of CS and cardiac arrest, (VII) Infections and sepsis especially in the setting of prolonged support, and (VIII) Trauma associated with CPR and invasive procedures.

There is no clear consensus on anticoagulation strategy with VA-ECMO use and practice differs significantly between centers and individual patients. The risk of thrombosis and hemorrhagic complications must be balanced in the clinical context. Similar to our center, the most commonly reported strategy is the use of intravenous heparin for the duration of VA-ECMO support. However, the use of bivalirudin and novel anticoagulants have also been described (159). Adding to the controversy, optimal anticoagulant dosing remains unclear and needs to be individualized [prophylactic vs. therapeutic level; (159, 160)]. There is also emerging evidence that holding anticoagulation while on VA-ECMO may be safe in select patients and may decrease hemorrhagic complications and the requirement for blood transfusions without increasing mortality (161, 162). Regardless of the strategy and dosing selected, coagulation status must be monitored meticulously during VA-ECMO support. Various laboratory tests can be used depending on institutional protocols and the anticoagulant selected, such as activated clotting time (ACT), heparin anti-Xa level, activated partial thromboplastin time (aPTT), global thromboelastography (TEG), and prothrombin time (PT). Maintaining the platelet count above 50,000/mm$^3$ and replacing coagulation factors as needed also reduces bleeding risk significantly.

Although thromboembolic complications have decreased in recent years with the introduction of biocompatible materials, they are still common and may have devastating clinical consequences, such as stroke (163, 164). In fact, embolic brain infarction has a reported prevalence of 1.7–15% with significant associated morbidity and mortality (165–168). Therefore, regular inspection of the circuit, including all connectors, is of critical importance. It is mandatory to continually monitor the pressure gradient across the oxygenator, the most common site for thrombus formation (169). Thrombosis at the pump head is rare but may lead to significant hemolysis and ultimately pump failure. Any thrombus beyond the oxygenator can cause systemic embolization as the blood is returned directly into the arterial circulation. Therefore, discovering a clot may necessitate the immediate replacement of the affected components. The most common etiology for thrombus development is blood-non-endothelialized extracorporeal circuit interactions that not only activates the coagulation pathway but also initiates a complement-mediated inflammatory response (170). Therefore, all patients are carefully anticoagulated using heparin or, less frequently, bivalirudin balancing the risk of bleeding and clotting. Heparin induced thrombocytopenia (HIT) is a relatively rare but highly prothrombotic condition. Monitoring platelet count on a regular basis is essential and further laboratory testing should be performed if any suspicion for HIT.

## Vascular Complications

The rate of access site complications is reported at around 20% and are mostly related to the urgent need to establish

large-bore peripheral vascular accesses (5, 171). The spectrum of complications includes posterior vascular wall perforation, vessel dissection, pseudoaneurysm development, and thrombosis/embolic events. Patients are prone to large hematoma formation (intramuscular, retroperitoneal) even in the setting of minor vascular injury owing to the systemic anticoagulation employed for the VA-ECMO circuit. Most of these complications may be managed conservatively, while others warrant urgent endovascular or open surgical repair. The presence of peripheral artery disease poses an increased risk. The routine use of ultrasound and/or fluoroscopic x-ray guidance is recommended while obtaining vascular access as it allows precise target vessel visualization reducing the risk of injury (56).

Another serious vascular complication associated with peripheral VA-ECMO use is ipsilateral lower extremity ischemia. The clinical presentation often includes pallor, cool extremity, and gangrene development. Pain and neurological deficits may be difficult to assess owing to the sedation while patient is on VA-ECMO. A pooled analysis of 20 studies including 1,866 patients supported with VA-ECMO for CS or cardiac arrest reported a 16.9% (12.5–22.6%) incidence of lower limb ischemia; the risk of compartment syndrome or need for fasciotomy was 10.3% (7.3–14.5%). Lower extremity amputation was necessary in 4.7% (2.3–9.3%) of patients (172). Several risk factors have been identified to increase the risk of limb ischemia. These include younger age owing to the smaller femoral vessel size, female gender, the presence of peripheral arterial disease, difficult vascular access, and the use of larger bore cannulas (173–175). The routine use of a small anterograde reperfusion catheter has been shown to further reduce the risk of limb ischemia (174, 176). Ideally, it should be placed at the time of VA-ECMO initiation (174). At our center, heparin is often infused into the catheter according to the low intensity protocol to prevent thrombus formation and distal embolization. In addition, routine monitoring using near-infrared spectroscopy (NIRS) and doppler ultrasound is recommended in the clinical practice (177).

Access site infections may occur in 7–20% of patients with femoral VA-ECMO support (5, 174). Meticulous attention should be given to aseptic technique at the time of cannulation but this may be challenging at times given the emergency nature of the procedure that is often performed while CPR is in progress. Infections may range from local cellulitis to systemic bacteremia and sepsis and require appropriate antibiotic management.

## North-South (Harlequin) Syndrome

North-South Syndrome is a complication unique to peripheral VA-ECMO (178). It may develop under circumstances when native cardiac function recovers pulsatility, yet pulmonary function remains inadequate. Unless the lungs are able to perform appropriate gas exchange, deoxygenated blood travels through the pulmonary circulation and into the LV. Given the native LV contractility, the deoxygenated blood is then ejected into the ascending aorta. As a result, a mixing cloud forms between the anterograde flowing deoxygenated blood and the fully oxygenated retrograde flow provided by the circuit (179) (**Figure 1**). The location of the mixing cloud depends on the native cardiac function and the level of competing ECMO flow.

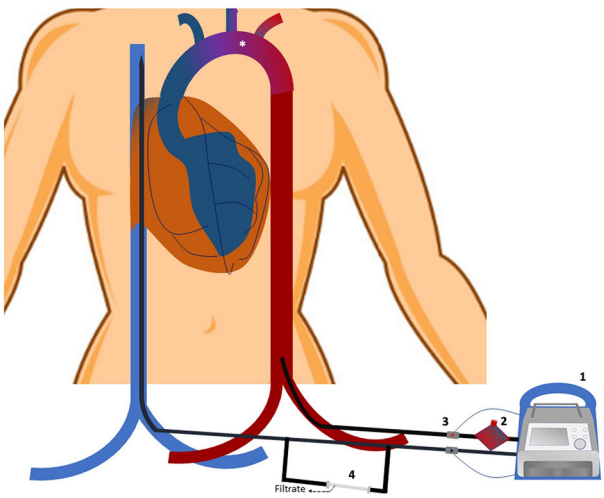


**FIGURE 1 |** Veno-arterial extracorporeal cardio-membrane oxygenation (VA-ECMO) circuit and North South syndrome. A venous cannula is inserted into the superior vena cava/right atrium to drain deoxygenated blood by the extracorporeal pump (1). After passing through the "membrane lung (2)," oxygenated blood is returned into the iliac artery through the arterial cannula. Proximal (venous) and distal (arterial) sensors monitor circuit flow (3). A continuous hemodialysis machine may be spliced into the venous limb of the circuit if needed to provide renal replacement therapy (4). In situations when the left ventricle recovers pulsatility yet the pulmonary gas exchange remains inadequate, deoxygenated blood may be ejected into the ascending aorta. As the fully oxygenated retrograde flow provided by the ECMO circuit collides with the deoxygenated blood in the aorta, a mixing cloud forms (*). Its location is determined by the native cardiac function and the level of competing ECMO support. If undetected, ischemia of the organs perfused by the anterograde flow may develop.

All organs perfused by the anterograde flow are at risk for ischemia, including the myocardium and the brain. Therefore, arterial oxygen saturation and blood gases should always be monitored using samples obtained from the right radial artery as the innominate artery is the first branch to receive deoxygenated blood from the proximal aortic arch. Further, near-infrared spectroscopy is a non-invasive tool developed recently to detect changes in regional tissue oxygenation and perfusion. Its routine use in patients supported with VA-ECMO may reduce the risk of hypoxic brain injury. If the differential cyanosis cannot be resolved by increasing the circuit flow, an additional cannula may be placed into the right internal jugular vein to achieve a hybrid configuration [veno-arterial-venous ECMO (VAV-ECMO)]. In this case oxygenated blood will be directed toward the right atrium by incorporating a "Y" connector into the arterial limb of the ECMO circuit. The oxygen rich blood will cross the pulmonary circulation thereby improving saturation in the proximal branches of the aorta (180).

## Acute Renal Failure

Acute renal failure is frequent in patients supported with VA-ECMO (55.6%) and is associated with increased mortality (181). Several factors may contribute to the renal injury including systemic hypoperfusion and hypotension prior to cannulation,

systemic inflammatory response, hemoglobinuria in the setting of hemolysis, microemboli of the renal vasculature and kidney hypoperfusion due to dysregulation of the renin angiotensin aldosterone system (169, 181–184). Renal replacement therapy is required in 46.0% of VA-ECMO supported patients and can be initiated by splicing a CVVH machine into the circuit (172).

### Infections

Infections are one of the most common complications in patients supported with VA-ECMO with a reported prevalence between 9 and 65% (185–188). Access site infections are common and might be related, at least in part, to the challenges maintaining a sterile field during emergency cannulation while patient is critically ill, and possibly, receiving cardiopulmonary resuscitation. Other common infectious sources include the urinary tract in the setting of prolonged indwelling catheter use, the respiratory system and surgical wounds. Several investigators described a strong correlation between the duration of VA-ECMO support and the development of infections (188–190). In addition, recent evidence suggests that VA-ECMO use is associated with alterations in the innate and adaptive immune systems, further increasing the risk (191). Common pathogens include Staphylococcus Aureus (often methicillin resistant), non-lactose fermenting gram-negative bacilli and Candida (187, 189). Infections, especially when severe, are associated with a significantly increased mortality, morbidity, delay in weaning and circuit failure (187, 189, 192, 193). In addition to prevention, close monitoring for signs of infection is critical in all patients, as these may be subtle or masked by the effects of the ECMO circuit, hematologic, or metabolic changes.

### Patient Immobility and Alternative Cannulation Configuration

One disadvantage of prolonged hemodynamic support via the femoral approach is the need for patient immobility to reduce the risk of cannula kinking and dislodgement. In an alternative VA-ECMO configuration, the venous drainage cannula is inserted through the right internal jugular vein and oxygenated blood is returned into the subclavian or axillary artery using an end-to-side vascular graft. While this strategy allows for extended support while ensuring appropriate cerebral perfusion and, potentially, patient ambulation, ipsilateral arm hypoperfusion is reported in 20% of patients. While early detection of arm hypoperfusion and compartment syndrome may prove challenging in the setting of continuous blood flow and vasoactive medication use, it is essential to avoid limb ischemia.

### Other Complications

Another complications that is not necessarily related to VA-ECMO include hyperbilirubinemia (12.2%) (194). Monitoring for this and management according to standard ICU cares is critical.

## WEANING FROM VA-ECMO SUPPORT

Following a few days of full cardiorespiratory support, decannulation may be considered once the initial condition necessitating VA-ECMO improved or resolved and vasoactive medications are reduced to a minimum or off. Regular weaning trials are performed to assess the patient's hemodynamic response to incremental decrease in support. However, to date, the literature on VA-ECMO weaning strategies and timing is limited and is often driven by institutional experience (195–197). In addition, the reported definition of successful weaning varies broadly (195, 198–200). These factors, in addition to the differences in CS etiology, lead to reported weaning rates of 31–76% (201). Further studies are needed to identify the most successful VA-ECMO weaning strategies, stratified based on the etiology of the CS.

## CONTRAINDICATIONS TO VA-ECMO USE

While VA-ECMO represents a potentially lifesaving intervention for acutely unstable patients, absolute and relative contraindications should be considered. Absolute contraindications are few and, in general, include life expectancy <1-year, acute or preexisting conditions that are incompatible with recovery and VA-ECMO weaning (neurological injury, disseminated malignancy) or if individual patient goals-of-care are not compatible with such level of cardiorespiratory support. Relative contraindications include advanced age (>75 years), unrepaired aortic dissection as the retrograde high velocity flow may further propagate the dissection flap, severe aortic regurgitation as this may lead to progressive left ventricular distension, advanced peripheral vascular disease when peripheral cannulation is considered, and contraindications to systemic anticoagulation (2). Caution should be exercised in patients with prior mitral valve replacement as VA-ECMO can dramatically decrease trans-mitral flow thereby increasing the risk of thrombus formation.

Having an exit strategy from VA-ECMO support is critically important and should always be considered before cannulation. Lack of such strategy may be considered a contraindication for cannulation. Broadly, the goals of VA-ECMO may be divided into bridge to recovery or bridge to advanced heart failure therapies (such as LVAD placement or heart transplantation). Defining the goals is complex with a multitude of factors contributing, such as clinical reason for hemodynamic collapse, end organ function, age, patient wishes and values. In addition, the chance of meaningful recovery may be unclear at the time of cannulation. When possible, discussion should be held with patient, family and multidisciplinary team using best clinical judgement to define the exit strategy as early as possible.

## DISCUSSION

The stagnant in-hospital mortality rates for CS over the past several decades has highlighted the need to develop increasingly granular risk stratification models and to introduce novel MCS strategies to improve outcomes for these patients.

In response to these critical needs, multiple steps have been taken. SCAI has published a novel classification schema for CS (Stage A-E) in 2019 (35). It was proved to be reproducible and to predict in-hospital mortality as well as 30-days patient survival with medical therapy alone and with a variety of MCS interventions (31, 202–205). Additionally, VA-ECMO has evolved to the point where it can be initiated within minutes by experienced clinicians and provides full cardiorespiratory support for several days. Therefore, this strategy enables the transfer of the sickest patients to experienced centers where additional diagnostic/therapeutic procedures may be performed while stable cardiorespiratory status is maintained by the VA-ECMO device. However, in times of global health crisis, such as during the COVID-19 pandemic, rationing the use of highly resource intensive therapies, like VA-ECMO, has to be considered. Complex clinical and ethical decisions must be made following the recommendation of multi-disciplinary triage committees that work alongside clinicians to facilitate effective and equitable allocation of scarce resources (206).

Ultimately, the combination of better risk stratification of CS and the emergence of novel MCS strategies may improve outcomes and survival in the most severe cases of CS (SCAI Stages C-E). Accordingly, European and US guidelines on the use of VA-ECMO in patients with CS are evolving and we anticipate updates in the near future as more data becomes available (2, 207–209). In the meantime, further prospective, randomized clinical trials are needed to expand the results of the ARREST trial and to evaluate the effects of VA-ECMO support on the survival of patients with CS of various etiologies.

## AUTHOR'S NOTE

Cardiogenic shock leads to ∼100,000 hospitalizations each year in the United States alone with a significant proportion of these patients dying during the index admission. While acute coronary syndrome remains the most common underlying cause, the incidence of cardiogenic shock due to other etiologies has been increasing in recent years. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is the most advanced temporary life support system that can uniquely provide full hemodynamic as well as respiratory support. Our paper provides a comprehensive review on the epidemiology and evolving definition of cardiogenic shock, including the most recent classification system introduced by the Society for Cardiac Angiography and Intervention (SCAI). We discuss the system components, cannulation strategies and hemodynamic aspects of VA-ECMO support in the context of contemporary observational and randomized data. Subsequently, we summarize the most common indications, contraindications and complications related to VA-ECMO usage.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## REFERENCES


1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of. *Eur Hear J.* (2016) 37:2129–200. doi: 10.1093/eurheartj/ehw128
2. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, et al. Contemporary management of cardiogenic shock: a scientific statement from the american heart association. *Circulation.* (2017) 136:e232–68. doi: 10.1161/cir.0000000000000525
3. Aissaoui N, Puymirat E, Tabone X, Charbonnier B, Schiele F, Lefèvre T, et al. Improved outcome of cardiogenic shock at the acute stage of myocardial infarction: a report from the USIK 1995, USIC 2000, and FAST-MI French nationwide registries. *Eur Heart J.* (2012) 33:2535–43. doi: 10.1093/eurheartj/ehs264
4. Basir MB, Schreiber T, Dixon S, Alaswad K, Patel K, Almany S, et al. Feasibility of early mechanical circulatory support in acute myocardial infarction complicated by cardiogenic shock: the detroit cardiogenic shock initiative. *Catheter Cardiovasc Interv.* (2018) 91:454–61. doi: 10.1002/ccd.27427
5. Bisdas T, Beutel G, Warnecke G, Hoeper MM, Kuehn C, Haverich A, et al. Vascular complications in patients undergoing femoral cannulation for extracorporeal membrane oxygenation support. *Ann Thorac Surg.* (2011) 92:626–31. doi: 10.1016/j.athoracsur.2011.02.018
6. Bréchot N, Luyt C-E, Schmidt M, Leprince P, Trouillet J-L, Léger P, et al. Venoarterial extracorporeal membrane oxygenation support for refractory cardiovascular dysfunction during severe bacterial septic shock. *Crit Care Med.* (2013) 41:1616–26. doi: 10.1097/CCM.0b013e31828a2370
7. Bréchot N, Hajage D, Kimmoun A, Demiselle J, Agerstrand C, Montero S, et al. Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study. *Lancet.* (2020) 396:545–52. doi: 10.1016/s0140-6736(20)30733-9
8. Califf RM, Bengtson JR. Cardiogenic shock. *N Engl J Med.* (1994) 330:1724–30. doi: 10.1056/NEJM199406163302406
9. Chioncel O, Mebazaa A, Harjola V-P, Coats AJ, Piepoli MF, Crespo-Leiro MG, et al. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the eSC heart failure long-Term registry. *Eur J Heart Fail.* (2017) 19:1242–54. doi: 10.1002/ejhf.890
10. Chung SY, Tong MS, Sheu JJ, Lee FY, Sung PH, Chen CJ, et al. Short-term and long-term prognostic outcomes of patients with sT-segment elevation myocardial infarction complicated by profound cardiogenic shock undergoing early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention. *Int J Cardiol.* (2016) 223:412–7. doi: 10.1016/j.ijcard.2016.08.068
11. DeRoo SC, Takayama H, Nemeth S, Garan AR, Kurlansky P, Restaino S, et al. Extracorporeal membrane oxygenation for primary graft dysfunction after heart transplant. *J Thorac Cardiovasc Surg.* (2019) 158:1576–84.e3. doi: 10.1016/j.jtcvs.2019.02.065
12. Goldberg RJ, Samad NA, Yarzebski J, Gurwitz J, Bigelow C, Gore JM. Temporal trends in cardiogenic shock complicating acute myocardial infarction. *N Engl J Med.* (1999) 340:1162–8. doi: 10.1056/nejm199904153401504
13. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. *Circulation.* (2009) 119:1211–9. doi: 10.1161/CIRCULATIONAHA.108.814947

14. Harjola VP, Lassus J, Sionis A, Køber L, Tarvasmäki T, Spinar J, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Hear Fail.* (2015) 17:501–9. doi: 10.1002/ejhf.260
15. Helgestad OKL, Josiassen J, Hassager C, Jensen LO, Holmvang L, Sørensen A, et al. Temporal trends in incidence and patient characteristics in cardiogenic shock following acute myocardial infarction from 2010 to 2017: a danish cohort study. *Eur J Heart Fail.* (2019) 21:1370–1378. doi: 10.1002/ejhf.1566
16. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK investigators. should we emergently revascularize occluded coronaries for cardiogenic shock. *N Engl J Med.* (1999) 341:625–34. doi: 10.1056/nejm199908263410901
17. Hochman JS, Sleeper LA, Webb JG, Dzavik V, Buller CE, Aylward P, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *Jama.* (2006) 295:2511–5. doi: 10.1001/jama.295.21.25111
18. Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic shock. *Ann Intern Med.* (1999) 131:47–59. doi: 10.7326/0003-4819-131-1-199907060-00010
19. Holmes DRJ, Bates ER, Kleiman NS, Sadowski Z, Horgan JH, Morris DC, et al. Contemporary reperfusion therapy for cardiogenic shock: the gUSTO-I trial experience. The GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *J Am Coll Cardiol.* (1995) 26:668–74. doi: 10.1016/0735-1097(95)00215-p
20. Hulman M, Artemiou P, Ondrusek M, Hudec V, Gasparovic I, Bena M, et al. Short-term mechanical circulatory support for severe primary graft dysfunction following orthotopic heart transplant. *Interact Cardiovasc Thorac Surg.* (2018) 27:229–33. doi: 10.1093/icvts/ivy050
21. Killip T 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol.* (1967) 20:457–64. doi: 10.1016/0002-9149(67)90023-9
22. Kohsaka S, Menon V, Lowe AM, Lange M, Dzavik V, Sleeper LA, et al. Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock. *Arch Intern Med.* (2005) 165:1643–50. doi: 10.1001/archinte.165.14.1643
23. Lee WC, Fang CY, Chen HC, Chen CJ, Yang CH, Hang CL, et al. Associations with 30-day survival following extracorporeal membrane oxygenation in patients with acute sT segment elevation myocardial infarction and profound cardiogenic shock. *Hear Lung.* (2016) 45:532–7. doi: 10.1016/j.hrtlng.2016.08.006
24. Muller G, Flecher E, Lebreton G, Luyt CE, Trouillet JL, Bréchot N, et al. The ENCOURAGE mortality risk score and analysis of long-term outcomes after VA-ECMO for acute myocardial infarction with cardiogenic shock. *Intensive Care Med.* (2016) 42:370–8. doi: 10.1007/s00134-016-4223-9
25. Ostadal P, Rokyta R, Kruger A, Vondrakova D, Janotka M, Smíd O, et al. Extra corporeal membrane oxygenation in the therapy of cardiogenic shock (ECMO-CS): rationale and design of the multicenter randomized trial. *Eur J Heart Fail.* (2017) 19 (Suppl. 2):124–7. doi: 10.1002/ejhf.857
26. Ouweneel DM, Eriksen E, Sjauw KD, van Dongen IM, Hirsch A, Packer EJ, et al. Percutaneous mechanical circulatory support vs. intra-Aortic balloon pump in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol.* (2017) 69:278–87. doi: 10.1016/j.jacc.2016.10.022
27. Pozzi M, Flagiello M, Armoiry X, Generali T, Adamou Nouhou K, Koffel C, et al. Extracorporeal life support in the multidisciplinary management of cardiogenic shock complicating acute myocardial infarction. *Catheter Cardiovasc Interv.* (2020) 95:E71–e7. doi: 10.1002/ccd.28316
28. Rihal CS, Naidu SS, Givertz MM, Szeto WY, Burke JA, Kapur NK, et al. 2015 SCAI/ACC/HFSA/STS Clinical Expert Consensus Statement on the Use of Percutaneous Mechanical Circulatory Support Devices in Cardiovascular Care: Endorsed by the American Heart Assocation, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; Affirmation of Value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie d'intervention. *J Am Coll Cardiol.* (2015) 65:e7–e26. doi: 10.1016/j.jacc.2015.03.036
29. Seyfarth M, Sibbing D, Bauer I, Fröhlich G, Bott-Flügel L, Byrne R, et al. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device vs. intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol.* (2008) 52:1584–8. doi: 10.1016/j.jacc.2008.05.065
30. Sheu JJ, Tsai TH, Lee FY, Fang HY, Sun CK, Leu S, et al. Early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with sT-segment elevation myocardial infarction complicated with profound cardiogenic shock. *Crit Care Med.* (2010) 38:1810–7. doi: 10.1097/CCM.0b013e3181e8acf7
31. Thayer KL, Zweck E, Ayouty M, Garan AR, Hernandez-Montfort J, Mahr C, et al. Invasive hemodynamic assessment and classification of in-Hospital mortality risk among patients with cardiogenic shock. *Circ Heart Fail.* (2020) 13:e007099. doi: 10.1161/CIRCHEARTFAILURE.120.007099
32. Thiele H, Allam B, Chatellier G, Schuler G, Lafont A. Shock in acute myocardial infarction: the cape horn for trials? *Eur Heart J.* (2010) 31:1828–35. doi: 10.1093/eurheartj/ehq220
33. Tsao NW, Shih CM, Yeh JS, Kao YT, Hsieh MH, Ou KL, et al. Extracorporeal membrane oxygenation-assisted primary percutaneous coronary intervention may improve survival of patients with acute myocardial infarction complicated by profound cardiogenic shock. *J Crit Care.* (2012) 27:530.e1–11. doi: 10.1016/j.jcrc.2012.02.012
34. Wu MY, Tseng YH, Chang YS, Tsai FC, Lin PJ. Using extracorporeal membrane oxygenation to rescue acute myocardial infarction with cardiopulmonary collapse: the impact of early coronary revascularization. *Resuscitation.* (2013) 84:940–5. doi: 10.1016/j.resuscitation.2012.12.019
35. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: this document was endorsed by the american college of cardiology (ACC), the american heart association (AHA), the society of critical care medicine (SCCM), and the society of thoracic surgeons (STS) in april 2019. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv.* (2019) 94:29–37. doi: 10.1002/ccd.28329
36. Baran DA, Long A, Jentzer JC. The stages of CS: clinical and translational update. *Curr Heart Fail Rep.* (2020) 17:333–40. doi: 10.1007/s11897-020-00496-6
37. GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med.* (1993) 329:673–82. doi: 10.1056/NEJM199309023291001
38. The International Study Group. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. *Lancet (London, England).* (1990) 336:71–5.
39. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet (London, England).* (1986) 1:397–402.
40. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. *Lancet.* (1992) 339:753–70.
41. Kolte D, Khera S, Dabhadkar KC, Agarwal S, Aronow WS, Timmermans R, et al. Trends in coronary angiography, revascularization, and outcomes of cardiogenic shock complicating non-ST-Elevation myocardial infarction. *Am J Cardiol.* (2016) 117:1–9. doi: 10.1016/j.amjcard.2015.10.006
42. Chioncel O, Parissis J, Mebazaa A, Thiele H, Desch S, Bauersachs J, et al. Epidemiology, pathophysiology and contemporary management of cardiogenic shock - a position statement from the heart failure association of the european society of cardiology. *Eur J Heart Fail.* (2020) 22:1315–41. doi: 10.1002/ejhf.1922
43. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. *Circulation.* (2008) 117:686–97. doi: 10.1161/CIRCULATIONAHA.106.613596
44. Abbott JD, Ahmed HN, Vlachos HA, Selzer F, Williams DO. Comparison of outcome in patients with sT-elevation vs. non-ST-elevation acute myocardial infarction treated with percutaneous coronary intervention (from the national heart, lung, and blood institute dynamic registry). *Am J Cardiol.* (2007) 100:190–5. doi: 10.1016/j.amjcard.2007.02.083
45. Hernandez GA, Lemor A, Blumer V, Rueda CA, Zalawadiya S, Stevenson LW, et al. Trends in utilization and outcomes of pulmonary artery

catheterization in heart failure with and without cardiogenic shock. *J Card Fail.* (2019) 25:364–71. doi: 10.1016/j.cardfail.2019.03.004
46. Berg DD, Bohula EA, van Diepen S, Katz JN, Alviar CL, Baird-Zars VM, et al. Epidemiology of shock in contemporary cardiac intensive care units. *Circ Cardiovasc Qual Outcomes.* (2019) 12:e005618. doi: 10.1161/CIRCOUTCOMES.119.005618
47. Fang J, Mensah GA, Alderman MH, Croft JB. Trends in acute myocardial infarction complicated by cardiogenic shock, 1979-2003, united states. *Am Heart J.* (2006) 152:1035–41. doi: 10.1016/j.ahj.2006.07.013
48. Yandrapalli S, Sanaani A, Harikrishnan P, Aronow WS, Frishman WH, Lanier GM, et al. Cardiogenic shock during heart failure hospitalizations: age-, sex-, and race-stratified trends in incidence and outcomes. *Am Heart J.* (2019) 213:18–29. doi: 10.1016/j.ahj.2019.03.015
49. Shah M, Patnaik S, Patel B, Ram P, Garg L, Agarwal M, et al. Trends in mechanical circulatory support use and hospital mortality among patients with acute myocardial infarction and non-infarction related cardiogenic shock in the united states. *Clin Res Cardiol.* (2018) 107:287–303. doi: 10.1007/s00392-017-1182-2
50. Kapur NK, Esposito M. Hemodynamic support with percutaneous devices in patients with heart failure. *Heart Fail Clin.* (2015) 11:215–30. doi: 10.1016/j.hfc.2014.12.012
51. Thiele H, Jobs A, Ouweneel DM, Henriques JPS, Seyfarth M, Desch S, et al. Percutaneous short-term active mechanical support devices in cardiogenic shock: a systematic review and collaborative meta-analysis of randomized trials. *Eur Hear J.* (2017) 38:3523–31. doi: 10.1093/eurheartj/ehx363
52. Garan AR, Takeda K, Salna M, Vandenberge J, Doshi D, Karmpaliotis D, et al. Prospective comparison of a percutaneous ventricular assist device and venoarterial extracorporeal membrane oxygenation for patients with cardiogenic shock following acute myocardial infarction. *J Am Heart Assoc.* (2019) 8:e012171. doi: 10.1161/JAHA.119.012171
53. Telukuntla KS, Estep JD. Acute mechanical circulatory support for cardiogenic shock. *Methodist Debakey Cardiovasc J.* (2020) 16:27–35. doi: 10.14797/mdcj-16-1-27
54. Thiele H, Ohman EM, de Waha-Thiele S, Zeymer U, Desch S. Management of cardiogenic shock complicating myocardial infarction: an update 2019. *Eur Hear J.* (2019) 40:2671–83. doi: 10.1093/eurheartj/ehz363
55. Yannopoulos D, Bartos J, Raveendran G, Walser E, Connett J, Murray TA, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. *Lancet.* (2020) 396:1807–16. doi: 10.1016/s0140-6736(20)32338-2
56. Yannopoulos D, Bartos JA, Martin C, Raveendran G, Missov E, Conterato M, et al. Minnesota resuscitation consortium's advanced perfusion and reperfusion cardiac life support strategy for out-of-Hospital refractory ventricular fibrillation. *J Am Heart Assoc.* (2016) 5:3732. doi: 10.1161/JAHA.116.003732
57. Bartos JA, Frascone RJ, Conterato M, Wesley K, Lick C, Sipprell K, et al. The minnesota mobile extracorporeal cardiopulmonary resuscitation consortium for treatment of out-of-hospital refractory ventricular fibrillation: program description, performance, and outcomes. *EClinicalMedicine.* (2020) 29–30:100632. doi: 10.1016/j.eclinm.2020.100632
58. Jain P, Shehab S, Muthiah K, Robson D, Granegger M, Drakos SG, et al. Insights into myocardial oxygen consumption, energetics, and efficiency under left ventricular assist device support using noninvasive pressure-Volume loops. *Circ Heart Fail.* (2019) 12:e006191. doi: 10.1161/CIRCHEARTFAILURE.119.006191
59. Nozawa T, Cheng CP, Noda T, Little WC. Relation between left ventricular oxygen consumption and pressure-volume area in conscious dogs. *Circulation.* (1994) 89:810–7. doi: 10.1161/01.cir.89.2.810
60. Burkhoff D, Sayer G, Doshi D, Uriel N. Hemodynamics of mechanical circulatory support. *J Am Coll Cardiol.* (2015) 66:2663–74. doi: 10.1016/j.jacc.2015.10.017
61. Kalra R, Kosmopoulos M, Goslar T, Raveendran G, Bartos JA, Yannopoulos D. Extracorporeal cardiopulmonary resuscitation for cardiac arrest. *Curr Opin Crit Care.* (2020) 26:228–35. doi: 10.1097/mcc.0000000000000717
62. Kosmopoulos M, Kalra R, Bartos JA, Raveendran G, Yannopoulos D. Contemporary approaches to cardiopulmonary resuscitation: physiology-guided approaches. *J Emerg Crit Care Med.* (2019) 4:19. doi: 10.21037/jeccm.2019.10.04
63. Fuhrman BP, Hernan LJ, Rotta AT, Heard CM, Rosenkranz ER. Pathophysiology of cardiac extracorporeal membrane oxygenation. *Artif Organs.* (1999) 23:966–9. doi: 10.1046/j.1525-1594.1999.06484.x
64. Swain L, Reyelt L, Bhave S, Qiao X, Thomas CJ, Zweck E, et al. Transvalvular ventricular unloading before reperfusion in acute myocardial infarction. *J Am Coll Cardiol.* (2020) 76:684–99. doi: 10.1016/j.jacc.2020.06.031
65. Vasu MA, O'Keefe DD, Kapellakis GZ, Vezeridis MP, Jacobs ML, Daggett WM, et al. Myocardial oxygen consumption: effects of epinephrine, isoproterenol, dopamine, norepinephrine, and dobutamine. *Am J Physiol.* (1978) 235:H237–41. doi: 10.1152/ajpheart.1978.235.2.H237
66. Schiller P, Vikholm P, Hellgren L. Experimental venoarterial extracorporeal membrane oxygenation induces left ventricular dysfunction. *ASAIO J.* (2016) 62:518–24. doi: 10.1097/MAT.0000000000000392
67. Kawashima D, Gojo S, Nishimura T, Itoda Y, Kitahori K, Motomura N, et al. Left ventricular mechanical support with impella provides more ventricular unloading in heart failure than extracorporeal membrane oxygenation. *ASAIO J.* (2011) 57:169–76. doi: 10.1097/MAT.0b013e31820e121c
68. Uriel N, Sayer G, Annamalai S, Kapur NK, Burkhoff D. Mechanical unloading in heart failure. *J Am Coll Cardiol.* (2018) 72:569–80. doi: 10.1016/j.jacc.2018.05.038
69. Ostadal P, Mlcek M, Kruger A, Hala P, Lacko S, Mates M, et al. Increasing venoarterial extracorporeal membrane oxygenation flow negatively affects left ventricular performance in a porcine model of cardiogenic shock. *J Transl Med.* (2015) 13:266. doi: 10.1186/s12967-015-0634-6
70. Schrage B, Becher PM, Bernhardt A, Bezerra H, Blankenberg S, Brunner S, et al. Left ventricular unloading is associated with lower mortality in patients with cardiogenic shock treated with venoarterial extracorporeal membrane oxygenation: results from an international, multicenter cohort study. *Circulation.* (2020) 142:2095–106. doi: 10.1161/CIRCULATIONAHA.120.048792
71. Kolte D, Khera S, Aronow WS, Mujib M, Palaniswamy C, Sule S, et al. Trends in incidence, management, and outcomes of cardiogenic shock complicating sT-elevation myocardial infarction in the united states. *J Am Hear Assoc.* (2014) 3:e000590. doi: 10.1161/jaha.113.000590
72. Nix C, Ishikawa K, Meyns B, Yasuda S, Adriaenssens T, Barth S, et al. Comparison of hemodynamic support by impella vs. peripheral extra-corporeal membrane oxygenation: a porcine model of acute myocardial infarction. *Front Cardiovasc Med.* (2020) 7:99. doi: 10.3389/fcvm.2020.00099
73. Paden ML, Conrad SA, Rycus PT, Thiagarajan RR. Extracorporeal life support organization registry report 2012. *Asaio j.* (2013) 59:202–10. doi: 10.1097/MAT.0b013e3182904a52
74. Sakamoto S, Taniguchi N, Nakajima S, Takahashi A. Extracorporeal life support for cardiogenic shock or cardiac arrest due to acute coronary syndrome. *Ann Thorac Surg.* (2012) 94:1–7. doi: 10.1016/j.athoracsur.2012.01.032
75. Chung ES, Lim C, Lee HY, Choi JH, Lee JS, Park KH. Results of extracorporeal membrane oxygenation (ECMO) support before coronary reperfusion in cardiogenic shock with acute myocardial infarction. *Korean J Thorac Cardiovasc Surg.* (2011) 44:273–8. doi: 10.5090/kjtcs.2011.44.4.273
76. Demondion P, Fournel L, Golmard JL, Niculescu M, Pavie A, Leprince P. Predictors of 30-day mortality and outcome in cases of myocardial infarction with cardiogenic shock treated by extracorporeal life support. *Eur J Cardiothorac Surg.* (2014) 45:47–54. doi: 10.1093/ejcts/ezt207
77. Esper SA, Bermudez C, Dueweke EJ, Kormos R, Subramaniam K, Mulukutla S, et al. Extracorporeal membrane oxygenation support in acute coronary syndromes complicated by cardiogenic shock. *Catheter Cardiovasc Interv.* (2015) 86 (Suppl. 1):S45–50. doi: 10.1002/ccd.25871
78. Negi SI, Sokolovic M, Koifman E, Kiramijyan S, Torguson R, Lindsay J, et al. Contemporary use of veno-arterial extracorporeal membrane oxygenation for refractory cardiogenic shock in acute coronary syndrome. *J Invasive Cardiol.* (2016) 28:52–7.
79. Faber C, McCarthy PM, Smedira NG, Young JB, Starling RC, Hoercher KJ. Implantable left ventricular assist device for patients with postinfarction ventricular septal defect. *J Thorac Cardiovasc Surg.* (2002) 124:400–1. doi: 10.1067/mtc.2002.124243.024
80. Jeppsson A, Liden H, Johnsson P, Hartford M, Rådegran K. Surgical repair of post infarction ventricular septal defects: a national experience. *Eur J cardio-thoracic Surg Off J Eur Assoc Cardio-thoracic Surg.* (2005) 27:216–21. doi: 10.1016/j.ejcts.2004.10.03

81. Kwon J, Lee D. The effectiveness of extracorporeal membrane oxygenation in a patient with post myocardial infarct ventricular septal defect. *J Cardiothorac Surg.* (2016) 11:143. doi: 10.1186/s13019-016-0537-5
82. McLaughlin A, McGiffin D, Winearls J, Tesar P, Cole C, Vallely M, et al. Veno-Arterial eCMO in the setting of post-Infarct ventricular septal defect: a Bridge to surgical repair. *Heart Lung Circ.* (2016) 25:1063–6. doi: 10.1016/j.hlc.2016.02
83. Aoyama N, Imai H, Kurosawa T, Fukuda N, Moriguchi M, Nishinari M, et al. Therapeutic strategy using extracorporeal life support, including appropriate indication, management, limitation and timing of switch to ventricular assist device in patients with acute myocardial infarction. *J Artif Organs Off J Japanese Soc Artif Organs.* (2014) 17:33–41. doi: 10.1007/s10047-013-0735-z
84. Lorusso R, Centofanti P, Gelsomino S, Barili F, Di Mauro M, Orlando P, et al. Venoarterial extracorporeal membrane oxygenation for acute fulminant myocarditis in adult patients: a 5-Year multi-Institutional experience. *Ann Thorac Surg.* (2016) 101:919–26. doi: 10.1016/j.athoracsur.2015.08.014
85. Asaumi Y, Yasuda S, Morii I, Kakuchi H, Otsuka Y, Kawamura A, et al. Favourable clinical outcome in patients with cardiogenic shock due to fulminant myocarditis supported by percutaneous extracorporeal membrane oxygenation. *Eur Hear J.* (2005) 26:2185–92. doi: 10.1093/eurheartj/ehi411
86. Diddle JW, Almodovar MC, Rajagopal SK, Rycus PT, Thiagarajan RR. Extracorporeal membrane oxygenation for the support of adults with acute myocarditis. *Crit Care Med.* (2015) 43:1016–25. doi: 10.1097/CCM.0000000000000920
87. Mirabel M, Luyt C-E, Leprince P, Trouillet J-L, Léger P, Pavie A, et al. Outcomes, long-term quality of life, and psychologic assessment of fulminant myocarditis patients rescued by mechanical circulatory support. *Crit Care Med.* (2011) 39:1029–35. doi: 10.1097/CCM.0b013e31820ead45
88. Hsu K-H, Chi N-H, Yu H-Y, Wang C-H, Huang S-C, Wang S-S, et al. Extracorporeal membranous oxygenation support for acute fulminant myocarditis: analysis of a single center's experience. *Eur J Cardio-Thoracic Surg Off J Eur Assoc Cardio-Thoracic Surg.* (2011) 40:682–8. doi: 10.1016/j.ejcts.2010.12.050
89. Chen Y-S, Yu H-Y, Huang S-C, Chiu K-M, Lin T-Y, Lai L-P, et al. Experience and result of extracorporeal membrane oxygenation in treating fulminant myocarditis with shock: what mechanical support should be considered first? *J Hear lung Transplant Off Publ Int Soc Hear Transplant.* (2005) 24:81–7. doi: 10.1016/j.healun.2003.09.038
90. Cheng R, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, et al. Clinical outcomes in fulminant myocarditis requiring extracorporeal membrane oxygenation: a weighted meta-analysis of 170 patients. *J Card Fail.* (2014) 20:400–6. doi: 10.1016/j.cardfail.2014.03.005
91. Saito S, Toda K, Miyagawa S, Yoshikawa Y, Hata H, Yoshioka D, et al. Diagnosis, medical treatment, and stepwise mechanical circulatory support for fulminat myocarditis. *J Artif organs Off J Japanese Soc Artif Organs.* (2018) 21:172–9. doi: 10.1007/s10047-017-1011-4
92. Wu IH, Ko WJ, Chou NK, Chao A, Lin FY. Extracorporeal membrane oxygenation in treatment of cardiogenic shock caused by acute myocarditis. *J Formos Med Assoc.* (1998) 97:364–6.
93. Mody KP, Takayama H, Landes E, Yuzefpolskaya M, Colombo PC, Naka Y, et al. Acute mechanical circulatory support for fulminant myocarditis complicated by cardiogenic shock. *J Cardiovasc Transl Res.* (2014) 7:156–64. doi: 10.1007/s12265-013-9521-9
94. Hékimian G, Jovanovic T, Bréchot N, Lebreton G, Leprince P, Trouillet J-L, et al. When the heart gets the flu: fulminant influenza B myocarditis: a case-series report and review of the literature. *J Crit Care.* (2018) 47:61–4. doi: 10.1016/j.jcrc.2018.06.001
95. Nakajima S, Seguchi O, Fujita T, Hata H, Yamashita K, Sato T, et al. Successful treatment of near-fatal fulminant myocarditis using bi-ventricular assist device support. *J Artif Organs Off J Japanese Soc Artif Organs.* (2016) 19:293–6. doi: 10.1007/s10047-016-0899-4
96. Bohné M, Chung D-U, Tigges E, van der Schalk H, Waddell D, Schenker N, et al. Short-term use of "ECMELLA" in the context of fulminant eosinophilic myocarditis with cardiogenic shock. *BMC Cardiovasc Disord.* (2020) 20:519. doi: 10.1186/s12872-020-01808-3
97. Sawamura A, Okumura T, Hirakawa A, Ito M, Ozaki Y, Ohte N, et al. Early prediction model for successful bridge to recovery in patients with fulminant myocarditis supported with percutaneous venoarterial extracorporeal membrane oxygenation- insights from the CHANGE PUMP study. *Circ J.* (2018) 82:699–707. doi: 10.1253/circj.CJ-17-0549
98. Montero S, Aissaoui N, Tadié J-M, Bizouarn P, Scherrer V, Persichini R, et al. Fulminant giant-cell myocarditis on mechanical circulatory support: management and outcomes of a french multicentre cohort. *Int J Cardiol.* (2018) 253:105–12. doi: 10.1016/j.ijcard.2017.10.053
99. Ripoll JG, Ratzlaff RA, Menke DM, Olave MC, Maleszewski JJ, Díaz-Gómez JL. Hemodynamic transesophageal echocardiography-Guided venous-Arterial extracorporeal membrane oxygenation support in a case of giant cell myocarditis. *Case reports Crit Care.* (2016) 2016:5407597. doi: 10.1155/2016/5407597
100. Milas A, Shah A, Anand N, Saunders-Kurban M, Patel S. Respiratory syncytial virus associated myocarditis requiring venoarterial extracorporeal membrane oxygenation. *Case Rep Infect Dis.* (2017) 2017:7074508. doi: 10.1155/2017/7074508
101. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet (London, England).* (2012) 379:1835–46. doi: 10.1016/S0140-6736(11)61904-1
102. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2019 update: a report from the american heart association. *Circulation.* (2019) 139:e56–28. doi: 10.1161/CIR.0000000000000659
103. Janata K, Holzer M, Domanovits H, Müllner M, Bankier A, Kurtaran A, et al. Mortality of patients with pulmonary embolism. *Wien Klin Wochenschr.* (2002) 114:766–72.
104. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the american heart association. *Circulation.* (2011) 123:1788–830. doi: 10.1161/CIR.0b013e318214914f
105. Sekhri V, Mehta N, Rawat N, Lehrman SG, Aronow WS. Management of massive and nonmassive pulmonary embolism. *Arch Med Sci.* (2012) 8:957–69. doi: 10.5114/aoms.2012.32402
106. Smulders YM. Pathophysiology and treatment of haemodynamic instability in acute pulmonary embolism: the pivotal role of pulmonary vasoconstriction. *Cardiovasc Res.* (2000) 48:23–33. doi: 10.1016/s0008-6363(00)00168-1
107. McIntyre KM, Sasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. *Am J Cardiol.* (1971) 28:288–94. doi: 10.1016/0002-9149(71)90116-0
108. Matthews JC, McLaughlin V. Acute right ventricular failure in the setting of acute pulmonary embolism or chronic pulmonary hypertension: a detailed review of the pathophysiology, diagnosis, and management. *Curr Cardiol Rev.* (2008) 4:49–59. doi: 10.2174/157340308783565384
109. Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. *Chest.* (1995) 108:978–81. doi: 10.1378/chest.108.4.978
110. Suguta M, Hoshizaki H, Anno M, Naito S, Tada H, Nogami A, et al. Right ventricular infarction with cardiogenic shock treated with percutaneous cardiopulmonary support: a case report. *Jpn Circ J.* (1999) 63:813–5. doi: 10.1253/jcj.63.813
111. Scherer M, Sirat AS, Moritz A, Martens S. Extracorporeal membrane oxygenation as perioperative right ventricular support in patients with biventricular failure undergoing left ventricular assist device implantation. *Eur J Cardio-Thoracic Surg Off J Eur Assoc Cardio-Thoracic Surg.* (2011) 39:939–44; discussion 944. doi: 10.1016/j.ejcts.2010.09.044
112. Meneveau N, Guillon B, Planquette B, Piton G, Kimmoun A, Gaide-Chevronnay L, et al. Outcomes after extracorporeal membrane oxygenation for the treatment of high-risk pulmonary embolism: a multicentre series of 52 cases. *Eur Heart J.* (2018) 39:4196–204. doi: 10.1093/eurheartj/ehy464
113. George B, Parazino M, Omar HR, Davis G, Guglin M, Gurley J, et al. A retrospective comparison of survivors and non-survivors of massive pulmonary embolism receiving veno-arterial extracorporeal membrane oxygenation support. *Resuscitation.* (2018) 122:1–5. doi: 10.1016/j.resuscitation.2017.11.034

114. Yusuff HO, Zochios V, Vuylsteke A. Extracorporeal membrane oxygenation in acute massive pulmonary embolism: a systematic review. *Perfusion.* (2015) 30:611–6. doi: 10.1177/0267659115583377
115. Kmiec L, Philipp A, Floerchinger B, Lubnow M, Unterbuchner C, Creutzenberg M, et al. Extracorporeal membrane oxygenation for massive pulmonary embolism as bridge to therapy. *ASAIO J.* (2020) 66:146–52. doi: 10.1097/MAT.0000000000000953
116. Corsi F, Lebreton G, Bréchot N, Hekimian G, Nieszkowska A, Trouillet J-L, et al. Life-threatening massive pulmonary embolism rescued by venoarterial-extracorporeal membrane oxygenation. *Crit Care.* (2017) 21:76. doi: 10.1186/s13054-017-1655-8
117. Weinberg A, Tapson VF, Ramzy D. Massive pulmonary embolism: extracorporeal membrane oxygenation and surgical pulmonary embolectomy. *Semin Respir Crit Care Med.* (2017) 38:66–2. doi: 10.1055/s-0036-1597559
118. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Respir J.* (2019) 54:190160. doi: 10.1183/13993003.01647-2019
119. Hoffmann C, Wolf E. Older age groups and country-specific case fatality rates of COVID-19 in Europe, USA and Canada. *Infection.* (2021) 49:111–6. doi: 10.1007/s15010-020-01538-w
120. Grech V. Unknown unknowns - Covid-19 and potential global mortality. *Early Hum Dev.* (2020) 144:105026. doi: 10.1016/j.earlhumdev.2020.105026
121. Khan IH, Zahra SA, Zaim S, Harky A. At the heart of COVID-19. *J Card Surg.* (2020) 35:1287–294. doi: 10.1111/jocs.14596
122. Xiong T-Y, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. *Eur Heart J.* (2020) 41:1798–800. doi: 10.1093/eurheartj/ehaa231
123. Driggin E, Madhavan M V, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the cOVID-19 pandemic. *J Am Coll Cardiol.* (2020) 75:2352–71. doi: 10.1016/j.jacc.2020.03.031
124. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol.* (2020) 5:831–40. doi: 10.1001/jamacardio.2020.1286
125. Zeng J-H, Liu Y-X, Yuan J, Wang F-X, Wu W-B, Li J-X, et al. First case of cOVID-19 complicated with fulminant myocarditis: a case report and insights. *Infection.* (2020) 48:773–7. doi: 10.1007/s15010-020-01424-5
126. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. *Eur Heart J.* (2021) 42:206. doi: 10.1093/eurheartj/ehaa190
127. Valchanov K, Krishnan U, Hoole SP, Davies WR, Pettit S, Jones N, et al. COVID-19 patient with coronary thrombosis supported with ECMO and impella 5.0 ventricular assist device: a case report. *Eur Hear J Case Rep.* (2020) 4:1–6. doi: 10.1093/ehjcr/ytaa342
128. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-Infected pneumonia in Wuhan, China. *JAMA.* (2020) 323:1061–9. doi: 10.1001/jama.2020.1585
129. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with cOVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England).* (2020) 395:1054–62. doi: 10.1016/S0140-6736(20)30566-3
130. Bartlett RH, Ogino MT, Brodie D, McMullan DM, Lorusso R, MacLaren G, et al. Initial ELSO guidance document: ECMO for cOVID-19 patients with severe cardiopulmonary failure. *ASAIO J.* (2020) 66:472–74. doi: 10.1097/MAT.0000000000001173
131. Chow J, Alhussaini A, Calvillo-Argüelles O, Billia F, Luk A. Cardiovascular collapse in cOVID-19 infection: the role of venoarterial extracorporeal membrane oxygenation (VA-ECMO). *CJC Open.* (2020) 2:273–7. doi: 10.1016/j.cjco.2020.04.003
132. Loforte A, Di Mauro M, Pellegrini C, Monterosso C, Pelenghi S, Degani A, et al. Extracorporeal membrane oxygenation for COVID-19 respiratory distress syndrome: an italian society for cardiac surgery report. *ASAIO J.* (2021) 67:385–91. doi: 10.1097/MAT.0000000000001399
133. Li X, Guo Z, Li B, Zhang X, Tian R, Wu W, et al. Extracorporeal membrane oxygenation for coronavirus disease 2019 in Shanghai, China. *ASAIO J.* (2020) 66:475–81. doi: 10.1097/MAT.0000000000001172
134. Mustafa AK, Alexander PJ, Joshi DJ, Tabachnick DR, Cross CA, Pappas PS, et al. Extracorporeal membrane oxygenation for patients with COVID-19 in severe respiratory failure. *JAMA Surg.* (2020) 155:990–2. doi: 10.1001/jamasurg.2020.3950
135. Stub D, Bernard S, Pellegrino V, Smith K, Walker T, Sheldrake J, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). *Resuscitation.* (2015) 86:88–94. doi: 10.1016/j.resuscitation.2014.09.010
136. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. *Crit Care Med.* (2013) 41:1186–96. doi: 10.1097/CCM.0b013e31827ca4c8
137. Lamhaut L, Hutin A, Puymirat E, Jouan J, Raphalen J-H, Jouffroy R, et al. A pre-Hospital extracorporeal cardio pulmonary resuscitation (ECPR) strategy for treatment of refractory out hospital cardiac arrest: an observational study and propensity analysis. *Resuscitation.* (2017) 117:109–17. doi: 10.1016/j.resuscitation.2017.04.014
138. Schober A, Sterz F, Herkner H, Wallmueller C, Weiser C, Hubner P, et al. Emergency extracorporeal life support and ongoing resuscitation: a retrospective comparison for refractory out-of-hospital cardiac arrest. *Emerg Med J.* (2017) 34:277–81. doi: 10.1136/emermed-2015-205232
139. Fjølner J, Greisen J, Jørgensen MRS, Terkelsen CJ, Ilkjaer LB, Hansen TM, et al. Extracorporeal cardiopulmonary resuscitation after out-of-hospital cardiac arrest in a danish health region. *Acta Anaesthesiol Scand.* (2017) 61:176–85. doi: 10.1111/aas.12843
140. Lee JJ, Han SJ, Kim HS, Hong KS, Choi HH, Park KT, et al. Out-of-hospital cardiac arrest patients treated with cardiopulmonary resuscitation using extracorporeal membrane oxygenation: focus on survival rate and neurologic outcome. *Scand J Trauma Resusc Emerg Med.* (2016) 24:74. doi: 10.1186/s13049-016-0266-8
141. Pozzi M, Koffel C, Armoiry X, Pavlakovic I, Neidecker J, Prieur C, et al. Extracorporeal life support for refractory out-of-hospital cardiac arrest: should we still fight for? A single-centre, 5-year experience. *Int J Cardiol.* (2016) 204:70–6. doi: 10.1016/j.ijcard.2015.11.165
142. Haneya A, Philipp A, Diez C, Schopka S, Bein T, Zimmermann M, et al. A 5-year experience with cardiopulmonary resuscitation using extracorporeal life support in non-postcardiotomy patients with cardiac arrest. *Resuscitation.* (2012) 83:1331–7. doi: 10.1016/j.resuscitation.2012.07.009
143. Leick J, Liebetrau C, Szardien S, Fischer-Rasokat U, Willmer M, van Linden A, et al. Door-to-implantation time of extracorporeal life support systems predicts mortality in patients with out-of-hospital cardiac arrest. *Clin Res Cardiol.* (2013) 102:661–9. doi: 10.1007/s00392-013-0580-3
144. Kim SJ, Jung JS, Park JH, Park JS, Hong YS, Lee SW. An optimal transition time to extracorporeal cardiopulmonary resuscitation for predicting good neurological outcome in patients with out-of-hospital cardiac arrest: a propensity-matched study. *Crit Care.* (2014) 18:535. doi: 10.1186/s13054-014-0535-8
145. Sakamoto T, Morimura N, Nagao K, Asai Y, Yokota H, Nara S, et al. Extracorporeal cardiopulmonary resuscitation vs. conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: a prospective observational study. *Resuscitation.* (2014) 85:762–768. doi: 10.1016/j.resuscitation.2014.01.031
146. Wang C-H, Chou N-K, Becker LB, Lin J-W, Yu H-Y, Chi N-H, et al. Improved outcome of extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest–a comparison with that for extracorporeal rescue for in-hospital cardiac arrest. *Resuscitation.* (2014) 85:1219–24. doi: 10.1016/j.resuscitation.2014.06.022
147. Johnson NJ, Acker M, Hsu CH, Desai N, Vallabhajosyula P, Lazar S, et al. Extracorporeal life support as rescue strategy for out-of-hospital and emergency department cardiac arrest. *Resuscitation.* (2014) 85:1527–32. doi: 10.1016/j.resuscitation.2014.08.028
148. Kagawa E, Dote K, Kato M, Sasaki S, Nakano Y, Kajikawa M, et al. Should we emergently revascularize occluded coronaries for cardiac

arrest?: rapid-response extracorporeal membrane oxygenation and intra-arrest percutaneous coronary intervention. *Circulation.* (2012) 126:1605–13. doi: 10.1161/CIRCULATIONAHA.111.067538
149. Avalli L, Maggioni E, Formica F, Redaelli G, Migliari M, Scanziani M, et al. Favourable survival of in-hospital compared to out-of-hospital refractory cardiac arrest patients treated with extracorporeal membrane oxygenation: an italian tertiary care centre experience. *Resuscitation.* (2012) 83:579–83. doi: 10.1016/j.resuscitation.2011.10.013
150. Yannopoulos D, Bartos JA, Raveendran G, Conterato M, Frascone RJ, Trembley A, et al. Coronary artery disease in patients with out-of-Hospital refractory ventricular fibrillation cardiac arrest. *J Am Coll Cardiol.* (2017) 70:1109–17. doi: 10.1016/j.jacc.2017.06.059
151. Kudenchuk PJ, Brown SP, Daya M, Rea T, Nichol G, Morrison LJ, et al. Amiodarone, lidocaine, or placebo in out-of-Hospital cardiac arrest. *N Engl J Med.* (2016) 374:1711–22. doi: 10.1056/NEJMoa1514204
152. Kalra R, Bartos JA, Kosmopoulos M, Carlson C, John R, Shaffer A, et al. Echocardiographic evaluation of cardiac recovery after refractory out-of-hospital cardiac arrest. *Resuscitation.* (2020) 154:38–46. doi: 10.1016/j.resuscitation.2020.06.037
153. Schrage B, Burkhoff D, Rübsamen N, Becher PM, Schwarzl M, Bernhardt A, et al. Unloading of the left ventricle during venoarterial extracorporeal membrane oxygenation therapy in cardiogenic shock. *JACC Hear Fail.* (2018) 6:1035–43. doi: 10.1016/j.jchf.2018.09.009
154. Meani P, Gelsomino S, Natour E, Johnson DM, Rocca HB, Pappalardo F, et al. Modalities and effects of left ventricle unloading on extracorporeal life support: a review of the current literature. *Eur J Hear Fail.* (2017) 19 (Suppl. 2):84–91. doi: 10.1002/ejhf.850
155. Russo JJ, Aleksova N, Pitcher I, Couture E, Parlow S, Faraz M, et al. Left ventricular unloading during extracorporeal membrane oxygenation in patients with cardiogenic shock. *J Am Coll Cardiol.* (2019) 73:654–62. doi: 10.1016/j.jacc.2018.10.085
156. Vogel DJ, Murray J, Czapran AZ, Camporota L, Ioannou N, Meadows CIS, et al. Veno-arterio-venous ECMO for septic cardiomyopathy: a single-centre experience. *Perfusion.* (2018) 33:57–64. doi: 10.1177/0267659118766833
157. Mastroianni C, Nenna A, Lebreton G, D'Alessandro C, Greco SM, Lusini M, et al. Extracorporeal membrane oxygenation as treatment of graft failure after heart transplantation. *Ann Cardiothorac Surg.* (2019) 8:99–108. doi: 10.21037/acs.2018.12.08
158. Lehmann S, Uhlemann M, Etz CD, Garbade J, Schroeter T, Borger M, et al. Extracorporeal membrane oxygenation: experience in acute graft failure after heart transplantation. *Clin Transplant.* (2014) 28:789–96. doi: 10.1111/ctr.12380
159. Kaseer H, Soto-Arenall M, Sanghavi D, Moss J, Ratzlaff R, Pham S, et al. Heparin vs bivalirudin anticoagulation for extracorporeal membrane oxygenation. *J Card Surg.* (2020) 35:779–86. doi: 10.1111/jocs.14458
160. Raman J, Alimohamed M, Dobrilovic N, Lateef O, Aziz S. A comparison of low and standard anti-coagulation regimens in extracorporeal membrane oxygenation. *J Hear lung Transplant Off Publ Int Soc Hear Transplant.* (2019) 38:433–9. doi: 10.1016/j.healun.2019.01.1313
161. Chung YS, Cho DY, Sohn DS, Lee WS, Won H, Lee DH, et al. Is stopping heparin safe in patients on extracorporeal membrane oxygenation treatment? *ASAIO J.* (2017) 63:32–6. doi: 10.1097/MAT.0000000000000442
162. Wood KL, Ayers B, Gosev I, Kumar N, Melvin AL, Barrus B, et al. Venoarterial-Extracorporeal membrane oxygenation without routine systemic anticoagulation decreases adverse events. *Ann Thorac Surg.* (2020) 109:1458–66. doi: 10.1016/j.athoracsur.2019.08.040
163. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for aRDS in adults. *N Engl J Med.* (2011) 365:1905–14. doi: 10.1056/NEJMct1103720
164. Oliver WC. Anticoagulation and coagulation management for eCMO. *Semin Cardiothorac Vasc Anesth.* (2009) 13:154–75. doi: 10.1177/1089253209347384
165. Xie A, Lo P, Yan TD, Forrest P. Neurologic complications of extracorporeal membrane oxygenation: a Review. *J Cardiothorac Vasc Anesth.* (2017) 31:1836–46. doi: 10.1053/j.jvca.2017.03.001
166. Omar HR, Mirsaeidi M, Shumac J, Enten G, Mangar D, Camporesi EM. Incidence and predictors of ischemic cerebrovascular stroke among patients on extracorporeal membrane oxygenation support. *J Crit Care.* (2016) 32:48–51. doi: 10.1016/j.jcrc.2015.11.009
167. Lorusso R, Barili F, Mauro M Di, Gelsomino S, Parise O, Rycus PT, et al. In-Hospital neurologic complications in adult patients undergoing venoarterial extracorporeal membrane oxygenation: results from the extracorporeal life support organization registry. *Crit Care Med.* (2016) 44:e964–72. doi: 10.1097/CCM.0000000000001865
168. Iacobelli R, Fletcher-Sandersjöö A, Lindblad C, Keselman B, Thelin EP, Broman LM. Predictors of brain infarction in adult patients on extracorporeal membrane oxygenation: an observational cohort study. *Sci Rep.* (2021) 11:3809. doi: 10.1038/s41598-021-83157-5
169. Zanatta P, Forti A, Bosco E, Salvador L, Borsato M, Baldanzi F, et al. Microembolic signals and strategy to prevent gas embolism during extracorporeal membrane oxygenation. *J Cardiothorac Surg.* (2010) 5:5. doi: 10.1186/1749-8090-5-5
170. Murphy DA, Hockings LE, Andrews RK, Aubron C, Gardiner EE, Pellegrino VA, et al. Extracorporeal membrane oxygenation-hemostatic complications. *Transfus Med Rev.* (2015) 29:90–101. doi: 10.1016/j.tmrv.2014.12.001
171. Rupprecht L, Lunz D, Philipp A, Lubnow M, Schmid C. Pitfalls in percutaneous eCMO cannulation. *Hear Lung Vessel.* (2015) 7:320−6.
172. Cheng R, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. *Ann Thorac Surg.* (2014) 97:610–6. doi: 10.1016/j.athoracsur.2013.09.008
173. Foley PJ, Morris RJ, Woo EY, Acker MA, Wang GJ, Fairman RM, et al. Limb ischemia during femoral cannulation for cardiopulmonary support. *J Vasc Surg.* (2010) 52:850–3. doi: 10.1016/j.jvs.2010.05.012
174. Lamb KM, DiMuzio PJ, Johnson A, Batista P, Moudgill N, McCullough M, et al. Arterial protocol including prophylactic distal perfusion catheter decreases limb ischemia complications in patients undergoing extracorporeal membrane oxygenation. *J Vasc Surg.* (2017) 65:1074–9. doi: 10.1016/j.jvs.2016.10.059
175. Lamb KM, Hirose H, Cavarocchi NC. Preparation and technical considerations for percutaneous cannulation for veno-arterial extracorporeal membrane oxygenation. *J Card Surg.* (2013) 28:190–2. doi: 10.1111/jocs.12058
176. Tanaka D, Hirose H, Cavarocchi N, Entwistle JWC. The impact of vascular complications on survival of patients on venoarterial extracorporeal membrane oxygenation. *Ann Thorac Surg.* (2016) 101:1729–34. doi: 10.1016/j.athoracsur.2015.10.095
177. Patton-Rivera K, Beck J, Fung K, Chan C, Beck M, Takayama H, et al. Using near-infrared reflectance spectroscopy (NIRS) to assess distal-limb perfusion on venoarterial (V-A) extracorporeal membrane oxygenation (ECMO) patients with femoral cannulation. *Perfusion.* (2018) 33:618–23. doi: 10.1177/0267659118777670
178. Rao P, Khalpey Z, Smith R, Burkhoff D, Kociol RD. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest. *Circ Hear Fail.* (2018) 11:e004905. doi: 10.1161/circheartfailure.118.004905
179. Prisco AR, Aguado-Sierra J, Butakoff C, Vazquez M, Houzeaux G, Eguzkitza B, et al. Concomitant respiratory failure can impair myocardial oxygenation in patients with acute cardiogenic shock supported by vA-ECMO. *J Cardiovasc Transl Res.* (2021). doi: 10.1007/s12265-021-10110-2. [Epub ahead of print].
180. Abrams D, Combes A, Brodie D. Extracorporeal membrane oxygenation in cardiopulmonary disease in adults. *J Am Coll Cardiol.* (2014) 63:2769–78. doi: 10.1016/j.jacc.2014.03.046
181. Lee SW, Yu M-Y, Lee H, Ahn SY, Kim S, Chin HJ, et al. Risk factors for acute kidney injury and in-Hospital mortality in patients receiving extracorporeal membrane oxygenation. *PLoS ONE.* (2015) 10:e0140674. doi: 10.1371/journal.pone.0140674
182. Semmekrot BA, Pesman GJ, Span PN, Sweep CGJ, van Heijst AFJ, Monnens LAH, et al. Serial plasma concentrations of atrial natriuretic peptide, plasma renin activity, aldosterone, and antidiuretic hormone in neonates on extracorporeal membrane oxygenation. *ASAIO J.* (2002) 48:26–33. doi: 10.1097/00002480-200201000-00007
183. McILwain RB, Timpa JG, Kurundkar AR, Holt DW, Kelly DR, Hartman YE, et al. Plasma concentrations of inflammatory cytokines rise rapidly during ECMO-related sIRS due to the release of preformed stores in the intestine. *Lab Invest.* (2010) 90:128–39. doi: 10.1038/labinvest.2009.119

184. Williams DC, Turi JL, Hornik CP, Bonadonna DK, Williford WL, Walczak RJ, et al. Circuit oxygenator contributes to extracorporeal membrane oxygenation-induced hemolysis. *ASAIO J.* (2015) 61:190–5. doi: 10.1097/MAT.0000000000000173
185. Hsu M-S, Chiu K-M, Huang Y-T, Kao K-L, Chu S-H, Liao C-H. Risk factors for nosocomial infection during extracorporeal membrane oxygenation. *J Hosp Infect.* (2009) 73:210–6. doi: 10.1016/j.jhin.2009.07.016
186. Burket JS, Bartlett RH, Vander Hyde K, Chenoweth CE. Nosocomial infections in adult patients undergoing extracorporeal membrane oxygenation. *Clin Infect Dis an Off Publ Infect Dis Soc Am.* (1999) 28:828–33. doi: 10.1086/515200
187. Aubron C, Cheng AC, Pilcher D, Leong T, Magrin G, Cooper DJ, et al. Infections acquired by adults who receive extracorporeal membrane oxygenation: risk factors and outcome. *Infect Control Hosp Epidemiol.* (2013) 34:24–30. doi: 10.1086/668439
188. Schmidt M, Bréchot N, Hariri S, Guiguet M, Luyt CE, Makri R, et al. Nosocomial infections in adult cardiogenic shock patients supported by venoarterial extracorporeal membrane oxygenation. *Clin Infect Dis Off Publ Infect Dis Soc Am.* (2012) 55:1633–41. doi: 10.1093/cid/cis78
189. Sun H-Y, Ko W-J, Tsai P-R, Sun C-C, Chang Y-Y, Lee C-W, et al. Infections occurring during extracorporeal membrane oxygenation use in adult patients. *J Thorac Cardiovasc Surg.* (2010) 140:1125–32.e2. doi: 10.1016/j.jtcvs.2010.07.017
190. Steiner CK, Stewart DL, Bond SJ, Hornung CA, McKay VJ. Predictors of acquiring a nosocomial bloodstream infection on extracorporeal membrane oxygenation. *J Pediatr Surg.* (2001) 36:487–92. doi: 10.1053/jpsu.2001.21609
191. Frerou A, Lesouhaitier M, Gregoire M, Uhel F, Gacouin A, Reizine F, et al. Venoarterial extracorporeal membrane oxygenation induces early immune alterations. *Crit Care.* (2021) 25:9. doi: 10.1186/s13054-020-03444-x
192. Vogel AM, Lew DF, Kao LS, Lally KP. Defining risk for infectious complications on extracorporeal life support. *J Pediatr Surg.* (2011) 46:2260–4. doi: 10.1016/j.jpedsurg.2011.09.013
193. Bizzarro MJ, Conrad SA, Kaufman DA, Rycus P. Infections acquired during extracorporeal membrane oxygenation in neonates, children, and adults. *Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc.* (2011) 12:277–81. doi: 10.1097/PCC.0b013e3181e28894
194. Thiagarajan RR, Barbaro RP, Rycus PT, McMullan DM, Conrad SA, Fortenberry JD, et al. Extracorporeal life support organization registry international report 2016. *Asaio J.* (2017) 63:60–7. doi: 10.1097/mat.0000000000000475
195. Aissaoui N, El-Banayosy A, Combes A. How to wean a patient from veno-arterial extracorporeal membrane oxygenation. *Intensive Care Med.* (2015) 41:902–5. doi: 10.1007/s00134-015-3663-y
196. Pappalardo F, Pieri M, Arnaez Corada B, Ajello S, Melisurgo G, De Bonis M, et al. Timing and strategy for weaning from venoarterial ECMO are complex issues. *J Cardiothorac Vasc Anesth.* (2015) 29:906–11. doi: 10.1053/j.jvca.2014.12.011
197. Cavarocchi NC, Pitcher HT, Yang Q, Karbowski P, Miessau J, Hastings HM, et al. Weaning of extracorporeal membrane oxygenation using continuous hemodynamic transesophageal echocardiography. *J Thorac Cardiovasc Surg.* (2013) 146:1474–9. doi: 10.1016/j.jtcvs.2013.06.055
198. Mebazaa A, Combes A, van Diepen S, Hollinger A, Katz JN, Landoni G, et al. Management of cardiogenic shock complicating myocardial infarction. *Intensive Care Med.* (2018) 44:760–3. doi: 10.1007/s00134-018-5214-9
199. Luo X, Wang W, Hu S, Sun H, Gao H, Long C, et al. Extracorporeal membrane oxygenation for treatment of cardiac failure in adult patients. *Interact Cardiovasc Thorac Surg.* (2009) 9:296–300. doi: 10.1510/icvts.2008.197681
200. Aissaoui N, Luyt C-E, Leprince P, Trouillet J-L, Léger P, Pavie A, et al. Predictors of successful extracorporeal membrane oxygenation (ECMO) weaning after assistance for refractory cardiogenic shock. *Intensive Care Med.* (2011) 37:1738–45. doi: 10.1007/s00134-011-2358-2
201. Ortuno S, Delmas C, Diehl J-L, Bailleul C, Lancelot A, Naili M, et al. Weaning from veno-arterial extra-corporeal membrane oxygenation: which strategy to use? *Ann Cardiothorac Surg.* (2019) 8:E1–E8. doi: 10.21037/acs.2018.08.05
202. Hanson ID, Tagami T, Mando R, Kara Balla A, Dixon SR, Timmis S, et al. SCAI shock classification in acute myocardial infarction: insights from the national cardiogenic shock initiative. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv.* (2020) 96:1137–42. doi: 10.1002/ccd.29139
203. Schrage B, Dabboura S, Yan I, Hilal R, Neumann JT, Sörensen NA, et al. Application of the sCAI classification in a cohort of patients with cardiogenic shock. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv.* (2020) 96:E213–E9. doi: 10.1002/ccd.28707
204. Baran DA, Long A, Badiye AP, Stelling K. Prospective validation of the sCAI shock classification: single center analysis. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv.* (2020) 96:1339–47. doi: 10.1002/ccd.29319
205. Jentzer JC, van Diepen S, Barsness GW, Henry TD, Menon V, Rihal CS, et al. Cardiogenic shock classification to predict mortality in the cardiac intensive care unit. *J Am Coll Cardiol.* (2019) 74:2117–28. doi: 10.1016/j.jacc.2019.07.077
206. Supady A, Curtis JR, Abrams D, Lorusso R, Bein T, Boldt J, et al. Allocating scarce intensive care resources during the COVID-19 pandemic: practical challenges to theoretical frameworks. *Lancet Respir Med.* (2021) 9:430–434. doi: 10.1016/S2213-2600(20)30580-4
207. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Socie. *Eur Hear J.* (2018) 39:119–77. doi: 10.1093/eurheartj/ehx39
208. Peura JL, Colvin-Adams M, Francis GS, Grady KL, Hoffman TM, Jessup M, et al. Recommendations for the use of mechanical circulatory support: device strategies and patient selection: a scientific statement from the American heart association. *Circulation.* (2012) 126:2648–67. doi: 10.1161/CIR.0b013e3182769a54
209. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail.* (2010) 16:e1–94. doi: 10.1016/j.cardfail.2010.04.004


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# Complete Revascularisation in Impella-Supported Infarct-Related Cardiogenic Shock Patients Is Associated With Improved Mortality

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**Background:** Acute myocardial infarction-related cardiogenic shock (AMI-CS) still has high likelihood of in-hospital mortality. The only trial evidence currently available for the intra-aortic balloon pump showed no benefit of its routine use in AMI-CS. While a potential benefit of complete revascularisation has been suggested in urgent revascularisation, the CULPRIT-SHOCK trial demonstrated no benefit of multivessel compared to culprit-lesion only revascularisation in AMI-CS. However, mechanical circulatory support was only used in a minority of patients.

**Objectives:** We hypothesised that more complete revascularisation facilitated by Impella support is related to lower mortality in AMI-CS patients.

**Methods:** We analysed data from 202 consecutive Impella-treated AMI-CS patients at four European high-volume shock centres (age 66 ± 11 years, 83% male). Forty-seven percentage ($n = 94$) had cardiac arrest before Impella implantation. Revascularisation was categorised as incomplete if residual SYNTAX-score (rS) was >8.

**Results:** Overall 30-day mortality was 47%. Mortality was higher when Impella was implanted post-PCI (Impella-post-PCI: 57%, Impella-pre-PCI: 38%, $p = 0.0053$) and if revascularisation was incomplete (rS ≤ 8: 37%, rS > 8: 56%, $p = 0.0099$). Patients with both pre-PCI Impella implantation and complete revascularisation had significantly lower mortality (33%) than those with incomplete revascularisation and implantation post PCI (72%, $p < 0.001$).

**Conclusions:** Our retrospective analysis suggests that complete revascularisation supported by an Impella microaxial pump implanted prior to PCI is associated with lower mortality than incomplete revascularisation in patients with AMI-CS.

**Keywords: microaxial flow-pumps, acute heart failure, myocardial infarction, cardiogenic shock, revascularisation**

## INTRODUCTION

Acute myocardial infarction (AMI) is one of the major contributors to cardiogenic shock (CS) (1). The "Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock" (SHOCK) trial demonstrated that urgent invasive assessment and revascularization improves long term survival (2). Based on this trial, current society guidelines recommend urgent revascularisation in AMI-CS (3). However, even two decades later, mortality in AMI-CS remains high with almost every second patient dying (2, 4–7).

Mechanical circulatory support (MCS) raised hope to improve outcome in AMI-CS. Although the intra-aortic balloon pump (IABP) was the most frequently used MCS device, it failed to improve survival compared to standard medical therapy (6, 8) and thus is no longer recommended for routine use (Class IIIA in the ESC Guidelines) (3). Today, a variety of more powerful MCS devices are available, including Impella, TandemHeart and extracorporeal membrane oxygenation (ECMO) (9). However, due to lacking prospective randomised data, current guidelines for use of MCS in AMI-CS are based on expert opinion and generally do not favour one system over another (3, 10).

Previous trials investigating Impella pumps in AMI-CS were not adequately powered regarding clinically meaningful outcome differences. Additionally, high proportions of patients with out-of-hospital cardiac arrest (OHCA) had a strong and negative influence on the reported mortality rates, and lacked standardisation of timing of Impella placement (11, 12). Several observational studies reported a positive association of Impella support prior to PCI on mortality, especially in patients who did not suffer cardiac arrest before device implantation (13–19). Whether approaches aiming for early implementation of Impella support in AMI-CS relate to improved outcome is currently investigated in the adequately powered DanGer-Shock trial (20). Since DanGer-Shock will most probably require some more years before data are reported, deciding about the use of MCS is based on individual experience.

While it is nowadays recommended to achieve complete revascularisation in stable AMI patients (21), the historic belief of complete revascularisation in AMI-CS has been challenged by the results of the CULPRIT-SHOCK trial, demonstrating lower mortality in AMI-CS patients receiving culprit-lesion-only compared to multivessel revescularisation (22). A major limitation to more complete revascularisation in that trial was haemodynamic instability during PCI in the multivessel group. Whether complete revascularisation in AMI-CS would be associated with improved outcome if patients were stabilised more rigorously by more liberal use of MCS devices in AMI-CS, has not been determined in a prospective study yet. Recently, the American National Shock Initiative Investigators reported about AMI-CS patients treated by a common strategy of early revascularisation on Impella support. In 198 patients with multivessel disease presenting with AMI-CS, revascularization of non-culprit lesions was associated with similar survival compared with culprit-only PCI (23).

Completeness of revascularisation has been addressed in PCI trials in the past using the residual Syntax score (rS) with a value of 8 or less indicating complete revascularisation (21). While the Syntax score was originally derived from a randomised study excluding AMI patients, it has been widely used in AMI patients and rS demonstrated its prognostic relevance in this particular setting as well (24–28). The more recent publications even used a similar threshold for incomplete revascularisation of rS of 8 with persistent prognostic relevance as (26–28). Most recently, the ACTION Core group from Paris used the rS for their analysis on complete revascularisation in the CULPRIT-SHOCK trial. In their analysis, rS was independently associated with early and late mortality (29).

In order to provide more detailed insight into that matter, we collected observational data from four shock centres running Impella programs and report about a total of 202 AMI-CS patients treated with Impella microaxial flow-pumps in clinical routine. We compared 30-day mortality in those patients in relation to completeness of revascularisation using residual syntax score as a previously investigated surrogate for completeness of revascularisation (21).

## METHODS

### Study Design

This was a retrospective, observational analysis that included data from all patients undergoing implantation of an Impella CP microaxial flow-pump in AMI-CS between 2012 and 2018 in all four centres when complete revascularisation during the index procedure was the intended strategy based on previous guideline recommendations (30). De-identified data were entered into a combined database. All data were collected in accordance with the Declaration of Helsinki and approved by the local ethics committee of each centre.

In general, all participating centres use algorithms for AMI-CS aiming for rapid detection and treatment of cardiogenic shock (19, 31). Patients with AMI are taken to the cath labs when in shock and rapid revascularisation and initiation of MCS is used in patients requiring higher amounts of vasopressors and inotropes in conjunction with increased levels of serum lactate as a sign of systemic hypoperfusion when LV-EF is impaired (32). Impella implantation is initiated during the initial cath lab procedure.

### Patient Population

Based on a previous analysis (19), we calculated a required sample size of $n = 196$ patients to give us 80% power to detect an absolute 10% reduction in mortality with an error of $< 0.05$. All 202 AMI-CS patients included in the analysis had been supported with an Impella CP at four different shock centres in Germany (University hospitals in Hannover, Bonn and Düsseldorf) and Italy (Padua).

The primary outcome measure of this study was to evaluate if more complete revascularisation defined by a rS of 8 or less would

**Abbreviations:** AMI, acute myocardial infarction; CS, cardiogenic shock; ECMELLA, combination of Impella and ECMO; ECMO, extracorporeal membrane oxygenation; IABP, intraaortic balloon pump; LV, left ventricle/ left ventricular; MCS, mechanical circulatory support; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

**TABLE 1 |** Baseline and procedural characteristics of the present prospective cohort.

| | **All patients** ***n* = 202** | **rS-score ≤ 8** ***n* =130** | **rS-score > 8** ***n* = 72** | ***p*-value** **rS≤8 vs. >8** |
|---|---|---|---|---|
| Age, mean (SD), years | 66 ± 11 | 65 ± 12 | 67 ± 11 | 0.1449 |
| Gender- male, *n* (%) | 168 (83) | 111 (85) | 57 (79) | 0.2601 |
| Height, mean (SD), cm | 174 ± 10 | 175 ± 11 | 172 ± 8 | 0.1321 |
| Weight, mean (SD), kg | 84 ± 15 | 85 ± 16 | 81 ± 11 | 0.1099 |
| BMI, mean (SD), kg/m² | 28.8 ± 13.7 | 29.3 ± 16.4 | 27.7 ± 3.7 | 0.5109 |
| Admission lactate, mean (SD), mmol/L | 5.7 ± 4.5 | 6.0 ± 4.6 | 5.3 ± 4.3 | 0.2645 |
| **Pre-existing conditions** | | | | |
| Hypertension, *n* (%) | 133 (66) | 86 (66) | 47 (65) | 0.9005 |
| Diabetes mellitus, *n* (%) | 64 (32) | 36 (28) | 28 (39) | 0.1024 |
| Hyperlipidaemia, *n* (%) | 68 (34) | 40 (31) | 28 (39) | 0.2443 |
| Smoking, *n* (%) | 63 (31) | 45 (35) | 18 (25) | 0.1593 |
| CKD, *n* (%) | 43 (21) | 23 (18) | 20 (28) | 0.0842 |
| LV-EF, mean (SD), % | 26 ± 11 | 26 ± 11 | 27 ± 11 | 0.6170 |
| Cardiac arrest prior to Impella, *n* (%) | 94 (46) | 67 (52) | 27 (38) | 0.0558 |
| ROSC, mean (SD), min | 25 ± 20 | 26 ± 20 | 24 ± 20 | 0.7649 |
| Impella pre-PCI, *n* (%) | 96 (48) | 60 (46) | 36 (50) | 0.6022 |
| Combination with ECMO, *n* (%) | 27 (13) | 20 (15) | 7 (10) | 0.2595 |
| Duration of shock prior to Impella, mean (SD), h | 3.3 ± 6.8 | 2.2 ± 3.3 | 5.4 ± 10.3 | **0.0014** |
| Infarct location, *n* (%) | | | | **0.0201** |
| left main | 38 (19) | 22 (17) | 16 (22) | |
| LAD | 106 (52) | 77 (59) | 29 (40) | |
| LCX | 24 (12) | 13 (10) | 11 (15) | |
| RCA | 25 (12) | 14 (11) | 11 (15) | |
| Bypass graft | 9 (4) | 4 (3) | 5 (7) | |
| Initial Syntax Score, mean (SD) | 29 ± 13 | 24 ± 12 | 37 ± 12 | **<0.0001** |
| Residual Syntax Score, mean (SD) | 8 ± 10 | 2 ± 2 | 19 ± 11 | **<0.0001** |
| TIMI flow at the end of procedure, *n* (%) | | | | **<0.001** |
| TIMI 0/I | 15 (7) | 2 (2) | 13 (18) | |
| TIMI II | 16 (8) | 11 (8) | 5 (7) | |
| TIMI III | 171 (85) | 117 (90) | 54 (75) | |
| Type of myocardial infarction, *n* (%) | | | | **0.033** |
| STEMI | 121 (60) | 85 (65) | 36 (50) | |
| NSTEMI | 81 (40) | 45 (35) | 36 (50) | |
| Extent of CAD, *n* (%) | | | | **0.001** |
| 1-vessel disease | 34 (17) | 30 (23) | 4 (6) | |
| 2-vessel disease | 39 (19) | 29 (22) | 10 (14) | |
| 3-vessel disease | 129 (64) | 71 (55) | 58 (80) | |

*BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LV-EF, left-ventricular ejection fraction; NSTEMI, Non-ST-segement elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; ROSC, Return of spontaneous circulation; STEMI, ST-segement elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.*
*Bold values indicate significant p-values < 0.05*

be associated with lower 30 day mortality than less complete revascularisation in AMI-CS patients. In a second step, the same principle was applied to patients with or without Impella implantation prior to PCI.

Since we previously demonstrated higher mortality in AMI-CS patients who suffered cardiac arrest (17, 19) or when hemodynamic support was initiated post-PCI (13, 15, 19), the analysis of the overall cohort was also stratified based on the presence or absence of cardiac arrest and timing of Impella implantation.

## Data Collection and Definitions

Basic demographic data, coronary anatomy, laboratory data and documented complications during in-hospital stay were collected. AMI-CS was defined as hypotension (systolic blood pressure <90 mmHg or need for inotropes or vasopressors to maintain systolic blood pressure >90 mmHg) and evidence of end organ hypoperfusion as indicated by altered mental status, clammy skin, or elevated lactate (>2 mmol/l) after adequate fluid resuscitation. Individual variables were fully available for all patients (32). Bleeding was defined by GUSTO criteria (33) and

haemolysis during Impella support was defined as LDH ≥1,000 and haptoglobin <0.3 g/l in 2 consecutive blood samples within 24 h.

## Clinical Follow-Up

Patient follow-up was for the period of hospitalisation, and vital status was determined from medical records. The follow-up of those patients who were discharged from hospital before 30 days was obtained by documents of primary care physicians or rehabilitation hospitals. In case of discharge from hospital or rehabilitation within 30 days, further follow-up was performed by phone. Vital status for 30 days was confirmed in 201/202 patients with the remaining patient discharged home alive on day 11.

## Statistical Analysis

Numbers are given as *n* (%), mean ± standard deviation (SD) for normally distributed variables, or median and interquartile range (IQR) for non-normally distributed variables. Statistical analysis was performed with ANOVA and corrected for multiple comparisons with a Bonferroni correction; Kruskal-Wallis-Test was used for non-parametric tests (17). Chi-square tests were used to compare patient characteristics. Cumulative mortality was estimated by Kaplan-Meier analysis and compared between groups by the log-rank test.

Univariate Cox proportional hazard regression analyses included variables potentially associated with mortality rates were performed to identify factors associated with risk of 30-day mortality. Factors considered included: infarct related artery other than LAD, initial Syntax score, NSTEMI, number of vessels, shock duration until Impella implantation. Then stepwise multivariate Cox regression analyses including variables significantly linked to mortality in the respective univariate analyses ($p < 0.05$) were performed. Analysis for correlation and multicollinearities were performed before multivariate regressions analysis. Results from regression analyses are expressed as hazard ratios (HR) including 95% confidence interval (CI).

Data were analysed using GraphPad Prism 6.0 (GraphPad Software, Inc., La Jolla, CA) and SPSS Statistics 24 (IBM SPSS Statistics 24). A $p < 0.05$ was considered statistically significant.

## Propensity Score Matching

A propensity score matching was performed to minimise confounder bias when comparing 30-day mortality in patients with rS ≤ 8 to patients with rS > 8. Variables related to incomplete revascularization in univariate regressions analysis were taken in to account in propensity score-matching: Infarct related artery other than LAD, initial Syntax score, NSTEMI, numbers of vessels, and shock duration prior to Impella implantation. Matching was realised by a stepwise match on the logit of the estimated propensity score (1:1) between cases and control groups using a nearest neighbour model. Callipers width was equal to 0.2. A balanced distribution of these parameters was achieved. Propensity score-matching was analysed using R program 3.3.3, and SPSS 25 (IBM SPSS Statistics 25).

**TABLE 2 |** Thirty-day adverse events.

| | **All *n* = 202** |
|---|---|
| Definite stent thrombosis | 2 (1%) |
| Ischemic stroke | 6 (3%) |
| Haemorrhagic stroke | 6 (3%) |
| Peripheral ischaemia of the leg requiring surgery or intervention | 18 (9%) |
| Haemolysis | 67 (33%) |
| **Bleeding [based on GUSTO definitions (33)]** | |
| Lif1e-threatening/severe | 20 (10%) |
| Moderate | 45 (22%) |
| Mild | 12 (6%) |
| Sepsis | 73 (36%) |
| Renal replacement therapy | 88 (44%) |
| Combination with vaECMO | 28 (14%) |

*vaECMO, veno-arterial extracorporeal membrane oxygenation.*

# RESULTS

## Patient Characteristics

The overall patient population consisted of 202 AMI-CS patients that had been treated with an Impella CP device. Patient characteristics are summarised in **Table 1**. Mean age in our cohort was 66 ± 11 years and 83% were male. Cardiac arrest had occurred in 94 patients (47%) prior to Impella implantation. Impella was implanted pre-PCI in 96 patients (48%). The type of AMI was STEMI in 60% and NSTEMI in 40%. In general, an average lactate of 5.7 mmol/l and LV-EF of 26% indicate that the patients supported with Impella CP in this analysis were in profound AMI-CS (34, 35).

The most frequent adverse events were the need for renal replacement therapy, bleeding, sepsis and haemolysis (**Table 2**).

## Impact of Complete Revascularisation on Mortality

Mean rS was 7.6 in the overall cohort, 130 patients (64%) had an rS ≤ 8, 72 patients (36%) had an rS > 8 with a mean of 18.5 ± 10.6. Patients with rS ≤ 8 had significantly lower 30 day mortality than patients with incomplete revascularisation [rS ≤ 8 37% vs. rS > 8 56%, $p = 0.0099$, HR 0.58, 95%CI (0.33–0.85), **Figure 1**]. Comparing characteristics of complete compared to incomplete revascularized patients showed that patients with rS ≤ 8 trended to have less pre-existing chronic kidney disease but had a higher rate of pre-Impella cardiac arrest; otherwise, these patients had similar baseline characteristics. In multivariate analysis, only initial Syntax score and duration of shock prior to Impella support remained as independent predictors for incomplete revascularisation (**Table 3**). As uneven distribution of factors such as type of infarction, number of vessels affected, presence of LAD as culprit, shock duration prior to Impella placement, and baseline Syntax score might have contributed to the observed difference between complete and incomplete revascularisation, we also performed a 1:1 propensity score matching regarding these factors, which reduced the number of cases in the complete revascularisation group from 130 to 56 and from 72 to 56 in

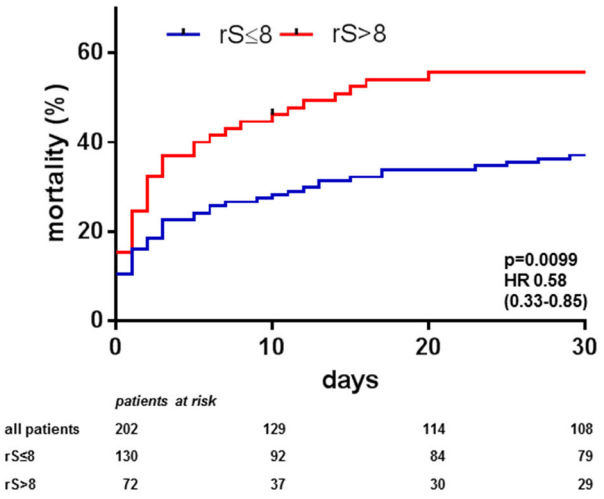


**FIGURE 1 |** Central illustration. Thirty-day mortality in acute myocardial infarction cardiogenic shock (AMI-CS) on Impella depending on completeness of revascularisation: Observed 30-days mortality in AMI-CS treated with Impella was lower if complete revascularisation defined by an residual Syntax score ≤ 8 was achieved by percutaneous coronary intervention (PCI) compared to less complete revascularisation (rS > 8).

the incomplete revascularisation group. The mortality rates were slightly affected (rS ≤ 8: 42% after matching compared to 37% prior to matching; rS > 8: 51% after matching compared to 56% prior to matching), but the strong reduction in cases in the rS ≤ 8 group resulted in a $p > 0.05$. Nevertheless, the trend was in the direction reported prior to propensity score matching (**Supplementary Figure 1**).

Overall 30-day mortality was lower when Impella was implanted pre-PCI (38%, $n = 40/106$) compared to when Impella was implanted post-PCI [57%, $n = 55/96$; $p = 0.0034$, HR 0.54, 95%CI (0.33–0.79), **Figure 2A**]. While patients receiving Impella post-PCI were younger (64 ± 12 vs. 68 ± 11 years, $p = 0.0241$), they had higher admission lactate levels (6.8 ± 5.0 vs. 4.7 ± 3.7 mmol/l, $p = 0.0008$), longer shock duration prior to Impella (4.2 ± 8.6 vs. 2.5 ± 4.4 h, $p = 0.0869$) and had had cardiac arrest more often prior to implantation (55 vs. 39%, $p = 0.0186$). However, both groups depicted similar LV (pre-PCI 25 ± 11% vs. post-PCI 27 ± 11%, $p = 0.3420$) and renal function (eGFR: pre-PCI 58 ± 28 vs. post-PCI 58 ± 26 ml/min, $p = 0.8989$) prior to support, and success in revascularisation (rS: pre-PCI 8 ± 12 vs. post-PCI 7 ± 9, $p = 0.2961$). Initial Syntax-score was higher in the pre-PCI compared to the post-PCI group (31 ± 14 vs. 26 ± 12, $p = 0.0033$). As circulatory support initiated prior to PCI will improve peri-procedural haemodynamics, we also assessed mortality depending on both co-variates. Patients with both pre-PCI Impella implantation and complete revascularisation had significantly lower mortality than those with incomplete revascularisation and implantation post PCI [33 vs. 72%, HR 0.30, 95%CI (0.10–0.41), $p < 0.001$, **Figure 2B**].

Duration of shock prior to Impella implantation was shorter in patients with complete revascularisation (rS ≤ 8 2.2 ± 3.3 h vs. rS > 8 5.4 ± 10.3 h, $p = 0.0014$), and most of the benefit of complete revascularisation on mortality was observed in patients with shorter shock duration prior to Impella implantation (**Supplementary Figure 2A**). Furthermore, mortality could potentially be affected if additive treatment with V-A ECMO were required either due to biventricular failure or need for more potent circulatory support owing to more severe shock. While numerically more patients received ECMELLA support in the completely revascularised group (rS ≤ 8 15% vs. rS > 8 10%, $p = 0.2595$), the overall impact of incomplete revascularisation on mortality was not changed by ECMELLA compared to Impella-only support. In patients with Impella-only support, mortality was significantly lower in the group with rS ≤ 8 compared to less complete revascularisation, and within the ECMELLA group a similar trend was observed (**Supplementary Figure 2B**). Patients with both pre-PCI Impella implantation and complete revascularisation had significantly lower mortality (33%) than those with incomplete revascularisation and implantation post PCI (72%, $p < 0.001$).

Of the 94 patients who suffered cardiac arrest prior to Impella implantation, 53 died and most common cause of death ($n = 39$, 74%) was due to early haemodynamic instability despite rapid circulatory support. That proportion was larger than in patients without prior cardiac arrest, in whom 39% died due to early haemodynamic failure indicating that late unmasking of underlying anoxic brain damage was not the major driver of increased mortality in patients with cardiac arrest prior to Impella implantation.

## DISCUSSION

In our analysis of 202 AMI-CS patients on Impella support treated by stratified protocols in four high-volume European shock centres, achieving complete revascularisation characterised by a residual Syntax score of 8 or less (21) was associated with lower 30 day mortality than less complete revascularisation. The most promising outcome was observed in patients with [pre PCI] implantation of Impella and complete revascularisation compared to patients with Impella implantation post PCI and incomplete revascularisation.

Recently, the American National Shock Initiative Investigators reported that in their experience multi-vessel PCI in AMI-CS was safe, when patients had been supported with an Impella microaxial flow-pump to rapidly stabilise haemodynamics (23). On first sight, theirs and our results appear to be in contradiction to the randomised CULPRIT-SHOCK trial, in which mortality was even higher when multivessel compared to culprit lesion only PCI was attempted (22). While excess mortality in the multivessel group was mainly driven by anoxic brain damage related to resuscitation prior to revascularisation, the rate of refractory cardiogenic shock was reduced by 12% in the mutlivessel group (22). However, in that trial only 12% of patients received circulatory support by Impella (overall mechanical support by Impella, ECMO, and/or TandemHeart was provided in ∼18–19%) and even less were supported by ECMO. The extent

**TABLE 3 |** Uni- and multi-variate analysis of predictors for incomplete revascularisation.

| Parameter | Univariate regressions analysis | | Multivariate regressions analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95%CI) | *p* |
| Infarct related artery other than LAD | 2.15 (1.19–3.87) | 0.01 | 1.15 (0.56–2.38) | 0.698 |
| Initial syntax score | 1.09 (1.06–1.13) | <0.001 | 1.09 (1.06–1.12) | <0.001 |
| NSTEMI | 2.01 (1.10–3.67) | 0.023 | 1.41 (0.67–2.93) | 0.365 |
| Number of vessels | 2.44 (1.51–3.94) | <0.001 | 1.56 (0.88–2.78) | 0.130 |
| Duration shock until Impella implantation | 1.08 (1.02–1.15) | <0.001 | 1.09 (1.01–1.17) | 0.024 |

*LAD, left anterior descending coronary artery; NSTEMI, Non-ST-segement elevation myocardial infarction.*

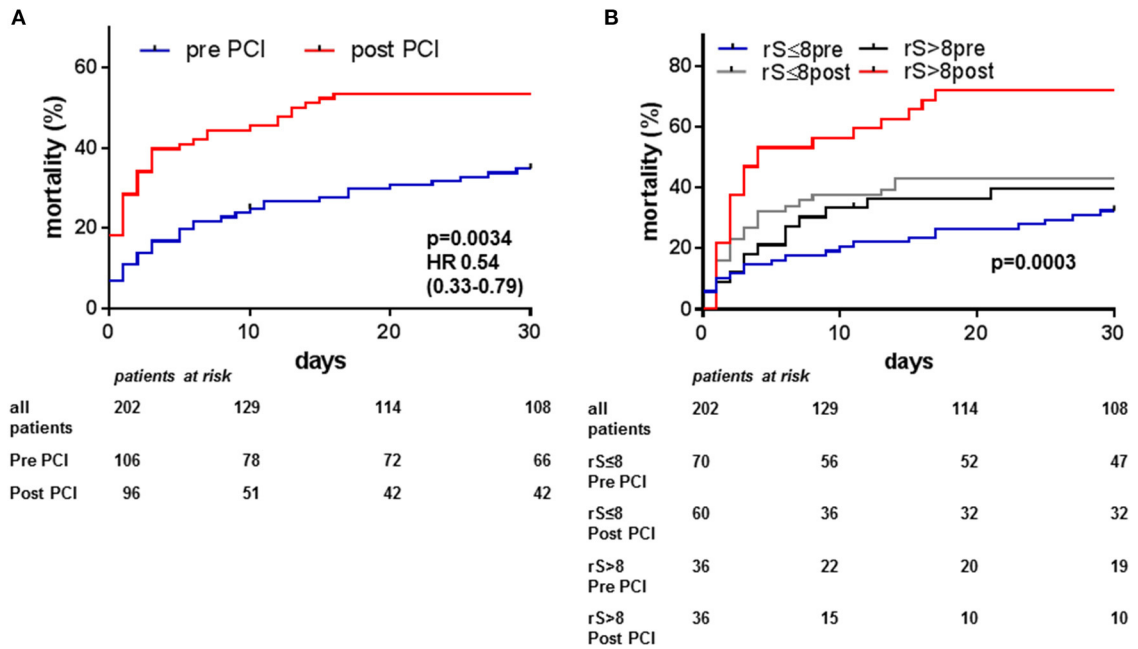


**FIGURE 2 |** Thirty-day mortality in acute myocardial infarction cardiogenic shock (AMI-CS) on Impella depending on timing of Impella support and completeness of revascularisation: Observed 30-days mortality in AMI-CS treated with Impella was lower if Impella was implanted pre PCI compared to post PCI **(A)**. Lowest mortality was observed in patients receiving Impella pre PCI and achieving complete revascularisation defined by an residual Syntax score (rS) ≤ 8 **(B)**.

of systemic hypoperfusion was similar with an average lactate about 5.0 mmol/l (66% > 2.0 mmol/l) compared to the 5.7 mmol/l (73% > 2.0 mmol/l) in our analysis (22). Recently, that trial and others in stable AMI patients have led to a change in recommendations for revascularisation strategies, whereby guidelines do now prefer culprit-lesion only PCI in AMI-CS (3), but complete revascularisation in stable AMI, contrary to the recommendations given several years before (30). Nevertheless, a large national Korean AMI registry demonstrated lower mortality in multivessel AMI-CS patients when complete compared to culprit-lesion only revascularisation was performed (36). Very recently, a sub-analysis from the CULPRIT-SHOCK trial reported that complete revascularisation was only achieved in roughly 25% of their AMI-CS patients treated using an multi-vessel PCI approach. In their analysis, rS was independently associated with early and late mortality (29). Similarly, findings from the Italian IMP-IT registry using Impella suggested a survival benefit when complete revascularisation was achieved in AMI-CS patients (37).

In patients with stable moderate- and high-risk ACS, incomplete revascularisation with rS above 8 is associated with poor short- and long-term outcome (21). When this parameter was applied to almost 90,000 patients in a meta-analysis, the mortality benefit associated with complete revascularisation was consistent across studies irrespective of revascularization modalities (38). Recently an increasing trend of Impella use over time has been observed along with increased mortality, acute kidney injury, stroke and costs associated with Impella use. Moreover, compared with IABP, Impella was associated with higher mortality, bleeding, acute kidney injury, and stroke. Interestingly, a wide variation in Impella utilisation across hospitals was observed, and hospitals with higher utilisation did

not necessarily have better outcomes than lower-use hospitals (39). When trying to perform propensity score matching to patients enrolled in the IABP-Shock II-trial, no benefit had been detected by Impella in AMI-CS, however, the analysis included heterogeneous treatment strategies (40). Recently, retrospective data did suggest that using defined treatment strategies for Impella in AMI-CS could potentially have a beneficial impact on mortality (19, 41). Retrospective observational comparisons between registries and clinical trials inherit the risk of severe selection bias regarding patients selected in clinical practise compared to patients enrolled in clinical trials. For example, of the 202 AMI-CS patients included in the present analysis, 154 (76%) would have fulfilled the inclusion/exclusion criteria of the IABP-Shock II-trial (6), but only 35 (17%) would have qualified for the DanGer-Shock trial (20). Our reported data represent evidence from real clinical practise in AMI-CS, whenever the treating interventional cardiologist felt the need for MCS based on the clinical patient presentation including higher lactate, impaired LV ejection fraction and raised vasopressor demand. As our registry is retrospective, differences in baseline characteristics can influence the allocation to the different treatment strategies as well as the observed outcome. Therefore, we intended to perform a propensity score-matching, after which there was still a trend toward lower mortality in the rS $\leq$ 8 group, however, the sample size was significantly reduced by the matching and the resulting *p*-value did not achieve statistical significance afterwards. Nevertheless, it has not been our intention to claim superiority of complete revascularisation on MCS over other approaches, we merely wanted to illustrate that results of complete compared to incomplete revascularisation might be different when patients are haemodynamically stabilised during the revascularisation procedure and we should not draw the conclusion that complete revascularisation always results in worse outcome.

In addition to failing cardiac output as a direct consequence of myocardial compromise in AMI-CS, a major contributor to mortality in AMI-CS trials is anoxic brain damage that has occurred prior to hospital admission and prior to insertion of a hemodynamic support device in patients suffering out-of-hospital cardiac arrest [cardiac arrest before enrolment: 28% in IABP-Shock II (6), 54% in CULPRIT-SHOCK (22), 46% in our analysis] as a consequence of AMI-related arrhythmias (17). As a matter of fact, post-arrest brain injury was the most relevant factor in excess mortality between the groups in CULPRIT-SHOCK with an absolute difference of 8.2% in favour of culprit-only PCI. However, regarding manifestation of refractory cardiogenic shock, there was an absolute 8.4% difference in favour of multivessel PCI in the same trial (22). So even while the primary endpoint including mortality was positive toward the culprit-only group based on a non-shock related factor, the more specific shock-related outcome, e.g., refractory cardiogenic shock, was lower in the multivessel-PCI group indicating that complete revacularisation might indeed positively influence shock outcome. Brain injury also highly impacted on the IMPRESS-in-SEVERE-SHOCK trial, in which 92% of patients were post-arrest and which did not demonstrate improved survival on Impella support in a small population of AMI-CS patients (12). While the authors stated that Impella was not effective in CS, not many patients in that study actually had the potential to survive with good neurological outcome. The IABP-Shock II entry criteria (applied in many of the AMI-CS trials) excluded patients who had undergone resuscitation for more than 30 min or were in a coma with fixed dilatation of pupils. In our analysis, pre-implantation cardiac arrest in AMI-CS was associated with a 78% higher 30-day mortality. While in routine treatment a MCS device will not be withheld from AMI-CS patients just because the patient had cardiac arrest before as long as no reliable prediction can be performed to prognosticate neurological outcome, in clinical trials a protocol ensuring exclusion of any comatose post-arrest patients should be employed to test the hypothesis whether mortality can be reduced by standardised use of MCS devices. However, this will exclude a large number of patients and the trial recruitment will be much slower. Nevertheless, such a clear stratified protocol for non-comatose AMI-CS patients testing Impella support compared to standard treatment is currently enrolling, the DanGer-Shock trial (20). Notably, comatose patients after out-of-hospital cardiac arrest and those with prolonged shock duration above 24 h are excluded, in an effort to remove patients who may not derive any benefit from the device due to already established extensive systemic or neurologic damage.

While evidence for MCS use from prospective trials is eagerly awaited and use of IABP in AMI-CS is strongly discouraged, individual decision making is required (32). In order to obtain at least some clarity, we combined our experience from four shock centres with regular Impella use for AMI-CS treatment. When using Impella microaxial flow-pumps to stabilise haemodynamics, we observed better outcome in patients with complete revascularisation compared to those with incomplete revascularisation. Whether complete revascularisation on MCS is superior to current standard treatment, which focuses on culprit lesion only revascularisation without routine circulatory support, needs to be addressed in a randomised-controlled clinical trial.

## LIMITATIONS

First, our analysis is based on observational data; so neither controls nor randomised treatment were available. Impella support was initiated whenever the interventional cardiologist felt the need for rapid mechanical circulatory support being justified by elevated lactate levels, impaired LV-ejection fraction on transthoracic echo, and increased vasopressor demand and/or compromised haemodynamics. Obviously, the analysis can only cover patients who survived until implantation of MCS. The results of our analysis are meant to be hypothesis generating given the longer shock duration prior to Impella use and the more complex disease including more NSTEMI in the incomplete revascularisation group. Until prospective trials are conducted, retrospective analyses like ours might, however, suggest using Impella in properly selected patients and appeared at least to be safe if not advantageous to aim for complete revascularisation if the patient is haemodynamically stabilised. While triggering

factors for Impella placement might therefore have been different for patients with Impella implanted prior compared to after PCI and those achieving complete compared to incomplete revascularisation, the timing of placement did not significantly affect completeness of revascularisation. Nevertheless, we cannot exclude that higher baseline Syntax score and more patients with TIMI 0/1 flow might have impacted on the overall message, which, however, is in line with a recent sub-analysis from the CULPRIT-SHOCK trial regarding completeness of revascularisation (29). An approach to use propensity score matching for potentially differing baseline parameters indicated a similar trend, but the statistical power was too low owing to the reduction in sample size.

## CONCLUSIONS

As long as we are waiting for data from randomised trials, deciding about certain forms of MCS is an individual decision based on the interventionist's experience. While routine use of circulatory support is not suggested, under certain conditions, complete revascularisation supported by an Impella microaxial pump implanted before PCI in AMI-CS might contribute to improved outcomes.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies approved by the HAnnover Cardiac Unloading REgistry (HACURE) has a prospective and observational design. The current analysis is in accordance with the Declaration of Helsinki, approved by the ethics committee at Hannover Medical School (#3566-2017). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

AS, NW, RW, and GT designed the study and drafted the manuscript. J-TS, AZ, JW, CS, and GM critically revised the manuscript. All authors acquired and analysed the data and agree to be accountable for all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.678748/full#supplementary-material

**Supplementary Figure 1 |** Thirty-day mortality in acute myocardial infarction cardiogenic shock (AMI-CS) on Impella depending on completeness of revascularisation following propensity score matching: Observed 30-days mortality in AMI-CS treated with Impella trended to be lower if complete revascularisation defined by an residual Syntax score $\leq 8$ was achieved by percutaneous coronary intervention (PCI) compared to less complete revascularisation ($rS > 8$) following propensity score matching for type of infarction, number of vessels affected, presence of LAD as culprit, and baseline Syntax score.

**Supplementary Figure 2 |** Thirty-day mortality in acute myocardial infarction cardiogenic shock (AMI-CS) on Impella depending on completeness of revascularisation and extent of cardiogenic shock: Observed 30-days mortality in AMI-CS patients treated with Impella was lower if complete revascularisation defined by an residual Syntax score $\leq 8$ was achieved by percutaneous coronary intervention (PCI) compared to less complete revascularisation ($rS > 8$) independent from the time in shock prior to Impella implantation **(A)** and whether patients were supported by Impella alone or in combination with V-A ECMO (ECMELLA, **B**).

**Supplementary Table 1 |** Characteristics and Outcome depending on time of Impella implantation before vs. after PCI.

## REFERENCES


1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis treatment of acute chronic heart failure: The Task Force for the diagnosis treatment of acute chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* (2016) 37:2129–200. doi: 10.1093/eurheartj/ehw128
2. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. *N Engl J Med.* (1999) 341:625–34. doi: 10.1056/NEJM199908263410901
3. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* (2019) 40:87–165. doi: 10.15829/1560-4071-2019-8-151-226
4. Mebazaa A, Tolppanen H, Mueller C, Lassus J, DiSomma S, Baksyte G, et al. Acute heart failure and cardiogenic shock: a multidisciplinary practical guidance. *Intensive Care Med.* (2016) 42:147–63. doi: 10.1007/s00134-015-4041-5
5. Schwarz B, Abdel-Wahab M, Robinson DR Richardt G. Predictors of mortality in patients with cardiogenic shock treated with primary percutaneous coronary intervention and intra-aortic balloon counterpulsation. *Med Klin Intensivmed Notfmed.* (2016) 111:715–22. doi: 10.1007/s00063-015-0118-8
6. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med.* (2012) 367:1287–96. doi: 10.1056/NEJMoa1208410
7. Harjola VP, Lassus J, Sionis A, Kober L, Tarvasmaki T, Spinar J, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Heart Fail.* (2015) 17:501–9. doi: 10.1002/ejhf.260
8. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet.* (2013) 382:1638–45. doi: 10.1016/S0140-6736(13)61783-3
9. Burkhoff D, Sayer G, Doshi D Uriel N. Hemodynamics of mechanical circulatory support. *J Am Coll Cardiol.* (2015) 66:2663–74. doi: 10.1016/j.jacc.2015.10.017
10. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology

Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. (2013) 127:e362–425. doi: 10.1161/CIR.0b013e3182742c84
11. Ouweneel DM, Engstrom AE, Sjauw KD, Hirsch A, Hill JM, Gockel B, et al. Experience from a randomized controlled trial with Impella 2.5 versus IABP in STEMI patients with cardiogenic pre-shock. Lessons learned from the IMPRESS in STEMI trial. *Int J Cardiol.* (2016) 202:894–6. doi: 10.1016/j.ijcard.2015.10.063
12. Ouweneel DM, Eriksen E, Sjauw KD, van Dongen IM, Hirsch A, Packer EJ, et al. Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol.* (2017) 69:278–87. doi: 10.1016/j.jacc.2016.10.022
13. Basir MB, Schreiber TL, Grines CL, Dixon SR, Moses JW, Maini BS, et al. Effect of early initiation of mechanical circulatory support on survival in cardiogenic shock. *Am J Cardiol.* (2017) 119:845–51. doi: 10.1016/j.amjcard.2016.11.037
14. O'Neill WW, Grines C, Schreiber T, Moses J, Maini B, Dixon SR Ohman EM. Analysis of outcomes for 15,259 US patients with acute myocardial infarction cardiogenic shock (AMICS) supported with the Impella device. *Am Heart J.* (2018) 202:33–8. doi: 10.1016/j.ahj.2018.03.024
15. O'Neill WW, Schreiber T, Wohns DH, Rihal C, Naidu SS, Civitello AB, et al. The current use of Impella 2.5 in acute myocardial infarction complicated by cardiogenic shock: results from the USpella Registry. *J Interv Cardiol.* (2014) 27:1–11. doi: 10.1111/joic.12080
16. Vetrovec GW, Anderson M, Schreiber T, Popma J, Lombardi W, Maini B, et al. The cVAD registry for percutaneous temporary hemodynamic support: a prospective registry of Impella mechanical circulatory support use in high-risk PCI, cardiogenic shock, and decompensated heart failure. *Am Heart J.* (2018) 199:115–21. doi: 10.1016/j.ahj.2017.09.007
17. Sieweke JT, Berliner D, Tongers J, Napp LC, Flierl U, Zauner F, et al. Mortality in patients with cardiogenic shock treated with the Impella CP microaxial pump for isolated left ventricular failure. *Eur Heart J Acute Cardiovasc Care*. (2020) 9:138–148. doi: 10.1177/2048872618757393
18. Meraj PM, Doshi R, Schreiber T, Maini B O'Neill WW. Impella 2.5 initiated prior to unprotected left main PCI in acute myocardial infarction complicated by cardiogenic shock improves early survival. *J Interv Cardiol.* (2017) 30:256–63. doi: 10.1111/joic.12377
19. Schäfer A, Werner N, Burkhoff D, Sieweke J-T, Zietzer A, Masyuk M, et al. Influence of timing and predicted risk on mortality in Impella-treated infarct-related cardiogenic shock patients. *Front Cardiovasc Med.* (2020) 7:74. doi: 10.3389/fcvm.2020.00074
20. Junker Udesen NL, Moller JE, Lindholm MG, Eiskjaer H, Schäfer A, Werner N, et al. Rationale and design of the Danish German cardiogenic shock trial - DanGer Shock trial. *Am Heart J.* (2019) 214:60–8. doi: 10.1016/j.ahj.2019.04.019
21. Genereux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O, et al. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. *J Am Coll Cardiol.* (2012) 59:2165–74. doi: 10.1016/j.jacc.2012.03.010
22. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med.* (2017) 377:2419–32. doi: 10.1056/NEJMoa1710261
23. Lemor A, Basir MB, Patel K, Kolski B, Kaki A, Kapur N, et al. Multi- versus culprit-vessel percutaneous coronary intervention in cardiogenic shock. *JACC Cardiovasc Interv*. (2020) 13(10):1171–1178. doi: 10.1016/j.jcin.2020.03.012
24. Singbal Y, Fryer M, Garrahy P Lim R. Baseline and residual SYNTAX score in predicting outcomes after acute infarct angioplasty. *EuroIntervention.* (2017) 12:1995–2000. doi: 10.4244/EIJ-D-15-00269
25. Malkin CJ, George V, Ghobrial MS, Krishnan A, Siotia A, Raina T, et al. Residual SYNTAX score after PCI for triple vessel coronary artery disease: quantifying the adverse effect of incomplete revascularisation. *EuroIntervention.* (2013) 8:1286–95. doi: 10.4244/EIJV8I11A197
26. Khan R, Al-Hawwas M, Hatem R, Azzalini L, Fortier A, Joliecoeur EM, et al. Prognostic impact of the residual SYNTAX score on in-hospital outcomes in patients undergoing primary percutaneous coronary intervention. *Catheter Cardiovasc Interv.* (2016) 88:740–7. doi: 10.1002/ccd.26413
27. Burgess SN, French JK, Nguyen TL, Leung M, Richards DAB, Thomas L, et al. The impact of incomplete revascularization on early and late outcomes in ST-elevation myocardial infarction. *Am Heart J.* (2018) 205:31–41. doi: 10.1016/j.ahj.2018.07.017
28. Braga CG, Cid-Alvarez AB, Dieguez AR, Alvarez BA, Otero DL, Sanchez RO, et al. Prognostic impact of residual SYNTAX score in patients with ST-elevation myocardial infarction and multivessel disease: analysis of an 8-year all-comers registry. *Int J Cardiol.* (2017) 243:21–6. doi: 10.1016/j.ijcard.2017.04.054
29. Barthelemy O, Rouanet S, Brugier D, Vignolles N, Bertin B, Zeitouni M, et al. Predictive value of the residual SYNTAX score in patients with cardiogenic shock. *J Am Coll Cardiol.* (2021) 77:144–55. doi: 10.1016/j.jacc.2020.11.025
30. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* (2014) 35:2541–619. doi: 10.1093/eurheartj/ehu278
31. Akin M, Sieweke J-T, Zauner F, Garcheva V, Tongers J, Napp LC, et al. Mortality in patients with out-of-hospital cardiac arrest undergoing a standardised protocol including therapeutic hypothermia and routine coronary angiography - experience from the HAnnover COoling REgistry (HACORE). *JACC Cardiovasc Interv.* (2018) 11:1811–20. doi: 10.1016/j.jcin.2018.06.022
32. Schäfer A, Werner N, Westenfeld R, Moller JE, Schulze PC, Karatolios K, et al. Clinical scenarios for use of transvalvular microaxial pumps in acute heart failure and cardiogenic shock - a European experienced users working group opinion. *Int J Cardiol.* (2019) 291:96–104. doi: 10.1016/j.ijcard.2019.05.044
33. Gusto Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. (1993) 329:673–82. doi: 10.1056/NEJM199309023291001
34. Frydland M, Moller JE, Wiberg S, Lindholm MG, Hansen R, Henriques JP, et al. Lactate is a prognostic factor in patients admitted with suspected ST-elevation myocardial infarction. *Shock.* (2019) 51:321–7. doi: 10.1097/SHK.0000000000001191
35. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: this document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. *Catheter Cardiovasc Interv*. (2019) 94:29–37. doi: 10.1002/ccd.28329
36. Lee JM, Rhee TM, Hahn JY, Kim HK, Park J, Hwang D, et al. Multivessel percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction with cardiogenic shock. *J Am Coll Cardiol.* (2018) 71:844–56. doi: 10.1016/j.jacc.2017.12.028
37. Aurigemma C, Burzotta F, Chieffo A, Briguori C, Piva T, De Marco F, et al. Clinical impact of revascularization extent in patients undergoing impella-protected PCI enrolled in a nationwide registry. *JACC Cardiovasc Interv*. (2021) 14:717–9. doi: 10.1016/j.jcin.2021.01.017
38. Garcia S, Sandoval Y, Roukoz H, Adabag S, Canoniero M, Yannopoulos D Brilakis ES. Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. *J Am Coll Cardiol.* (2013) 62:1421–31. doi: 10.1016/j.jacc.2013.05.033
39. Amin AP, Spertus JA, Curtis JP, Desai N, Masoudi FA, Bach RG, et al. The evolving landscape of impella use in the united states among patients undergoing percutaneous coronary intervention with mechanical circulatory support. *Circulation.* (2020) 141:273–84. doi: 10.1161/CIRCULATIONAHA.119.044007
40. Schrage B, Ibrahim K, Loehn T, Werner N, Sinning JM, Pappalardo F, et al. Impella support for acute myocardial infarction complicated by cardiogenic shock. *Circulation.* (2019) 139:1249–58. doi: 10.1161/CIRCULATIONAHA.118.036614
41. Basir MB, Kapur NK, Patel K, Salam MA, Schreiber T, Kaki A, et al. Improved outcomes associated with the use of shock protocols: updates from the National Cardiogenic Shock Initiative. *Catheter Cardiovasc Interv.* (2019) 93:1173–1183. doi: 10.1002/ccd.28307

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# Monocyte Dysfunction Detected by the Designed Ankyrin Repeat Protein F7 Predicts Mortality in Patients Receiving Veno-Arterial Extracorporeal Membrane Oxygenation

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**Background:** Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is used for critically ill patients requiring hemodynamic support but has been shown to induce an inflammatory response syndrome potentially leading to severe complications and poor outcome. Monocytes are comprised of different subsets and play a central role in the innate immune system. The *unique* small binding proteins, Designed Ankyrin Repeat Protein "F7" and single chain variable fragment "MAN-1," specifically detect the activated conformation of the leukocyte integrin Mac-1 enabling the highly sensitive detection of monocyte activation status. The aim of this study was to characterize monocyte function and heterogeneity and their association with outcome in VA-ECMO patients.

**Methods:** VA-ECMO patients were recruited from the ICUs of the University Hospital in Freiburg, Germany. Blood was sampled on day 0 and day 3 after VA-ECMO placement, after VA-ECMO explantation and from healthy controls. Monocyte subset distribution, baseline activation and stimulability were analyzed by flow cytometry using the unique small binding proteins F7 and MAN-1 and the conventional activation markers CD163, CD86, CD69, and CX3CR1. Furthermore, expression of monocyte activation markers in survivors and non-survivors on day 0 was compared. Simple logistic regression was conducted to determine the association of monocyte activation markers with mortality.

**Results:** Twenty two patients on VA-ECMO and 15 healthy controls were recruited. Eleven patients survived until discharge from the ICU. Compared to controls, baseline monocyte activation was significantly increased, whereas stimulability was decreased. The percentage of classical monocytes increased after explantation, while the percentage of intermediate monocytes decreased. Total, classical, and intermediate

monocyte counts were significantly elevated compared to controls. On day 0, baseline binding of F7 was significantly lower in non-survivors than survivors. The area under the ROC curve associated with mortality on day 0 was 0.802 ($p = 0.02$).

**Conclusions:** Distribution of monocyte subsets changes during VA-ECMO and absolute classical and intermediate monocyte counts are significantly elevated compared to controls. Monocytes from VA-ECMO patients showed signs of dysfunction. Monocyte dysfunction, as determined by the *unique tool* F7, could be valuable for predicting mortality in patients receiving VA-ECMO and may be used as a novel biomarker guiding early clinical decision making in the future.

**Keywords: extracorporeal membrane oxygenation, monocyte, Mac-1, inflammation, DARPin®, activation**

## INTRODUCTION

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is being increasingly used as a last resort for critically ill patients with circulatory failure. Although the underlying technology has substantially improved, the mortality rate in these patients remains high at over 50% (1, 2). Contributing to this high mortality rate are severe, life-threatening complications such as bleeding, thrombosis, and capillary leakage syndrome which have been associated with a systemic inflammatory response syndrome occurring after ECMO initiation. This overshooting inflammatory response is triggered by contact of blood components with extracorporeal surfaces (3).

The inflammatory reaction to ECMO therapy is complex. Recent studies report altered function and response to stimulation of immune cells in ECMO patients, also referred to as *immunoparalysis*. It has been suggested that this phenomenon might also affect outcome in these patients, e.g., by increased vulnerability toward infection (4, 5).

Monocytes play a crucial role in the development and progression of a wide range of inflammatory conditions (6–8). They can be differentiated according to their expression of the surface markers CD14 and CD16 into classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$), and non-classical ($CD14^{+}CD16^{++}$) monocytes, each with distinct functions (9). Only limited information is available on monocyte subset *distribution* and *function* in ECMO patients.

Several markers of monocyte activation have been described including CD163 (10, 11), CD86 (12, 13), CD69 (14, 15), CX3CR1 (16), and the leukocyte integrin Mac-1 [=CD11b or $\alpha_M\beta_2$-integrin (17)]. Importantly, Mac-1 exists in a resting and activated conformation on the monocyte surface depending on the activation status and the change in integrin conformation occurs within minutes of leukocyte activation (18, 19). The sensitivity of detecting monocyte activation can be dramatically increased by specifically detecting the activated conformation of Mac-1 using the following *unique tools:* the small binding proteins, single chain variable fragment (scFv) MAN-1 and Designed Ankyrin Repeat Protein (DARPin) F7.

These small binding proteins, compared to conventional immunoglobulins, are more stable, have similar or even higher affinities to their targets and are more easily produced and selected, entailing lower costs (20). MAN-1 and F7 have previously been used to detect monocyte activation in a clinical setting, e.g., in septic patients or patients with myocardial infarction (19, 21).

The aim of this study was to characterize monocyte function and heterogeneity and their association with outcome in VA-ECMO patients.

## MATERIALS AND METHODS

### Patient Recruitment

Patients were recruited prospectively from the intensive care units of the medical and heart surgical intensive care wards of the University Hospital in Freiburg, Germany from December 2019 until December 2020. Daily screening of the patient data management system was performed to identify patients receiving VA-ECMO. Patients were eligible if they were 18 years or older, had no hematological malignancies and a hemoglobin value above 8 g/dl. Blood was carefully drawn from an arterial line from patients after VA-ECMO implantation on day 0 ("d0," <24 h after VA-ECMO initiation), day 3 ("d3," 72 h ± 12 h after VA-ECMO initiation) and after explantation ("post explant.," <12 h after VA-ECMO explantation). Blood was immediately transferred to the laboratory where flow cytometric analysis was carried out. Clinical and laboratory parameters were obtained from the electronic patient data management system. Healthy volunteers were free of disease and had not taken any drugs in the past 14 days and blood was taken by antecubital vein puncture.

### Indications, Implantation, and Management of VA-ECMO

The decision on the placement of VA-ECMO was made by an experienced ECMO physician. Implantation and management were carried out as described previously (22). Most commonly, venous cannulas had a diameter of 21-23 F and arterial cannulas were 15-17 F. Distal limb perfusion was added if necessary.

Patients on VA-ECMO regularly received transfusions as indicated to maintain hemoglobin levels above 8 g/dl and a platelet count above 50,000/μl.

VA-ECMO was carried out using the Stöckert® centrifugal pump (LivaNova PLC, London, United Kingdom), the Maquet

Cardiohelp Systems with an HLS Set Advanced (Maquet Cardiopulmonary GmbH, Rastatt, Germany), the CARL system (Resuscitec, Freiburg, Germany) or the Deltastream system (Xenios AG, Heilbronn, Germany). All systems included one oxygenator.

## Flow Cytometry

### Antibodies

All antibodies were ordered from Biolegend, USA. 8.5 µl of the following antibodies were added to the Master-Mix: PerCP-Cy5.5 anti-HLA-DR (clone L243), PE anti-CD14 (clone HCD14), Pacific Blue anti-CD16 (clone 3G8), APC anti-CD45 (clone HI30), PE/Cy7 anti-CD66b (clone G10F5) and the master-mix was stored on ice in the dark after dilution with 45 µl PBS. 5 µl of Master-Mix was added per sample. The following FITC-conjugated antibodies were used to detect monocyte activation: anti-CX3CR1 (1:10 dilution, clone 2A9-1), anti-CD69 (1:5 dilution, clone FN50), anti-CD86 (1:10 dilution, clone BU63), anti-CD163 (1:10 dilution, clone GHI/61), and 5 µl were added to the specified sample. Adequate isotype controls were prepared. DARPin F7 was produced and purified as described previously (21). MAN-1 was kindly provided by Prof. Karlheinz Peter, Melbourne, Australia. DARPin F7 ($F_c = 2.5\,\mu g/ml$) and MAN-1 ($F_c = 10\,\mu g/ml$) are unconjugated but feature a His-tag which allows detection by an Alexa Fluor 488 anti-His-tag antibody (1 µl per sample).

### Protocol and Staining Procedure

100 µl of citrated blood was added per tube followed by stimulation with phorbol 12-myristate 13-acetate (PMA, 200 nM, or PBS for unstimulated samples, 15 min, 37°C). After red blood cell lysis (BD FACS Lysing Solution, BD, USA; 20 min, on ice), samples were washed with 2 ml of PBS + $Ca^{2+}/Mg^{2+}$ and resuspended in 100 µl of PBS + $Ca^{2+}/Mg^{2+}$. DARPin F7, MAN-1, anti-CD163, anti-CD69, anti-CD86 and anti-CX3CR1, and the Mastermix were added (15 min, on ice), followed by addition of the secondary antibody (anti-His-Tag Alexa, 15 min on ice). 400 µl of diluted Cell FIX™ solution (BD, USA) were added and samples were read on a BD FACS Canto II Flow Cytometer at medium flow rate.

Binding of MAN-1, F7, anti-CD163, anti-C86, anti-CD69, and anti-CX3CR1 was recorded as percentage after gating for classical monocytes using adequate isotype controls as previously described (21). Marker expression on monocytes was assessed in unstimulated samples (=*baseline*), and PMA-stimulated samples (=*stimulability*). In brief, the positive population was defined by a gate including the top 1% of the population in the FITC isotype control sample (anti-CD163, anti-C86, anti-CD69, and anti-CX3CR1) or the top 1% in the secondary Alexa-Fluor 488 anti-His-tag antibody only sample (F7 & MAN-1). The population shifting into this gate in unstimulated or stimulated samples was recorded as percentage. HLA-DR expression on classical monocytes was recorded as PerCP-Cy5.5 mean fluorescence intensity.

Monocyte subsets were defined by their expression of CD14 and CD16. Classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$), and non-classical ($CD14^{+}CD16^{++}$) monocytes were identified in the following way: after excluding $CD66b^{+}$ events cells, monocytes were pre-gated according to their location in the FSC/APC CD45 plot. Monocytes were then identified by their expression of HLA-DR and CD14. $HLA\text{-}DR^{+}CD14^{+}$ cells were then displayed in a PE CD14/Pacific Blue CD16 gate and subpopulations were identified as described previously using adequate isotype controls (23).

An extra sample was transferred to a Trucount™ tube (BD, USA) to allow absolute quantification of cells. 10,000 Trucount™ beads were recorded and monocyte concentration per ml was calculated as described in the manufacturer's instructions. Total monocyte count per ml for each patient was calculated by summarizing the number of classical, intermediate and non-classical monocytes. In the other samples 5,000 monocytes were recorded in the HLA-DR/CD14 gate. Data were analyzed using FlowJo V10.6.0.

## Statistics

Variables are presented as mean ± SEM or median (interquartile range). To account for repeated measures per patient, mixed effects models, which allow missing data, were used to analyze differences between means across different time points. Unpaired *t*-tests were used to analyze differences of means at single time points. Simple logistic regression analysis was performed to determine association of monocyte markers on day 0 with mortality. Areas under the receiver operating characteristics (ROC) curve were calculated to determine predictive accuracy of these parameters. A $p$-value $\leq 0.05$ was considered statistically significant. Analysis was performed using GraphPad Prism V9.0 (GraphPad Software, San Diego, California, USA).

# RESULTS

In a first step, the ability to detect monocyte activation in response to PMA stimulation was validated for all monocyte surface markers (F7, MAN-1, CX3CR1, CD163, CD86, CD69) in a group of healthy volunteers. These healthy volunteers also later served as a control group since monocyte function was assumed to be unaltered by medication or disease allowing them to serve as a reference. Fifteen healthy controls were recruited with a median age of 26 years (23–31). Seven were female, 8 were male. We found a significant increase in binding for all surface markers in response to stimulation with PMA. Activation-specific binding was particularly pronounced for the *unique tools* F7 and MAN-1 (**Supplementary Figure 1**).

Twenty-two patients receiving veno-arterial ECMO were recruited from December 2019 to December 2020. Eleven patients survived until discharge from the intensive care wards and were considered as "survivors." Eight patients were females. Thirteen patients were recruited from the medical intensive care wards, nine patients were recruited from the heart surgical intensive care ward. Seven patients received ECMO during cardiopulmonary resuscitation (eCPR) and 15 patients due to severe cardiogenic shock. The median sequential organ failure assessment (SOFA) score (Q1-Q3) was 11 (9–13). Blood was obtained from all patients on day 0. We were able to take blood from 13 patients on day 3 and 13 patients after ECMO

**TABLE 1 |** Clinical characteristics, laboratory parameters, and ventilation settings of VA-ECMO patients on day 0.

| Parameter | VA-ECMO patients |
|---|---|
| Patients, *n* (%) | 22 (100) |
| Age, y (Q1-Q3) | 63 (52-73) |
| Survivors, *n* (%) | 11 (50) |
| Female, *n* (%) | 8 (37) |
| **Type of VA-ECMO, *n* (%)** | |
| Stöckert Sorin | 12 (55) |
| Maquet | 7 (32) |
| Deltastream | 2 (9) |
| CARL | 1 (4) |
| Days on ECMO (median, Q1-Q3) | 6.0 (3.8-7.0) |
| ECMO Blood Flow (l/min, Q1-Q3) | 4.3 (3.8-4.8) |
| **Indication for VA-ECMO, *n* (%)** | |
| Cardiogenic shock (due to) | 15 (68) |
| Postoperative/postinterventional | 7 (32) |
| Myocardial infarction | 2 (9) |
| Ischemic cardiomyopathy | 1 (4) |
| Unknown cardiomyopathy | 1 (4) |
| Endocarditis | 1 (4) |
| Pulmonary embolism | 1 (4) |
| After CPR | 1 (4) |
| Mitral regurgitation | 1 (4) |
| eCPR (due to) | 1 (4) |
| Myocardial ischemia | 1 (4) |
| Unknown | 1 (4) |
| Cardiovascular disease, *n* (%) | 15 (68) |
| Atrial fibrillation, *n* (%) | 8 (36) |
| Diabetes mellitus, *n* (%) | 2 (9) |
| Hypertension, *n* (%) | 7 (32) |
| Active smoker, *n* (%) | 3 (14) |
| Hypercholesterolemia, *n* (%) | 4 (18) |
| Cancer, *n* (%) | 0 (0) |
| Acute renal failure, *n* (%) | 15 (68) |
| Continuous hemodialysis, *n* (%) | 9 (41) |
| Heparin, *n* (%) | 21 (95) |
| Dual anti-platelet therapy, *n* (%) | 9 (41) |
| Immunosuppression, *n* (%) | 1 (4) |
| Received transfusions, *n* (%) | 22 (100) |
| Cytosorb, *n* (%) | 1 (4) |
| Mechanical ventilation, *n* (%) | 22 (100) |
| SOFA score (Q1-Q3) | 11.0 (9.0-13.0) |
| WBC ($\times 10^3$ /µl, Q1-Q3) | 9.6 (7.5-14.0) |
| Platelets ($\times 10^3$ /µl, Q1-Q3) | 102.0 (74.0-140.0) |
| Hb (g/dl, Q1-Q3) | 8.7 (8.3-9.4) |
| Creatinine (mg/dl, Q1-Q3) | 1.7 (1.0-2.5) |
| Urea (mg/dl, Q1-Q3) | 58.0 (33.0-77.0) |
| Bilirubin (mg/dl, Q1-Q3) | 2.4 (1.5-3.3) |
| AST (U/l, Q1-Q3) | 161.0 (70.3-437.5) |
| ALT (U/l, Q1-Q3) | 63 (25.3-123.8) |
| CRP (mg/l, Q1-Q3) | 54.1 (25.3-101.0) |
| IL-6 (pg/ml) | 378.0 (297.5-1007) |
| Ferritin (ng/ml, Q1-Q3) | 371 (203.0-4163) |
| Lactate (mmol/l, Q1-Q3) | 3.25 (1.4-5.9) |
| $p_aO_2$ (mmHg, Q1-Q3) | 111 (76.8-167.3) |
| $p_aCO_2$ (mmHg, Q1-Q3) | 39.4 (35.3-45.5) |
| $F_iO$ (%, Q1-Q3) | 50.0 (40.0-50.0) |
| PEEP (mbar, Q1-Q3) | 8.0 (7.0-10.0) |
| Respiratory rate (/min, Q1-Q3) | 14.0 (12.0-18.0) |

*Data are presented as median (interquartile range, Q1-Q3) or number of patients (%). Denominator of the percentage is the total number of subjects in the group. Parameters from the patient data management system that were closest to the time point of blood sampling for flow cytometric analysis are presented. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; eCPR, extracorporeal cardiopulmonary resuscitation; $F_iO$, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; SOFA, sequential organ failure assessment score; WBC, white blood cells.*

explantation. The reduced number of patients on day 3 was due to early weaning off ECMO (two patients) or early death (seven patients). Patient characteristics and laboratory parameters are presented in **Table 1**.

We then investigated expression of activation-specific parameters on monocytes from VA-ECMO patients on day 0, day 3, and after explantation. We show the expression of these parameters on unstimulated (=*baseline*) and PMA-stimulated monocytes (=*stimulability*) and compare these parameters to our healthy control group.

According to most parameters, baseline monocyte activation and monocyte stimulability did not change significantly while patients were on ECMO and even after explantation. However, there were significant differences in baseline monocyte activation and stimulability compared to healthy controls which we will describe in detail for the different parameters investigated.

The highly-activation-specific and conformationally sensitive anti-Mac-1 binding protein F7 showed increased baseline monocyte activation compared to healthy controls (e.g., percentage binding: VA-ECMO day 3 vs. healthy controls: 33.8 ± 6.4 vs. 19.1 ± 3.1, $p = 0.04$, **Figure 1A**). The conformationally sensitive anti-Mac-1 binding protein MAN-1 also detected increased baseline monocyte activation in VA-ECMO patients, but only on day 3 (MAN-1: 35.5 ± 7.5 vs. 15.0 ± 2.6, p=0.01, **Figure 1C**). Monocyte stimulability on ECMO and even after explantation using these parameters was significantly reduced compared to healthy controls (e.g., percentage binding VA-ECMO day 0 vs. healthy controls F7: 43.1 ± 5.2 vs. 67.1 ± 3.3, $p = 0.001$, MAN-1: 33.1 ± 4.1 vs. 80.0 ± 2.0, $p < 0.001$, **Figures 1B,D**).

Baseline monocyte activation according to the expression of CD163 in VA-ECMO patients was significantly increased compared to healthy controls (e.g., percentage binding VA-ECMO day 0 vs. healthy controls: CD163: 43.8 ± 5.4 vs. 14.4 ± 3.6, $p < 0.001$), whereas stimulability was not significantly different (e.g., percentage binding VA-ECMO day 0 vs. healthy

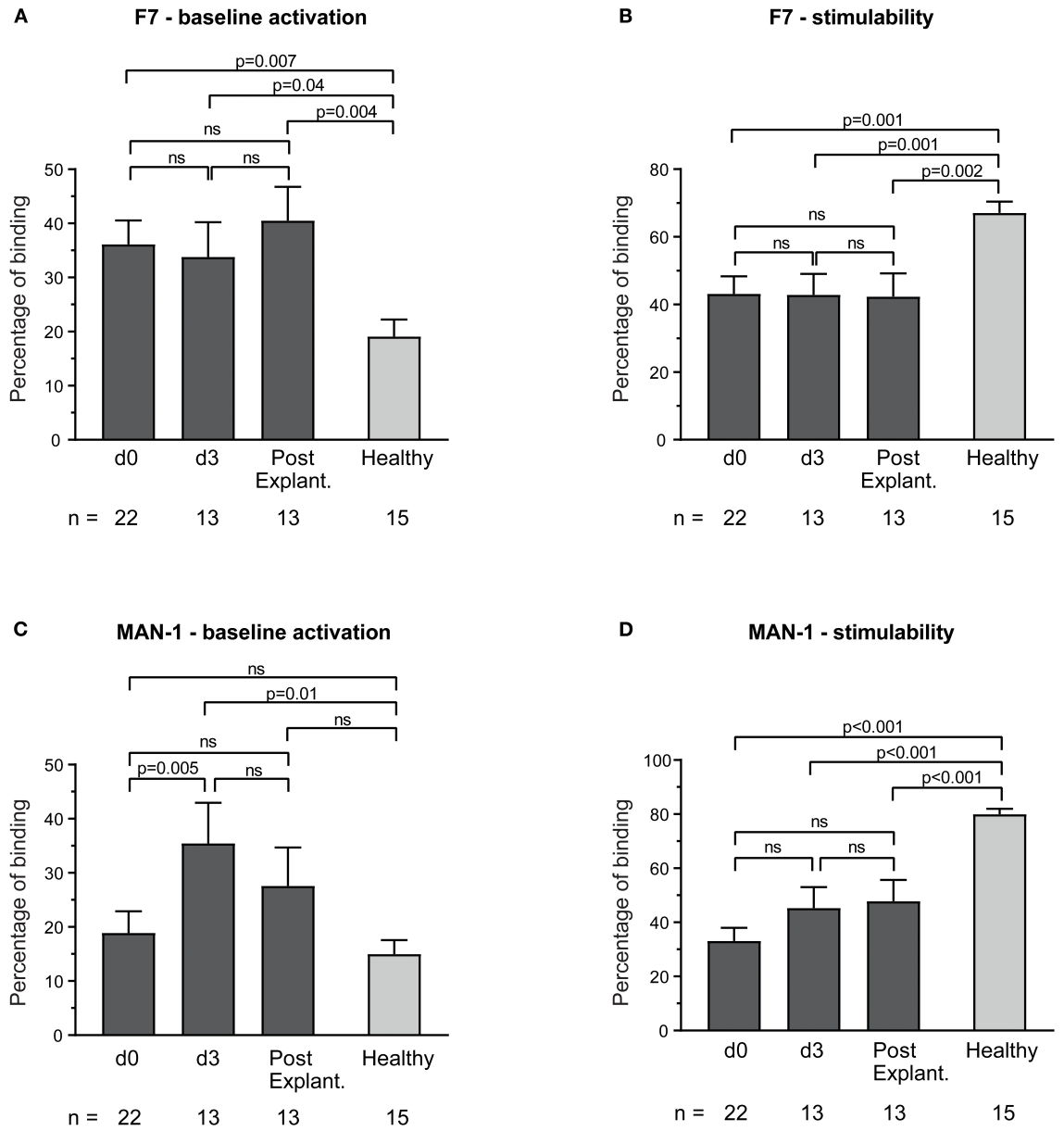


**FIGURE 1 |** Baseline monocyte activation and stimulability as determined by F7 binding **(A,B)** and MAN-1 **(C,D)**. The number of remaining patients analyzed at each time point during VA-ECMO therapy (d0, d3) and after explantation (post explant.) is presented below the individual bars. Baseline monocyte activation was measured in phosphate buffered saline treated samples. Stimulability was assessed in samples treated with phorbol 12-myristate 13-acetate to induce maximum monocyte activation. Binding of F7 and MAN-1 to $CD14^+$ monocytes is presented in percentage and was quantified as described in the Materials and Methods section. Mixed effects models were used to analyze differences between means across different time points (d0, d3, and post explantation vs. each other). Unpaired *t*-tests were used to analyze differences of means at single time points. ns, not significant. Data are presented as mean ± SEM.

controls: CD163: 39.4 ± 5.0 vs. 52.7 ± 6.5, $p = 0.11$, not significant, **Figures 2A,B**). Using CX3CR1 we found similar baseline monocyte activation in monocytes compared to healthy controls (e.g., percentage binding VA-ECMO day 0 vs. healthy controls: CX3CR1: 51.4 ± 5.4 vs. 51.8 ± 3.8, $p = 0.95$, not significant), but reduced stimulability (e.g., percentage binding VA-ECMO day 0 vs. healthy controls: CX3CR1: 39.6 ± 5.1 vs. 66.7 ± 5.2, $p < 0.001$, **Figures 2C,D**).

CD69 and CD86 surface expression on unstimulated monocytes in both healthy controls and VA-ECMO patients was low (**Figures 3A,C**). Although monocyte stimulability was preserved in healthy controls (**Supplementary Figure 1**), monocytes in VA-ECMO patients showed virtually no signs of stimulability (e.g., percentage binding VA-ECMO day 0 vs. healthy controls CD86: 0.7 ± 0.2 vs. 7.0 ± 2.1, $p = 0.001$, CD69: 0.7 ± 0.2 vs. 44.7 ± 5.8, $p < 0.001$, **Figures 3B,D**).

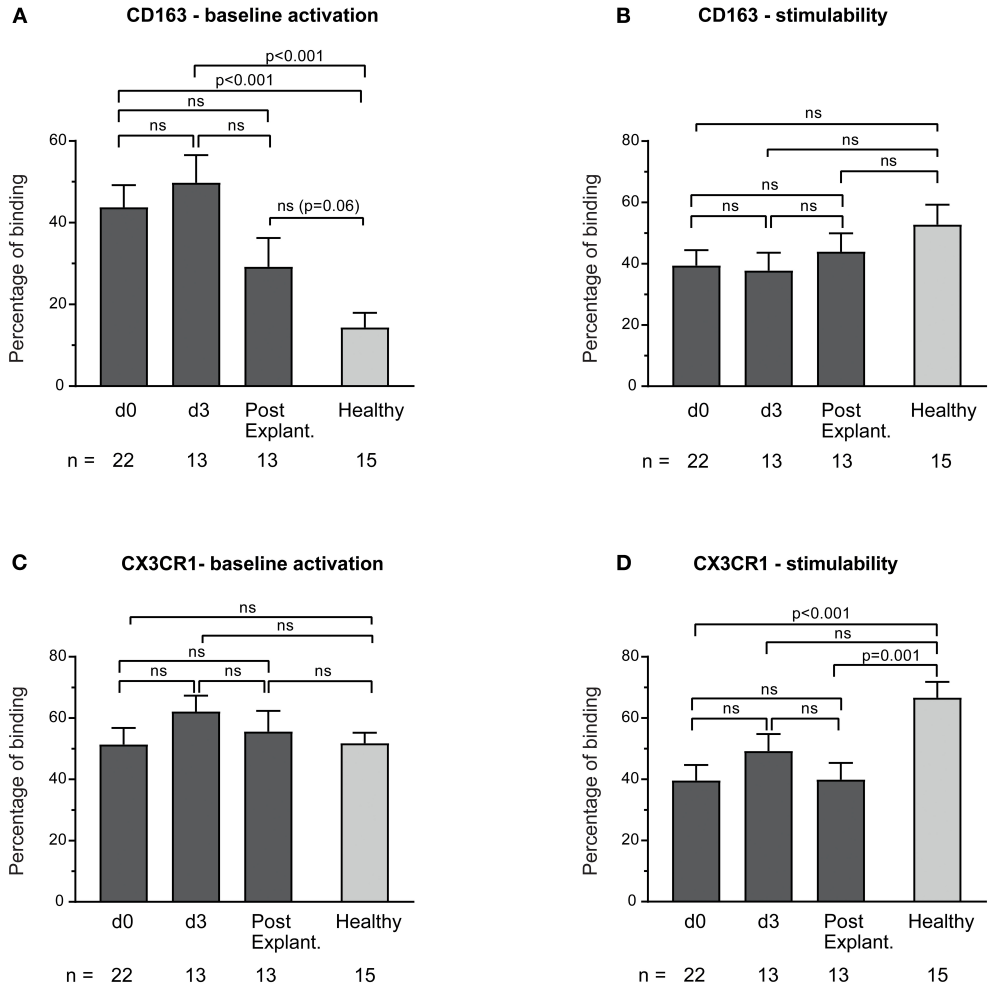


**FIGURE 2 |** Baseline monocyte activation and stimulability as determined by CD163 **(A,B)** and CX3CR1 **(C,D)** surface expression. The number of remaining patients analyzed at each time point during VA-ECMO therapy (d0, d3) and after explantation (post explant.) is presented below the individual bars. Baseline monocyte activation was measured in phosphate buffered saline treated samples. Stimulability was assessed in samples treated with phorbol 12-myristate 13-acetate to induce maximum monocyte activation. $CD14^+$ monocyte CD163 and CX3CR1 expression is presented in percentage and was quantified as described in the Materials and Methods section. Mixed effects models were used to analyze differences between means across different time points (d0, d3, and post explantation vs. each other). Unpaired *t*-tests were used to analyze differences of means at single time points. ns, not significant. Data are presented as mean ± SEM.

Baseline monocyte HLA-expression was significantly decreased in VA-ECMO patients, particularly on day 3 (MFI PerCP—Cy5.5 VA-ECMO day 3 vs. healthy controls: 1,852 ± 352.3 vs. 6,523 ± 939.7, $p < 0.001$, **Figure 4**).

The comparison of baseline activation and stimulability of monocytes at day 0 between survivors and non-survivors is presented in **Table 2**. Clinical characteristics and laboratory parameters of survivors and non-survivors are presented in **Supplementary Tables 1**, **2**. Baseline monocyte activation as determined by DARPin F7 was significantly decreased in non-survivors ($p = 0.03$). The area under the ROC curve for mortality was 0.802 ($p = 0.02$). Moreover, non-survivors also showed a clear trend toward reduced monocyte stimulability as determined by F7 ($p = 0.06$). The area under the ROC curve for mortality was 0.752 ($p = 0.05$). Other parameters, including MAN-1, did not show relevant differences in baseline monocyte activation or stimulability between survivors and non-survivors.

Markers of monocyte function on day 0 were also compared between patients receiving VA-ECMO due to cardiogenic shock and those receiving VA-ECMO due to eCPR (**Supplementary Table 3**). Clinical characteristics of these two groups are presented in **Supplementary Tables 4**, **5**. No significant differences regarding monocyte function were found between these groups.

Furthermore, monocyte heterogeneity in VA-ECMO patients according to the surface expression of CD14 and CD16 was investigated. Classical ($CD14^{++}CD16^-$), intermediate ($CD14^{++}CD16^+$), and non-classical monocytes ($CD14^+CD16^{++}$) were differentiated (**Figure 5**). We found shifts in the percentages of the three monocyte subsets during

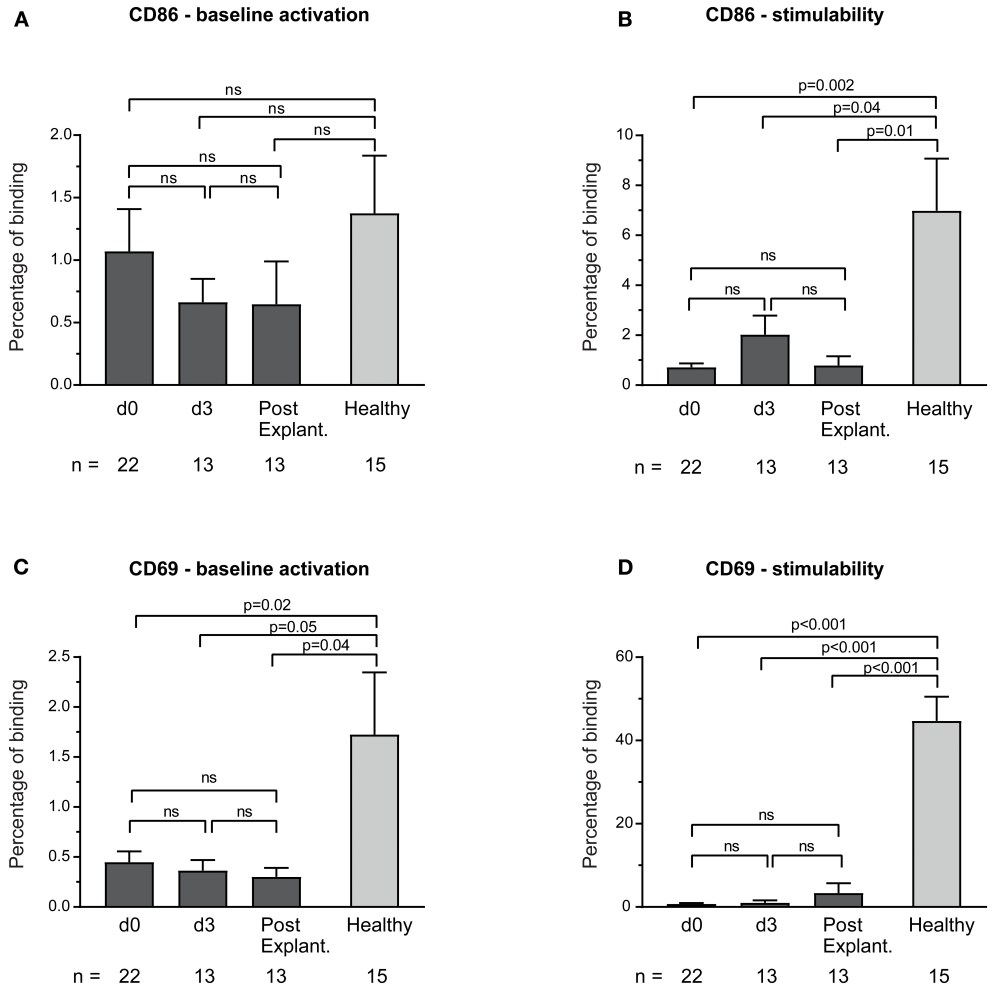


**FIGURE 3 |** Baseline monocyte activation and stimulability as determined by CD86 **(A,B)** and CD69 **(C,D)** surface expression. The number of remaining patients analyzed at each time point during VA-ECMO therapy (d0, d3) and after explantation (post explant.) is presented below the individual bars. Baseline monocyte activation was measured in phosphate buffered saline treated samples. Stimulability was assessed in samples treated with phorbol 12-myristate 13-acetate to induce maximum monocyte activation. $CD14^+$ monocyte CD69 and CD86 surface expression is presented in percentage and was quantified as described in the Materials and Methods section. ns, not significant. Baseline expression levels of CD86 and CD69 were low in healthy controls and patients. Mixed effects models were used to analyze differences between means across different time points (d0, d3, and post explantation vs. each other). Unpaired *t*-tests were used to analyze differences of means at single time points. Data are presented as mean ± SEM.

different days on ECMO and after weaning off ECMO. While there was a significant increase of classical monocytes from day 0 until after explantation (percentage of classical monocytes: day 0 vs. after explantation: 60.9 ± 3.5 vs. 70.7 ± 3.3, $p = 0.007$), intermediate monocytes decreased during this time (percentage of intermediate monocytes day 0 vs. after explantation: 17.6 ± 2.4 vs. 10.1 ± 1.3, $p = 0.02$). The percentage of non-classical monocytes in VA-ECMO patients did not significantly change at any time point. Compared to healthy controls, several differences in the distribution of monocyte populations were observed. For example, the percentage of classical monocytes was significantly increased after explantation (percentage of classical monocytes after explantation vs. healthy controls: 70.7 ± 3.3 vs. 59.0 ± 3.8, $p = 0.03$) and non-classical monocytes were significantly decreased on day 0 compared to healthy controls (percentage of non-classical monocytes day 0 vs. healthy controls: 5.4 ± 0.7 vs. 12.0 ± 2.9, $p = 0.01$).

Absolute monocyte counts of VA-ECMO patients did not significantly change during ECMO and after explantation. As expected, however, we found large differences compared to healthy controls (**Figure 6**). Total monocyte count on all days was significantly increased compared to healthy controls (e.g., total monocyte count/ml day 0 vs. healthy controls: 291,850 ± 56,218 vs. 137,180 ± 14,797, $p = 0.04$). Classical (except day 3) and intermediate monocytes counts were also significantly increased (monocyte count/ml day 0 vs. healthy controls: classical: 204,523 ± 37,798 vs. 94,126 ± 11,148, $p = 0.03$, intermediate: 70,386 ± 19,172 vs. 20,851 ± 3,482). Non-classical monocyte counts did not differ significantly from healthy monocytes.

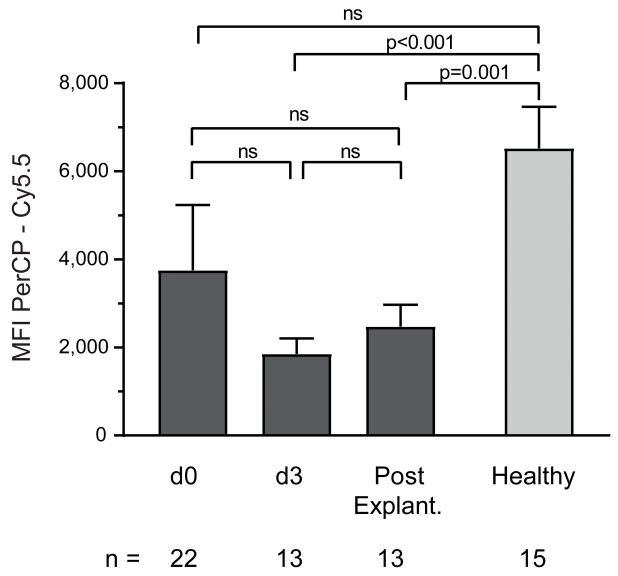


**FIGURE 4 |** Baseline monocyte HLA expression on $CD14^+$ monocytes. The number of remaining patients analyzed at each time point during VA-ECMO therapy (d0, d3) and after explantation (post explant.) is presented below the individual bars. HLA expression was quantified as the mean fluorescence intensity (MFI) in the PerCP—Cy5.5 channel and was measured in phosphate buffered saline treated samples as described in the Materials and Methods section. ns, not significant. Mixed effects models were used to analyze differences between means across different time points (d0, d3, and post explantation vs. each other). Unpaired *t*-tests were used to analyze differences of means at single time points. Data are presented as mean ± SEM.

**TABLE 2 |** Parameters of monocyte function and distribution in survivors vs. non-survivors on day 0.

| Parameter | Survivor | Non-survivor | *P*-value |
|---|---|---|---|
| F7 (–) [%] | 45.4 ± 5.7 | 26.9 ± 5.7 | **0.03** |
| MAN-1 (–) [%] | 22.0 ± 7.6 | 15.8 ± 2.7 | 0.45 |
| CD163 (–) [%] | 45.1 ± 7.7 | 42.5 ± 8.0 | 0.82 |
| CX3CR1 (–) [%] | 50.7 ± 8.4 | 52.1 ± 7.2 | 0.91 |
| CD69 (–) [%] | 0.3 ± 0.1 | 0.6 ± 0.2 | 0.06 |
| CD86 (–) [%] | 0.4 ± 0.1 | 1.1 ± 0.6 | 0.19 |
| HLA (–) [MFI] | 2058 ± 317 | 2289 ± 371 | 0.64 |
| F7 (+) [%] | 52.8 ± 7.6 | 33.4 ± 6.1 | 0.06 |
| MAN-1 (+) [%] | 39.3 ± 7.4 | 26.9 ± 6.1 | 0.21 |
| CD163 (+) [%] | 43.3 ± 7.8 | 35.5 ± 6.5 | 0.45 |
| CX3CR1 (+) [%] | 37.9 ± 7.5 | 41.3 ± 7.1 | 0.75 |
| CD69 (+) [%] | 1.0 ± 0.4 | 0.4 ± 0.1 | 0.20 |
| CD86 (+) [%] | 0.9 ± 0.3 | 0.9 ± 0.3 | 0.98 |
| Total monocytes/ml | 231,152 ± 42,618 | 352,547 ± 103,541 | 0.29 |
| Classical monocytes/ml | 151,932 ± 30,503 | 281,890 ± 85,492 | 0.15 |
| Intermediate monocytes/ml | 27,345 ± 6,394 | 119,940 ± 45,829 | **0.05** |
| Non-classical monocytes/ml | 13,761 ± 3,994 | 18,971 ± 5,620 | 0.45 |
| Classical monocytes [%] | 65.6 ± 3.9 | 56.2 ± 5.8 | 0.19 |
| Intermediate monocytes [%] | 14.7 ± 2.8 | 20.6 ± 3.7 | 0.22 |
| Non-classical Monocytes [%] | 5.9 ± 1.2 | 4.9 ± 0.9 | 0.47 |

*Baseline monocyte activation is indicated by (–), monocyte stimulability is indicated by (+). Survivors were defined as patients weaned off VA-ECMO and discharged from the intensive care ward. Monocyte activation was defined as described in the Materials and Methods section. p-values were calculated by an unpaired t-test. Significant p-values are written in bold. Data are presented as mean ± SEM. HLA, human leukocyte antigen; MFI, mean fluorescence intensity.*

Interestingly, we found significantly increased intermediate monocyte counts in non-survivors compared to survivors (**Table 2**). However, the area under the ROC curve for mortality was only 0.587 (not significant).

## DISCUSSION

Using several markers of monocyte function, our data show increased baseline monocyte activation and reduced monocyte stimulability in patients receiving VA-ECMO suggesting monocytes are *dysfunctional*. Amongst the different markers used to identify monocyte dysfunction, the *unique tool* DARPin F7 is the most promising as low levels of binding on day 0 were predictive of mortality.

A unifying characteristic of monocyte dysfunction in VA-ECMO patients was the reduced stimulability of monocytes which was observed for all markers except CD163. It is possible, that with a larger sample size a significant difference in stimulability could have also been observed for CD163. In contrast, increased baseline monocyte activation in VA-ECMO patients was detected using our *unique* activation-specific anti-Mac-1 binding proteins F7 and MAN-1 and the surface marker CD163. These findings need not be contradictory as these markers report different aspects of monocyte function that may differ and findings supporting both activation and immunocompromise have been previously described in a group of critically-ill septic patients (24).

Monocyte dysfunction as demonstrated in this study may be associated with a general *immunoparalysed state* in VA-ECMO patients. *Immunoparalysis* was recently reported in a heterogeneous group of adult and neonatal VV- and VA-ECMO patients based on findings of cytokine levels from LPS-stimulated whole blood (4).

Immunoparalysis in VA-ECMO patients is supported by several of our findings, such as decreased CX3CR1 expression in response to stimulation and reduced HLA-expression. Decreased expression of CX3CR1 was previously reported in severely septic patients and regarded as evidence of immunosuppression (25) while reduced monocyte HLA expression is often associated with immunoparalysis in critical illness, for example after cardiopulmonary bypass (26, 27). Moreover, our results show there was virtually a loss of CD86 and CD69 expression in response to stimulation in VA-ECMO patients possibly also reflecting immunoparalysis. While there is little information on monocyte CD69 expression in critically ill patients, a recent study found reduced monocyte CD86 stimulability to be associated with immunoparalysis in patients after cardiopulmonary bypass (28).

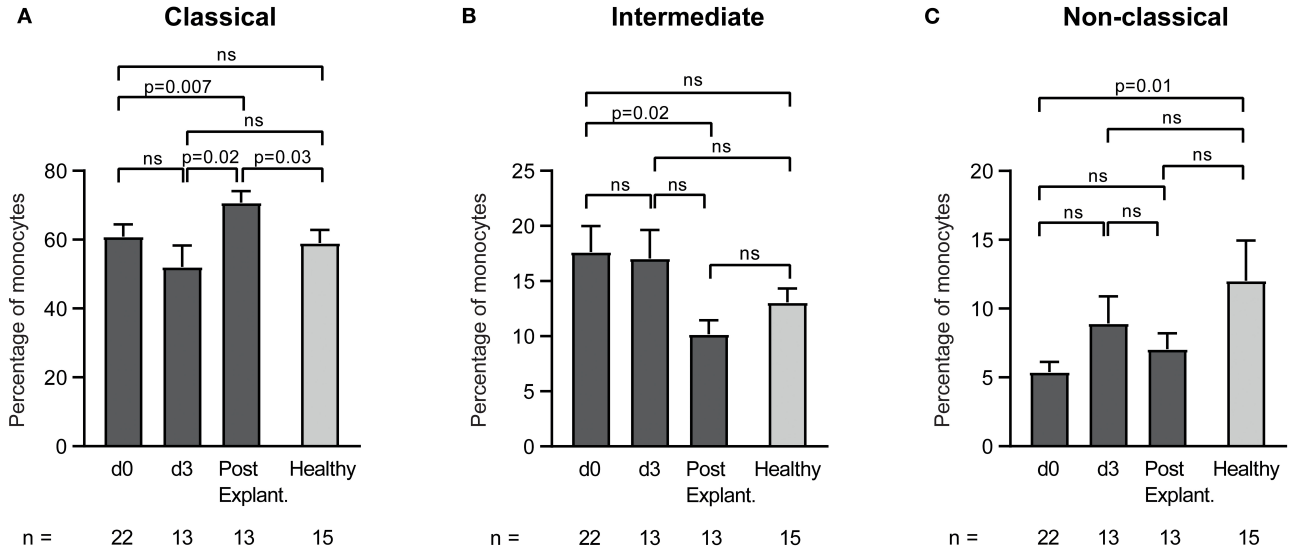


**FIGURE 5 |** Distribution of monocyte subsets in patients receiving veno-arterial extracorporeal membrane oxygenation on different days (d0, d3) and after explantation (post explant.) compared to healthy controls. The percentage of classical **(A)**, intermediate **(B)**, and non-classical **(C)** monocytes is presented. The number of remaining patients at every time point is indicated below. Data are presented as mean ± SEM. Mixed effects models were used to analyze differences between means across different time points (d0, d3, and post explantation vs. each other). Unpaired *t*-tests were used to analyze differences of means at single time points.

How the phenomenon of immunoparalysis develops in VA-ECMO patients is not clear, but most likely it is caused by a combination of factors, e.g., the large extracorporeal surfaces triggering immune cell activation and the severe underlying illness leading to ECMO therapy (29).

Importantly, immunoparalysis has been claimed to be associated with worse outcomes in critically ill patients, particularly in sepsis (30, 31) and recently, Combes et al. claimed that it might also be associated with worse outcomes in ECMO patients (32).

Our data is in line with these findings as monocyte dysfunction determined by the *unique tool* F7 was related to mortality. Baseline binding of F7 to monocytes from VA-ECMO patients on day 0 was significantly lower in non-survivors indicating more severe monocyte dysfunction. Logistic regression and analysis of area under the ROC curve demonstrated that low binding of F7 on day 0 was predictive of increased mortality. To the best of our knowledge, we are the first group to demonstrate this link between monocyte dysfunction in VA-ECMO patients and mortality. Therefore, in the future, monocyte dysfunction detected by F7 may be used as a novel *biomarker* guiding early clinical decision making.

Our results are supported by a previous study on septic patients in which low monocytic Mac-1 expression, as determined by a conventional anti-Mac-1 IgG antibody, was associated with poor outcome and an anti-inflammatory response syndrome which is commonly seen as an early stage of immunoparalysis (33). Analyzing monocytic Mac-1 expression and conformation is therefore well-suited to detect monocyte activation, -dysfunction and immunoparalysis in critically ill patients as it translates into clinical outcome.

Although F7 and MAN-1 both bind to the activated conformation of Mac-1, they do not share the same epitope and could be detecting slightly different conformational states of Mac-1. This could explain why increased baseline monocyte activation was detected at all time points by F7, but only on day 3 by MAN-1. In clinical practice, DARPin F7 may be advantageous compared to conventional anti-Mac-1 antibodies and even MAN-1 due to its inherently high sensitivity and stability, low cost, and ease of production (34).

To the best of our knowledge, this is the first study to investigate the distribution of monocyte subsets in VA-ECMO patients. We report significant changes in the proportion of classical and intermediate monocytes in patients on VA-ECMO compared to after ECMO explantation. In addition, we show increased total, classical, and intermediate absolute monocyte counts in patients receiving VA-ECMO and after explantation compared to healthy controls. Classical and intermediate monocytes are now widely recognized as pro-inflammatory mediators (35) and proportional changes could reflect the inflammatory reaction to VA-ECMO.

As we focused our study on monocytes, we cannot exclude that other leukocyte subsets were also increased. This is possible, given the inflammatory reaction in these patients but the median total white blood cell count on day 0 determined using automated cell counting in our central laboratory was within the upper normal range. This is in line with previous reports of lymphopenia, reduced or only stable neutrophil counts in ECMO patients (36) and emphasizes the finding of increased absolute monocyte counts in our study which could reflect the importance of monocytes for the inflammatory reaction and outcome in VA-ECMO patients. In this context, intermediate monocytes were

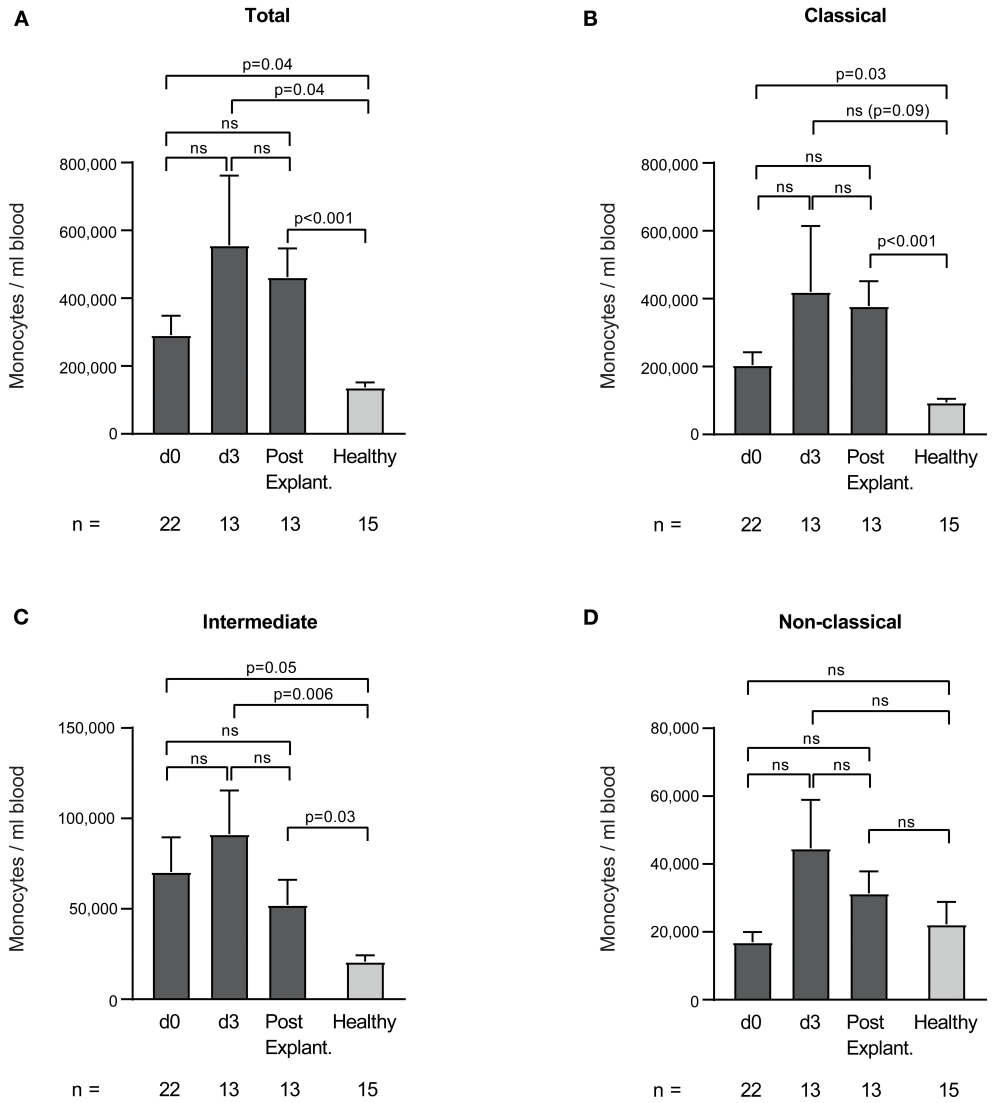


**FIGURE 6 |** Total **(A)**, classical **(B)**, intermediate **(C)**, and non-classical **(D)** monocyte counts per ml blood in patients receiving veno-arterial extracorporeal membrane oxygenation on different days (d0, d3) and after explantation (post explant.) compared to healthy controls. The number of remaining patients at every time point is indicated below. Data are presented as mean ± SEM. Mixed effects models were used to analyze differences between means across different time points (d0, d3, and post explantation vs. each other). Unpaired *t*-tests were used to analyze differences of means at single time points.

significantly increased in non-survivors indicating a possible detrimental role of this monocyte subset. Our data is in line with a study reporting increased levels of intermediate monocytes in patients with poor outcome after cardiac surgery (37). Further studies, however, are required to characterize the functional role of the different monocyte subsets in VA-ECMO patients in detail.

This study is not without limitations. Since it did not include a pre-ECMO time point the direct effect of ECMO initiation on monocyte function cannot be clearly determined. As this was an exploratory study, we used healthy, unmatched controls as a control group and therefore some of the results may have been influenced by the underlying disease. For example, since previous studies of septic shock and post cardiopulmonary bypass found monocyte dysfunction to be associated with immunocompromise, monocyte dysfunction in this study may be indicative of shock severity rather than use of VA-ECMO itself. Future studies would benefit from larger sample sizes and more suitable controls, such as patients with cardiogenic shock without ECMO support. Since all patients received transfusions in this study, we cannot exclude results were affected. Moreover, as this study only included a relatively small number of ECMO patients, it cannot be excluded that different ECMO circuits affected results.

## CONCLUSION

Monocytes from VA-ECMO patients are dysfunctional as baseline monocyte activation is significantly increased but monocyte stimulability is decreased. Distribution of monocyte subsets changes in patients receiving VA-ECMO over time and absolute classical and intermediate monocyte counts are significantly elevated compared to controls. Monocyte dysfunction, as determined by the *unique tool* DARPin F7 could be valuable for predicting mortality in patients receiving VA-ECMO and may be used as a novel biomarker guiding early clinical decision making in the future. Monocyte dysfunction, as demonstrated in this study for VA-ECMO patients, has been previously associated with immunocompromise in patients with septic and post-cardiotomy shock. Clinicians may therefore evaluate a lower threshold to initiate antimicrobial therapy in patients with cardiogenic shock severe enough to require VA-ECMO.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Freiburg. The patients or their legal representatives provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

PS: study design, acquisition, analysis and interpretation of data, preparation of manuscript. LO: acquisition and analysis of data. IB and MM: analysis and interpretation of data. KK: statistical counseling, analysis of data, and preparation of manuscript. TW and JE: data analysis, interpretation and preparation of manuscript. GT and CB: study design and interpretation of data. KP: study design, analysis and interpretation of data. PD: study design, analysis and interpretation of data, preparation of manuscript. All authors proof-read and accepted the final draft of the manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.689218/full#supplementary-material

## REFERENCES

1. Thiagarajan RR, Barbaro RP, Rycus PT, McMullan DM, Conrad SA, Fortenberry JD, et al. Extracorporeal life support organization registry international report 2016. *ASAIO J.* (2017) 63:60–7. doi: 10.1097/MAT.0000000000000475
2. Acharya D, Torabi M, Borgstrom M, Rajapreyar I, Lee K, Kern K, et al. Extracorporeal membrane oxygenation in myocardial infarction complicated by cardiogenic shock. *J Am Coll Cardiol.* (2020) 76:1001–2. doi: 10.1016/j.jacc.2020.06.062
3. Millar JE, Fanning JP, McDonald CI, McAuley DF, Fraser JF. The inflammatory response to extracorporeal membrane oxygenation (ECMO): a review of the pathophysiology. *Crit Care.* (2016) 20:387. doi: 10.1186/s13054-016-1570-4
4. Beshish AG, Bradley JD, McDonough KL, Halligan NLN, McHugh WM, Sturza J, et al. The functional immune response of patients on extracorporeal life support. *ASAIO J.* (2019) 65:77–83. doi: 10.1097/MAT.0000000000000748
5. Frerou A, Lesouhaitier M, Gregoire M, Uhel F, Gacouin A, Reizine F, et al. Venoarterial extracorporeal membrane oxygenation induces early immune alterations. *Crit Care.* (2021) 25:9. doi: 10.1186/s13054-020-03444-x
6. Shi C, Pamer EG. Monocyte recruitment during infection and inflammation. *Nat Rev Immunol.* (2011) 11:762–74. doi: 10.1038/nri3070
7. Inoue T, Sakai Y, Morooka S, Hayashi T, Takayanagi K, Takabatake Y. Expression of polymorphonuclear leukocyte adhesion molecules and its clinical significance in patients treated with percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol.* (1996) 28:1127–33. doi: 10.1016/S0735-1097(96)00308-7
8. Inwald DP, Kirkham FJ, Peters MJ, Lane R, Wade A, Evans JP, et al. Platelet and leucocyte activation in childhood sickle cell disease: association with nocturnal hypoxaemia. *Br J Haematol.* (2000) 111:474–81. doi: 10.1046/j.1365-2141.2000.02353.x
9. Gerhardt T, Ley K. Monocyte trafficking across the vessel wall. *Cardiovasc Res.* (2015) 107:321–30. doi: 10.1093/cvr/cvv147
10. Etzerodt A, Moestrup SK. CD163 and inflammation: biological, diagnostic, and therapeutic aspects. *Antioxid Redox Signal.* (2013) 18:2352–63. doi: 10.1089/ars.2012.4834
11. Goodale D, Phay C, Brown W, Gray-Statchuk L, Furlong P, Lock M, et al. Flow cytometric assessment of monocyte activation markers and circulating endothelial cells in patients with localized or metastatic breast cancer. *Cytometry B Clin Cytom.* (2009) 76B:107–17. doi: 10.1002/cyto.b.20449

12. Fleischer J, Soeth E, Reiling N, Grage-Griebenow E, Flad HD, Ernst M. Differential expression and function of CD80 (B7-1) and CD86 (B7-2) on human peripheral blood monocytes. *Immunology.* (1996) 89:592–8. doi: 10.1046/j.1365-2567.1996.d01-785.x
13. Durbin AP, Vargas MJ, Wanionek K, Hammond SN, Gordon A, Rocha C, et al. Phenotyping of peripheral blood mononuclear cells during acute dengue illness demonstrates infection and increased activation of monocytes in severe cases compared to classic dengue fever. *Virology.* (2008) 376:429–35. doi: 10.1016/j.virol.2008.03.028
14. Kusdra L, Rempel H, Yaffe K, Pulliam L. Elevation of CD69+Monocyte/Macrophages in patients with Alzheimer's disease. *Immunobiology.* (2000) 202:26–33. doi: 10.1016/S0171-2985(00)80049-2
15. Heron M, Grutters JC, van Velzen-Blad H, Veltkamp M, Claessen AME, van den Bosch JMM. Increased expression of CD16, CD69, and very late Antigen-1 on blood monocytes in active sarcoidosis. *Chest.* (2008) 134:1001–8. doi: 10.1378/chest.08-0443
16. Westhorpe CLV, Maisa A, Spelman T, Hoy JF, Dewar EM, Karapanagiotidis S, et al. Associations between surface markers on blood monocytes and carotid atherosclerosis in HIV-positive individuals. *Immunol Cell Biol.* (2014) 92:133–8. doi: 10.1038/icb.2013.84
17. Muller Kobold AC, Kallenberg CG, Tervaert JW. Monocyte activation in patients with Wegener's granulomatosis. *Ann Rheum Dis.* (1999) 58:237–45. doi: 10.1136/ard.58.4.237
18. Laudanna C, Kim JY, Constantin G, Butcher EC. Rapid leukocyte integrin activation by chemokines. *Immunol Rev.* (2002) 186:37–46. doi: 10.1034/j.1600-065X.2002.18604.x
19. Eisenhardt SU, Schwarz M, Schallner N, Soosairajah J, Bassler N, Huang D, et al. Generation of activation-specific human anti-alphaMbeta2 single-chain antibodies as potential diagnostic tools and therapeutic agents. *Blood.* (2007) 109:3521–8. doi: 10.1182/blood-2006-03-007179
20. Stumpp MT, Amstutz P. DARPins: a true alternative to antibodies. *Curr Opin Drug Discov Devel.* (2007) 10:153–9.
21. Siegel PM, Bojti I, Bassler N, Holien J, Flierl U, Wang X, et al. A DARPin targeting activated Mac-1 is a novel diagnostic tool and potential anti-inflammatory agent in myocarditis, sepsis and myocardial infarction. *Basic Res Cardiol.* (2021) 116:17. doi: 10.1007/s00395-021-00849-9
22. Staudacher DL, Gold W, Biever PM, Bode C, Wengenmayer T. Early fluid resuscitation and volume therapy in venoarterial extracorporeal membrane oxygenation. *J Crit Care.* (2017) 37:130–5. doi: 10.1016/j.jcrc.2016.09.017
23. Marimuthu R, Francis H, Dervish S, Li SCH, Medbury H, Williams H. Characterization of human monocyte subsets by whole blood flow cytometry analysis. *J Vis Exp.* (2018) 57941. doi: 10.3791/57941
24. Cheng S-C, Scicluna BP, Arts RJW, Gresnigt MS, Lachmandas E, Giamarellos-Bourboulis EJ, et al. Broad defects in the energy metabolism of leukocytes underlie immunoparalysis in sepsis. *Nat Immunol.* (2016) 17:406–13. doi: 10.1038/ni.3398
25. Pachot A, Cazalis M-A, Venet F, Turrel F, Faudot C, Voirin N, et al. Decreased expression of the Fractalkine receptor CX3CR1 on circulating monocytes as new feature of sepsis-induced immunosuppression. *J Immunol.* (2008) 180:6421. doi: 10.4049/jimmunol.180.9.6421
26. Chenouard A, Rimbert M, Joram N, Braudeau C, Roquilly A, Bourgoin P, et al. Monocytic human leukocyte antigen DR expression in young infants undergoing cardiopulmonary bypass. *Ann Thorac Surg.* (2020) 111:P1636–42. doi: 10.1016/j.athoracsur.2020.05.071
27. Döcke W-D, Höflich C, Davis KA, Röttgers K, Meisel C, Kiefer P, et al. Monitoring temporary immunodepression by flow cytometric measurement of monocytic HLA-DR expression: a multicenter standardized study. *Clin Chem.* (2005) 51:2341–7. doi: 10.1373/clinchem.2005.052639
28. Perros AJ, Esguerra-Lallen A, Rooks K, Chong F, Engkilde-Pedersen S, Faddy HM, et al. Coronary artery bypass grafting is associated with immunoparalysis of monocytes and dendritic cells. *J Cell Mol Med.* (2020) 24:4791–803. doi: 10.1111/jcmm.15154
29. Al-Fares A, Pettenuzzo T, Del Sorbo L. Extracorporeal life support and systemic inflammation. *Intensive Care Med Exp.* (2019) 7:46. doi: 10.1186/s40635-019-0249-y
30. Drewry AM, Ablordeppey EA, Murray ET, Beiter ER, Walton AH, Hall MW, et al. Comparison of monocyte human leukocyte antigen-DR expression and stimulated tumor necrosis factor alpha production as outcome predictors in severe sepsis: a prospective observational study. *Crit Care.* (2016) 20:334. doi: 10.1186/s13054-016-1505-0
31. Muszynski JA, Thakkar R, Hall MW. Inflammation and innate immune function in critical illness. *Curr Opin Pediatr.* (2016) 28:267–73. doi: 10.1097/MOP.0000000000000352
32. Combes A, Brodie D, Chen YS, Fan E, Henriques JPS, Hodgson C, et al. The ICM research agenda on extracorporeal life support. *Intensive Care Med.* (2017) 43:1306–18. doi: 10.1007/s00134-017-4803-3
33. Muller Kobold AC, Tulleken JE, Zijlstra JG, Sluiter W, Hermans J, Kallenberg CGM, et al. Leukocyte activation in sepsis; correlations with disease state and mortality. *Intensive Care Med.* (2000) 26:883–92. doi: 10.1007/s001340051277
34. Pluckthun A. Designed ankyrin repeat proteins (DARPins): binding proteins for research, diagnostics, and therapy. *Annu Rev Pharmacol Toxicol.* (2015) 55:489–511. doi: 10.1146/annurev-pharmtox-010611-134654
35. Stansfield BK, Ingram DA. Clinical significance of monocyte heterogeneity. *Clin Transl Med.* (2015) 4:5. doi: 10.1186/s40169-014-0040-3
36. Ki KK, Millar JE, Langguth D, Passmore MR, McDonald CI, Shekar K, et al. Current understanding of leukocyte phenotypic and functional modulation during extracorporeal membrane oxygenation: a narrative review. *Front Immunol.* (2021) 11:600684. doi: 10.3389/fimmu.2020.600684
37. Mossanen JC, Jansen TU, Pracht J, Liepelt A, Buendgens L, Stoppe C, et al. Elevated circulating CD14++CD16+ intermediate monocytes are independently associated with extracardiac complications after cardiac surgery. *Sci Rep.* (2020) 10:947. doi: 10.1038/s41598-020-57700-9


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# Impact of Age on Outcomes in Patients With Cardiogenic Shock

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**Background:** Advanced age is associated with poor outcomes in cardiovascular emergencies. We sought to determine the association of age, use of support devices and shock severity on mortality in cardiogenic shock (CS).

**Methods:** Characteristics and outcomes in CS patients included in the Cardiogenic Shock Work Group (CSWG) registry from 8 US sites between 2016 and 2019 were retrospectively reviewed. Patients were subdivided by age into quintiles and Society for Cardiovascular Angiography & Interventions (SCAI) shock severity.

**Results:** We reviewed 1,412 CS patients with a mean age of 59.9 ± 14.8 years, including 273 patients > 73 years of age. Older patients had significantly higher comorbidity burden including diabetes, hypertension and coronary artery disease. Veno-arterial extracorporeal membrane oxygenation was used in 332 (23%) patients, Impella in 410 (29%) and intra-aortic balloon pump in 770 (54%) patients. Overall in-hospital survival was 69%, which incrementally decreased with advancing age ($p < 0.001$). Higher age was associated with higher mortality across all SCAI stages ($p = 0.003$ for SCAI stage C; $p < 0.001$ for SCAI stage D; $p = 0.005$ for SCAI stage E), regardless of etiology ($p < 0.001$).

**Conclusion:** Increasing age is associated with higher in-hospital mortality in CS across all stages of shock severity. Hence, in addition to other comorbidities, increasing age should be prioritized during patient selection for device support in CS.

**Keywords: cardiogenic shock, age, mortality, mechanical circulatory support, outcome**

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## INTRODUCTION

Cardiogenic shock (CS) is associated with high in-hospital mortality despite increasing use of temporary mechanical circulatory support devices (t-MCS) (1–3). Outcomes in CS depend on multiple factors including patient characteristics, hemo-metabolic profile and severity of CS on presentation. Although there is lack of high-quality randomized evidence to support their use in CS, t-MCS devices are increasingly available and patients previously considered too high-risk are now being supported with these devices (4, 5).

Age is a known, non-modifiable risk factor for mortality in patients with CS (6). Most of the published CS literature, including clinical trials has focused on shock resulting from acute myocardial infarction (AMI) (7–9). While the durable left ventricular assist device literature has extensively investigated outcomes in older patients, there remains a paucity of literature involving the use of t-MCS in this age-group (10, 11). The decision to place an older patient on t-MCS needs to consider their baseline functional status, comorbidities, physiological reserve and goals of care in a heightened fashion (12, 13). Since these are not well-studied, programs often choose somewhat arbitrary upper age limits for t-MCS use for CS patients at their sites (6).

With the introduction of the Society for Cardiovascular Angiography and Intervention (SCAI) CS stages, patients can now be classified consistently based on their severity of shock (14, 15). Recent reports have noted that older patients with CS have lower short-term survival, despite similar shock severity (16). We sought to describe the relationships between age, SCAI stage, use of temporary MCS and mortality risk in patients with CS included in the Cardiogenic Shock Work Group (CSWG).

# METHODS

## Data Source

The CSWG is an academic research consortium with a national registry initiated in 2016 with 20 clinical sites across the United States contributing CS patient data. These sites include community and university hospitals with registry inclusion dependent on a minimum of 100 CS patients per year. For this analysis, CS patients at the first 8 sites contributing registry data between 2016 and 2019 were included. The registry includes a standardized set of data elements (patient, procedural, and outcomes) which were pre-defined by principal investigators and collected retrospectively. Patient demographic, laboratory and hemodynamic data were collected at a single time point as close to admission as possible, prior to t-MCS (i.e., intra-aortic balloon pump [IABP], Impella, veno-arterial extra corporeal membrane oxygenation [VA-ECMO], or extracorporeal centrifugal flow pumps) initiation. CS diagnosis was physician-adjudicated at each site and defined as a sustained episode of one out of the following: systolic blood pressure $< 90$ mmHg for at least 30 min/use of vasoactive agents/a cardiac index (CI) $<2.2$ L/min/m$^2$ in the absence of hypovolemia, determined to be secondary to cardiac dysfunction or use of an t-MCS device for clinically-suspected CS. Treatments for CS were left to the discretion of the clinicians at each center and were not guided by a prescribed algorithm. Quality assurance was achieved through adjudication at each site by the respective clinical coordinators and principal investigator. Values were centrally audited and screened by the CSWG research team for any discrepancies or major outliers and resolved with submitting site.

**Abbreviations:** t-MCS, temporary mechanical circulatory support; CS, cardiogenic shock; SCAI, Society for Cardiovascular Angiography & Interventions; MI, myocardial infarction; VA-EMCO, Veno-arterial extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; HF, heart failure.

## Study Population

Between 2016 and 2019, data from 1,565 CS patients were collected. CS etiology was reported by each site as due to AMI, acute decompensated heart failure (ADHF), or other. AMI was defined as any primary diagnosis of either non-ST-segment elevation or ST-segment elevation AMI. ADHF was defined as any primary diagnosis of acute on chronic HF, not otherwise related to AMI. Other causes included post-cardiotomy, myocarditis, or not otherwise specified CS. We excluded patients under 18 years old ($n = 1$, 0.06%) and those with unknown in-hospital mortality status ($n = 150$, 9.6%) leaving a study population of 1,414 CS patients from 8 hospitals for analysis.

We then employed the recently published SCAI CS staging system to stratify this cohort by SCAI stage as we have previously described (15). SCAI Stage A patients are those at risk for CS and were therefore not captured in our study population. Stage B patients are those exhibiting early symptoms not including hypoperfusion and therefore do not require vasoactive medications or MCS. Stage C patients include those with hypotension and hypoperfusion requiring intervention beyond volume resuscitation including those requiring either one vasopressor/inotrope or one MCS device. Stage D patients are those whose condition deteriorates despite initial intervention, defined in our dataset by the need for multiple drugs or MCS devices. Finally, Stage E patients are those who deteriorate further and require maximal support, defined in our dataset as requiring at least two MCS devices and two drugs during their hospitalization. Patients requiring CPR on admission were included in Stage E.

## Statistical Analysis

Patients were divided into the following age quintile groups: age <49 years, 49–58, 59–65, 66–72, and >73 years. Quintiles were generated to ensure similar representation of number of patients for each decade of patient age. The primary outcome of interest was survival during index admission, determined using chart review. Continuous characteristics of each age cohort are displayed as means with standard deviations and *p*-values reported from ANOVAs. Categorical variables were expressed as frequency and percent and compared using chi-square tests of independence. Missing values were excluded where noted. To determine the impact of age on in-patient mortality, we ran a multivariable logistic regression adjusting for several potential confounders including gender, weight, history of hypertension (HTN), etiology of CS, systolic blood pressure, SCAI stage, renal function and cardiac power output. Results are reports as adjusted odds ratios with 95% confidence intervals. An alpha level of 0.05 was used to determine statistical significance throughout the entire analysis. All statistical analysis was performed using SAS 9.

# RESULTS

## Study Population

Data from 1,412 CS patients from 8 clinical sites were analyzed. Baseline characteristics are summarized in **Table 1**. Of the study

**TABLE 1 |** Baseline characteristics for patients in cardiogenic shock, at the time of presentation, separated into quintiles by age.

| | **All (*N* = 1,412)** | | **Age quintiles** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | **< 49 (*N* = 284)** | | **49–58 (*N* = 319)** | | **59–65 (*N* = 268)** | | **66–72 (*N* = 271)** | | **73+ (*N* = 270)** | | ***p*-value** |
| | ***N*** | **(%)** | ***N*** | **(%)** | ***N*** | **(%)** | ***N*** | **(%)** | ***N*** | **(%)** | ***N*** | **(%)** | |
| Cause of shock | | | | | | | | | | | | | <0.001 |
| Myocardial infarction | 493 | 34.92 | 52 | 18.31 | 100 | 31.35 | 91 | 33.96 | 107 | 39.48 | 143 | 52.96 | |
| Heart failure | 712 | 50.42 | 165 | 58.1 | 168 | 52.66 | 152 | 56.72 | 133 | 49.08 | 94 | 34.81 | |
| Other | 177 | 12.54 | 61 | 21.48 | 43 | 13.48 | 22 | 8.21 | 25 | 9.23 | 26 | 9.63 | |
| Unknown | 30 | 2.12 | 6 | 2.11 | 8 | 2.51 | 3 | 1.12 | 6 | 2.21 | 7 | 2.59 | |
| **Demographics** | | | | | | | | | | | | | |
| Male | 1,025 | 72.59 | 201 | 70.77 | 247 | 77.43 | 204 | 76.12 | 193 | 71.22 | 180 | 66.67 | 0.03 |
| Race | | | | | | | | | | | | | 0.002 |
| White | 647 | 45.82 | 124 | 43.66 | 151 | 47.34 | 127 | 47.39 | 125 | 46.13 | 120 | 44.44 | |
| Hispanic/Latino | 31 | 2.2 | 8 | 2.82 | 11 | 3.45 | 3 | 1.12 | 4 | 1.48 | 5 | 1.85 | |
| African-American | 28 | 1.98 | 9 | 3.17 | 5 | 1.57 | 2 | 0.75 | 8 | 2.95 | 4 | 1.48 | |
| Asian | 31 | 2.2 | 6 | 2.11 | 5 | 1.57 | 7 | 2.61 | 6 | 2.21 | 7 | 2.59 | |
| Unknown | 593 | 42 | 103 | 36.27 | 133 | 41.69 | 113 | 42.16 | 117 | 43.17 | 127 | 47.04 | |
| **Medical history*** | | | | | | | | | | | | | |
| Hypertension | 681 | 53.54 | 79 | 30.27 | 117 | 41.2 | 143 | 57.66 | 154 | 64.17 | 188 | 78.66 | <0.001 |
| Diabetes | 489 | 34.88 | 56 | 19.79 | 101 | 31.86 | 103 | 38.58 | 117 | 43.82 | 112 | 41.79 | <0.001 |
| A-fibrillation | 296 | 29.16 | 36 | 15.65 | 62 | 27.31 | 74 | 36.27 | 68 | 36.36 | 56 | 33.53 | <0.001 |
| CKD | 323 | 27.17 | 41 | 16.73 | 61 | 23.74 | 65 | 28.14 | 81 | 36 | 75 | 32.47 | <0.001 |
| PVD | 60 | 5.82 | 1 | 0.47 | 5 | 2.21 | 14 | 7.07 | 15 | 7.69 | 25 | 12.5 | <0.001 |
| COPD | 101 | 7.97 | 8 | 3.1 | 17 | 6.03 | 23 | 9.31 | 32 | 13.28 | 21 | 8.79 | <0.001 |
| CVA/TIA | 159 | 12.92 | 22 | 8.73 | 22 | 8.06 | 33 | 13.58 | 39 | 16.96 | 43 | 18.45 | <0.001 |
| Valvular Ds. | 214 | 22.55 | 39 | 18.93 | 45 | 21.33 | 41 | 21.58 | 44 | 24.72 | 45 | 27.44 | 0.34 |
| Prior PCI | 293 | 29.9 | 35 | 16.75 | 65 | 28.51 | 66 | 34.92 | 70 | 38.04 | 57 | 33.53 | <0.001 |
| Prior CABG | 114 | 10.12 | 10 | 4.59 | 12 | 4.76 | 27 | 12.86 | 37 | 17.13 | 28 | 12.12 | <0.001 |
| VT | 216 | 21.2 | 44 | 19.05 | 54 | 23.68 | 57 | 27.94 | 45 | 23.81 | 16 | 9.58 | <0.001 |
| ICD | 329 | 32.8 | 79 | 34.65 | 90 | 40.36 | 75 | 37.31 | 65 | 34.95 | 20 | 12.12 | <0.001 |
| | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | |
| AST | 459.41 | 1492.57 | 475.5 | 1504.46 | 518.83 | 1498.7 | 461.42 | 1793.04 | 581.01 | 1729.93 | 230.18 | 532.79 | 0.33 |
| BUN | 32.38 | 20.47 | 25.71 | 15.35 | 33.3 | 21.44 | 31.54 | 18.64 | 37.28 | 23.94 | 34.71 | 20.5 | <0.001 |
| Lactate | 4.37 | 4.21 | 4.64 | 4.17 | 4.48 | 4.73 | 4.2 | 3.93 | 4.11 | 3.86 | 4.41 | 4.28 | 0.85 |
| $HCO_3$ | 22.12 | 5.45 | 22.92 | 5.53 | 22.06 | 5.77 | 22.1 | 5.63 | 22.06 | 5.1 | 21.45 | 5.08 | 0.18 |
| Serum creatinine | 1.76 | 1.14 | 1.61 | 1.26 | 1.69 | 0.96 | 1.76 | 1.11 | 1.97 | 1.25 | 1.8 | 1.09 | <0.001 |
| pH | 7.31 | 0.15 | 7.3 | 0.17 | 7.29 | 0.14 | 7.3 | 0.15 | 7.32 | 0.15 | 7.33 | 0.13 | 0.28 |
| Admission EF (%) | 24.94 | 15.53 | 22.73 | 16.48 | 21.5 | 13.57 | 21.54 | 12.93 | 25.19 | 14.83 | 32.6 | 16.79 | <0.001 |
| RAP | 14.19 | 6.93 | 13.49 | 6.54 | 14.63 | 7.32 | 14.24 | 7.32 | 14.27 | 7.27 | 14.35 | 5.95 | 0.49 |
| PCWP | 24.5 | 8.9 | 23.7 | 9.03 | 24.31 | 8.55 | 25.13 | 9.36 | 24.67 | 9.13 | 24.87 | 8.41 | 0.61 |
| Mean PAP | 32.73 | 9.86 | 32.66 | 10.21 | 32.48 | 9.7 | 32.85 | 10.21 | 33.21 | 10.01 | 32.51 | 9.12 | 0.94 |
| CPO | 0.63 | 0.41 | 0.69 | 0.57 | 0.65 | 0.36 | 0.62 | 0.44 | 0.63 | 0.36 | 0.55 | 0.21 | 0.02 |
| Heart rate | 92.02 | 22.72 | 99.11 | 25.54 | 93.05 | 20.64 | 91.79 | 21.7 | 89.74 | 21.67 | 85.42 | 21.7 | <0.001 |
| Cardiac index | 1.85 | 0.59 | 1.89 | 0.66 | 1.82 | 0.53 | 1.84 | 0.56 | 1.86 | 0.6 | 1.84 | 0.61 | 0.72 |
| MAP | 74.56 | 14.75 | 74.7 | 15.33 | 75.43 | 14.94 | 73.71 | 13.31 | 73.95 | 14.99 | 74.82 | 15.06 | 0.66 |
| SBP | 98.17 | 20.02 | 95.39 | 18.27 | 96.22 | 18.39 | 97.99 | 18.92 | 98.91 | 21.89 | 102.99 | 21.93 | <0.001 |
| GFR | 48.86 | 21.38 | 57.07 | 21.69 | 50.26 | 20.7 | 47.64 | 20.18 | 42.13 | 21.45 | 44.95 | 19.57 | <0.001 |

**Percentages and chi square tests of independence do not include missing values.*

*CKD, chronic kidney disease; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; CVA, cardiovascular accident; TIA, transient ischemic attack; PCI, percutaneous intervention; CABG, coronary artery bypass graft; VT, ventricular tachycardia; ICD, implantable cardioversion-defibrillator; SD, standard deviation; AST, aspartate transaminase; BUN, blood urea nitrogen; EF, ejection fraction; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; PAP, pulmonary artery pressure; CPO, cardiac power output; MAP, mean arterial pressure; SBP, systolic blood pressure; GFR, glomerular infiltration rate; SCAI, Society of Cardiovascular Angiography and Intervention; IABP, intra-aortic balloon pump; VA-ECMO, veno-arterial extra-corporeal membrane oxygenator.*

**TABLE 2 |** Distribution of SCAI stages across age quintiles.

| SCAI stage | All ($N$ = 1,412) | | Age quintiles | | | | | | | | | | $p$-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Age < 49 ($n$ = 284) | | 49–58 ($n$ = 319) | | 59–65 ($n$ = 268) | | 66–72 ($n$ = 271) | | >73 ($n$ = 270) | | |
| | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | |
| B | 46 | 3.26 | 16 | 5.63 | 9 | 2.82 | 9 | 3.36 | 6 | 2.21 | 6 | 2.22 | 0.005 |
| C | 263 | 18.63 | 53 | 18.66 | 69 | 21.63 | 36 | 13.43 | 47 | 17.34 | 58 | 21.48 | |
| D | 758 | 53.68 | 146 | 51.41 | 150 | 47.02 | 152 | 56.72 | 156 | 57.56 | 154 | 57.04 | |
| E | 212 | 15.01 | 45 | 15.85 | 62 | 19.44 | 48 | 17.91 | 34 | 12.55 | 23 | 8.52 | |
| Unknown | 133 | 9.42 | 24 | 8.45 | 29 | 9.09 | 23 | 8.58 | 28 | 10.33 | 29 | 10.74 | |

cohort, 1,025 (72.5%) patients were male and 493 (39.9%) presented with AMI-CS. The mean age of the combined cohort was 59.9 ± 14.8 years. The majority ($n$ = 758, 53.6%) of patients were in SCAI stage D, with 263 (18.6%) in stage C and 212 (15%) in stage E shock (**Table 2**). CS was treated with vasoactive and/or pressor agents in 1,043 (73.8%) patients. MCS devices included IABP in 770 (54.5%), Impella® in 410 (29%) and VA-ECMO in 333 (23.6%) patients, with several patients receiving multiple devices (**Table 3**). Overall survival was 69.5% at the time of hospital discharge.

## Patient Characteristics Across Age Groups

The distribution of patients across the age quintiles is displayed in **Table 1**. Older patients (age > 73) were more likely to be female and present with AMI as their etiology for CS compared to their younger counterparts. Patients above 66 years of age had a higher comorbidity burden, with a higher likelihood of Type 2 Diabetes (DM2) and prior percutaneous coronary intervention ($p < 0.001$). The prevalence of HTN and stroke increased with each quintile ($p < 0.001$). Prior to device implantation, all patients had comparable lactate and bicarbonate levels but older patients (66 and older) had significantly higher serum creatinine ($p < 0.001$) compared to younger patients. Filling pressures prior to device implantation were also comparable across all age groups; however, older patients were more likely to have right sided congestion. The distribution of SCAI shock stages differed across age groups, with a higher prevalence of SCAI shock stage C/D in older patients (66 and older).

## Analysis of Mortality During Index Admission

Older patients were at a higher risk of mortality, regardless of etiology ($p < 0.001$) (**Figure 1**). Although this trend was seen in both etiologies, the trend was statistically significant in patients with ADHF ($p < 0.001$) compared to the MI group. After adjusting for gender, weight, history of HTN, etiology, systolic blood pressure, SCAI stage, renal function and cardiac power output, each increase in age by quintile was significantly associated with 1.47 times the odds of in-hospital mortality (OR: 1.47, 95% CI: 1.20–1.79). Worsening SCAI stages were associated with a higher risk of mortality and within each stage, there was a higher risk of mortality with increasing age ($p = 0.003$ for SCAI stage C; $p < 0.001$ for SCAI stage D; $p = 0.005$ for SCAI stage E) (**Figure 2**).

## Use of t-MCS Across Age Group

**Table 3** summarizes the use of t-MCS devices in each quintile of age groups. Several ($n$ = 99, 7.0%) patients received multiple MCS devices during their hospitalization, especially in the first, second and third quintile. In most age groups, getting multiple devices was associated with worse outcomes. In fact, risk of mortality was higher with increasing age, regardless of whether the patient was supported on any t-MCS device(s) or not (**Figure 3**).

# DISCUSSION

We describe the association between age, severity of CS and use of t-MCS devices in one of the largest multi-center registries representing real-world CS patients in the contemporary era. Older age was associated with higher mortality that was additive to the effect of shock severity. Higher SCAI shock stages were associated with increased mortality risk in each age group, while older patients were more likely to die at each level of shock severity. The use of t-MCS was consistently associated with a higher mortality across each age group, regardless of severity of CS. This study provides real-world survival estimates for CS patients as a function of both age and shock severity.

Age has been identified as a major risk factor for both short and long-term mortality in patients with CS. Age cut-offs ranging from 60 to 75 have been proposed as thresholds for prediction of higher mortality in CS. Similar age cut-offs have been suggested for use of ECMO as therapy for CS, although its use in older patients remains controversial (6, 17). Although these studies have highlighted the impact of age on outcomes in CS, they have not accounted for the severity of CS. Moreover, the majority of published analyses have focused on CS from AMI. A recent 2 center study reported congruent findings of graded relationship between older age and lower survival in CS that was additive to the level of shock severity (16). Although CS was identified using a diagnosis code and a large percentage of patients were in early, stage B shock, our findings strengthen their observation that age and increasing shock severity are associated

**TABLE 3 |** Device distribution across age quintiles.

| Treatment | All (*N* = 1,412) | | Age quintiles | | | | | | | | | | *p*-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Age < 49 (*n* = 284) | | 49–58 (*n* = 319) | | 59–65 (*n* = 268) | | 66–72 (*n* = 271) | | >73 (*n* = 270) | | |
| | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | |
| # Devices | | | | | | | | | | | | | <0.001 |
| 0 | 223 | 15.79 | 69 | 24.3 | 52 | 16.3 | 39 | 14.55 | 30 | 11.07 | 33 | 12.22 | |
| 1 | 881 | 62.39 | 148 | 52.11 | 184 | 57.68 | 163 | 60.82 | 184 | 67.9 | 202 | 74.81 | |
| 2 | 271 | 19.19 | 60 | 21.13 | 71 | 22.26 | 56 | 20.9 | 53 | 19.56 | 31 | 11.48 | |
| 3 | 36 | 2.55 | 7 | 2.46 | 12 | 3.76 | 9 | 3.36 | 4 | 1.48 | 4 | 1.48 | |
| 4 | 1 | 0.07 | 0 | 0 | 0 | 0 | 1 | 0.37 | 0 | 0 | 0 | 0 | |
| **Device type** | | | | | | | | | | | | | |
| VA-ECMO | 332 | 23.51 | 101 | 35.56 | 91 | 28.53 | 63 | 23.51 | 52 | 19.19 | 25 | 9.26 | <0.001 |
| Impella | 410 | 29.04 | 62 | 21.83 | 93 | 29.15 | 94 | 35.07 | 83 | 30.63 | 78 | 28.89 | 0.02 |
| IABP | 770 | 54.53 | 122 | 42.96 | 176 | 55.17 | 140 | 52.24 | 162 | 59.78 | 170 | 62.96 | <0.001 |
| Mechanical ventilation* | 571 | 58.62 | 123 | 55.66 | 134 | 59.56 | 118 | 60.51 | 101 | 56.74 | 95 | 61.29 | 0.76 |
| Medical therapy* | 1,043 | 81.55 | 216 | 83.08 | 237 | 81.72 | 213 | 86.94 | 197 | 81.07 | 180 | 74.69 | 0.01 |

**Percentages and chi square tests of independence do not include missing values.*

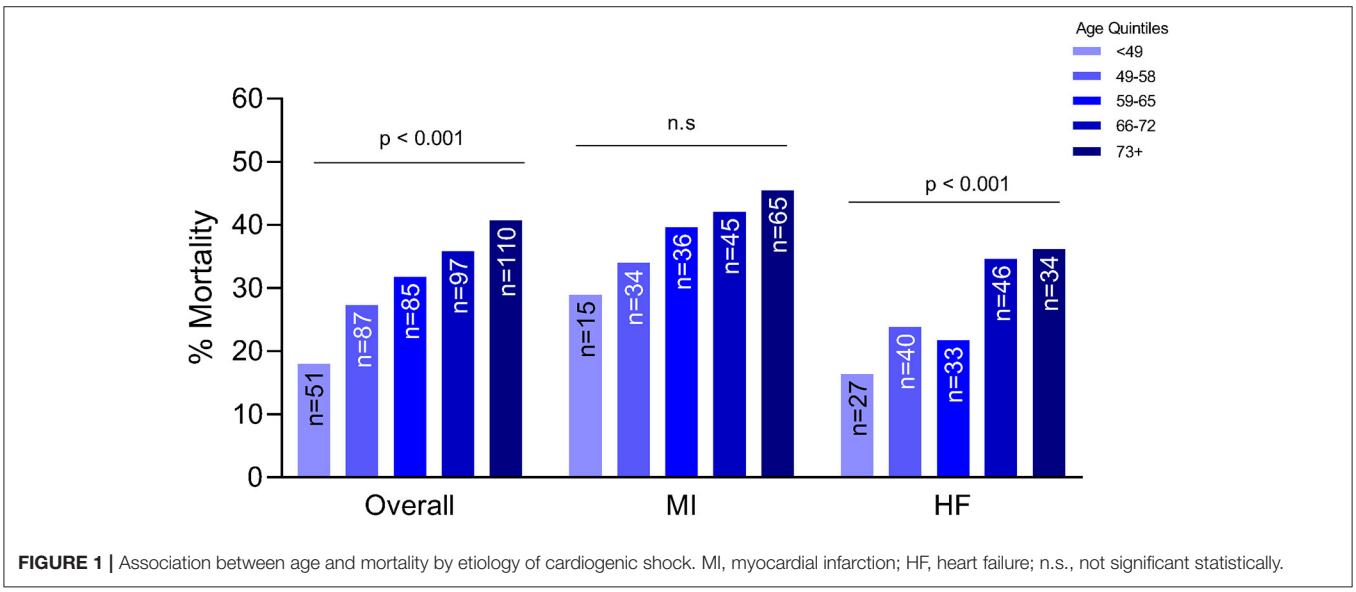


**FIGURE 1 |** Association between age and mortality by etiology of cardiogenic shock. MI, myocardial infarction; HF, heart failure; n.s., not significant statistically.

with worse outcomes. Our study expands on these prior analyses by including both AMI-CS and HF-CS patients, further stratified by the severity of CS using the SCAI shock stages and including a large number of patients in advanced stages of shock.

Numerous age-related factors can potentially contribute to worse outcomes in older patients, including frailty and reduced functional reserve, delayed or atypical clinical presentation as well as multiple comorbidities. Not surprisingly, older patients were more likely to have DM2 and hypertension, and more likely to have undergone prior percutaneous coronary intervention in our cohort. In our analysis, increasing age continued to be associated with higher odds of mortality after adjusting for the known risk factors such as gender, SCAI stage, renal function, cardiac power output etc. Recent data suggests that survival of CS patients > 65 years requiring ECMO is poor and less commonly includes transition to definitive advances therapies (18). Our data further suggests that age modifies the relationship between severity of shock and mortality in CS patients, especially considering that the hemodynamic and metabolic profiles are so evenly distributed across the age groups. These comorbidities become especially relevant in establishing goals of care for the older population.

For some other cardiovascular diseases such as aortic stenosis, older individuals who undergo trans-catheter aortic valve replacement (TAVR) are now experiencing comparable in-hospital recovery, and similar short and mid-term mortality

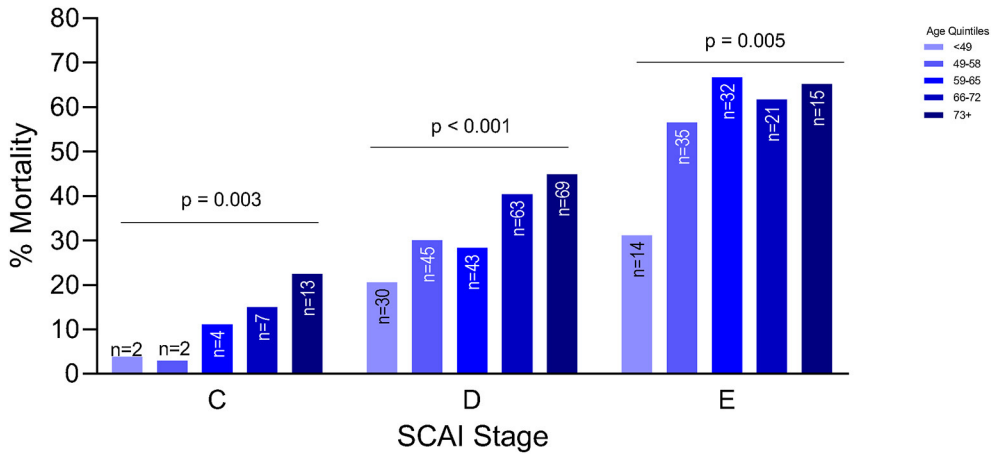


**FIGURE 2 |** Association between age and mortality by severity of cardiogenic shock as defined by the Society of Cardiovascular Angiography and Intervention (SCAI) classification.

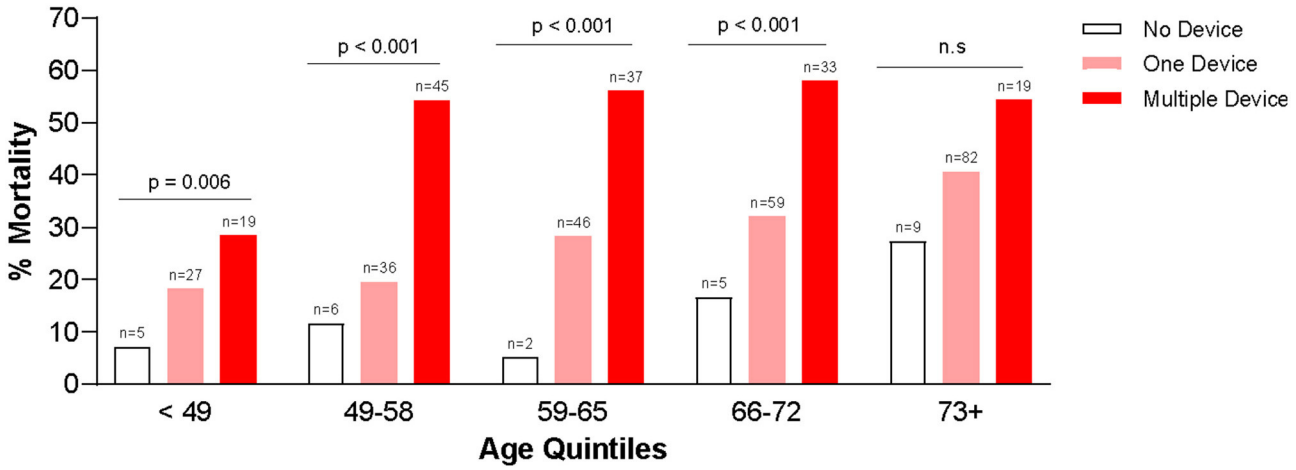


**FIGURE 3 |** Association between in-hospital mortality and use of temporary mechanical circulatory support devices.

compared to their younger counterparts (19). Similarly, revascularization has been shown to improve mortality in older patients with AMI complicated by CS in some reports but not in others (20–22). Although these reports are encouraging for management of common cardiovascular comorbidities such as CAD and aortic stenosis in the elderly, it is not enough reason to believe that this improvement in outcomes will be extended to a high risk scenario or aggressive interventions such as ECMO support in CS. CS is a very complicated illness to manage, often requiring significant time in intensive care, undergoing invasive therapies. Advancements in t-MCS technology have made this therapeutic modality more widely available; yet, they are associated with various inherent risks, including vascular complications, risk of infection and bleeding (23). Older adults with decreased physiologic reserve may be less likely to withstand such complications in order to derive the benefits provided by this therapy. This should be especially taken into consideration while managing older patients with CS since they may or may not be in favor of aggressive and invasive therapies in the setting of critical illness.

Selection of therapies, especially t-MCS in CS patients is never straightforward and has to be individualized based on baseline characteristics, etiology, clinical presentation and goals of care. While biological age should be used as one of multiple clinically relevant factors in the decision-making process, it is important to remember that older patients may have different goals of care than younger patients. However, numerical age by itself should not preclude patients from t-MCS. Especially in cases of AMI, patients are often critically ill when they arrive at the hospital, and clinicians have insufficient time and clinical information about the patient's risk factors to make well-informed decisions. Our data reveal the marked rise in risk of

mortality with use of t-MCS for older patients, regardless of severity of shock. This information can be reasonably be used to help providers determine best approach to an individual patient and inform patients and families about expected outcomes with a clearer explanation of risks and benefits. In the second iteration of the CSWG registry, participating sites are now collecting data on not just survival but adverse events, including vascular complications that result from a combination of CS and therapeutic interventions. This is essential, since quality of life and risk of AEs are often equally important as survival, especially in the elderly.

Our data are retrospective in nature and come with inherent limitations. Several confounding variables (e.g., frailty, nutritional status, baseline functional assessment, goals of care) remain unmeasured. Decisions to proceed with t-MCS (or not) were made by individual treating physicians, introducing a selection bias which may favor higher use of devices in younger patients. We are not aware of the "code-status" of included patients which would also direct treatment strategies. We did not collect the timing of device therapies relative to each other in those who received multiple devices. However, our real-world, multi-center registry report of more than 1,400 CS patients helps highlight the additive impact of age on shock severity when risk-stratifying these patients. Our ongoing data collection will allow us much more in-depth analysis of patient's hospital course, and will allow us to suggest an age "cut-off" for different scenarios in CS to try and answer the question "how old is too old" for t-MCS. More importantly, our future analyses may allow us to identify characteristics in the older patients that promote survival benefit with t-MCS in-spite of advanced age (e.g., reversible etiology of CS, post-cardiotomy, time to ECMO etc.). Lastly, acknowledging that survival at discharge is not the only goal with t-MCS, we are now collecting 30 day and 1-year outcomes in all patients which will add significant value to this discussion.

## CONCLUSIONS

Increasing age is associated with a higher mortality in CS, regardless of shock severity. Use of t-MCS devices is associated with increased mortality in all age groups and SCAI stages. Given the poor outcomes observed in the older patients, identifying selected patients who may benefit from more aggressive treatment strategies despite advanced age is a major unmet need. This would allow for a more informed risk stratification strategy in this critically ill patient population.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

MK, AG, SS, DB, and NK contributed to concept, data analysis, writing, and review. KT and NH for data analysis. JH-M, EW, CM, EV, EZ, and JA to data contribution, writing, and review. All authors contributed to the development and writing of the manuscript.

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## REFERENCES

1. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation.* (2017) 136:e232–68. doi: 10.1161/CIR.0000000000000525
2. Garan AR, Kirtane A, Takayama H. Redesigning care for patients with acute myocardial infarction complicated by cardiogenic shock: the shock team. *JAMA Surg.* (2016) 151:684–5. doi: 10.1001/jamasurg.2015.5514
3. Mendiratta P, Wei JY, Gomez A, Podrazik P, Riggs AT, Rycus P, et al. Cardiopulmonary resuscitation requiring extracorporeal membrane oxygenation in the elderly: a review of the extracorporeal life support organization registry. *ASAIO J.* (2013) 59:211–5. doi: 10.1097/MAT.0b013e31828fd6e5
4. Takayama H, Truby L, Koekort M, Uriel N, Colombo P, Mancini DM, et al. Clinical outcome of mechanical circulatory support for refractory cardiogenic shock in the current era. *J Heart Lung Transplant.* (2013) 32:106–11. doi: 10.1016/j.healun.2012.10.005
5. Tehrani BN, Rosner CM, Batchelor WB. Evolving paradigms in cardiogenic shock care. *Aging.* (2019) 11:4303–4. doi: 10.18632/aging.102075
6. Salna M, Takeda K, Kurlansky P, Ikegami H, Fan L, Han J, et al. The influence of advanced age on venous-arterial extracorporeal membrane oxygenation outcomes. *Eur J Cardiothorac Surg.* (2018) 53:1151–7. doi: 10.1093/ejcts/ezx510
7. Pöss J, Köster J, Fuernau G, Eitel I, de Waha S, Ouarrak T, et al. Risk stratification for patients in cardiogenic shock after acute myocardial infarction. *J Am College Cardiol.* (2017) 69:1913–20. doi: 10.1016/j.jacc.2017.02.027
8. Thiele H, Ohman EM, de Waha-Thiele S, Zeymer U, Desch S. Management of cardiogenic shock complicating myocardial infarction: an update 2019. *Eur Heart J.* (2019) 40:2671–83. doi: 10.1093/eurheartj/ehz363
9. Harjola V-P, Lassus J, Sionis A, Køber L, Tarvasmäki T, Spinar J, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Heart Fail.* (2015) 17:501–9. doi: 10.1002/ejhf.260
10. Rosenbaum AN, John R, Liao KK, Adatya S, Colvin-Adams MM, Pritzker M, et al. Survival in elderly patients supported with continuous flow left ventricular assist device as bridge to transplantation or destination therapy. *J Cardiac Fail.* (2014) 20:161–7. doi: 10.1016/j.cardfail.2013.12.015
11. Kilic A, Sultan I, Yuh DD, Shah AS, Baumgartner WA, Cameron DE, et al. Ventricular assist device implantation in the elderly: nationwide outcomes in the United States. *J Cardiac Surg.* (2013) 28:183–9. doi: 10.1111/jocs.12066
12. Saito S, Nakatani T, Kobayashi J, Tagusari O, Bando K, Niwaya K, et al. Is extracorporeal life support contraindicated in elderly patients? *Ann Thorac Surg.* (2007) 83:140–5. doi: 10.1016/j.athoracsur.2006.08.006
13. Masoumi A, Rosenblum HR, Garan AR. Cardiogenic shock in older adults. *Curr Cardiovasc Risk Rep.* (2016) 10:38. doi: 10.1007/s12170-016-0522-5
14. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, et al. SCAI clinical expert consensus statement on the classification of cardiogenic

shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April (2019). *Catheter Cardiovasc Interv.* (2019) 94:29–37. doi: 10.1002/ccd.28329
15. Thayer KL, Zweck E, Ayouty M, Garan AR, Hernandez-Montfort J, Mahr C, et al. Invasive hemodynamic assessment and classification of in-hospital mortality risk among patients with cardiogenic shock. *Circ Heart Fail.* (2020) 13:e007099. doi: 10.1161/CIRCHEARTFAILURE.120.007099
16. Jentzer JC, Schrage B, Holmes DR, Dabboura S, Anavekar NS. Influence of age and shock severity on short-term survival in patients with cardiogenic shock. *Eur Heart J Acute Cardiovasc Care.* (2021) 4:zuaa035. doi: 10.1093/ehjacc/zuaa035
17. Lee SN, Jo MS, Yoo KD. Impact of age on extracorporeal membrane oxygenation survival of patients with cardiac failure. *Clin Interv Aging.* (2017) 12:1347–53. doi: 10.2147/CIA.S142994
18. Chouairi F, Vallabhajosyula S, Mullan C, Mori M, Geirsson A, Desai NR, et al. Transition to advanced therapies in elderly patients supported by extracorporeal membrane oxygenation therapy. *J Cardiac Fail.* (2020) 26:1086–9. doi: 10.1016/j.cardfail.2020.07.019
19. Alsara O, Alsarah A, Laird-Fick H. Advanced age and the clinical outcomes of transcatheter aortic valve implantation. *J Geriatr Cardiol.* (2014) 11:163–70. doi: 10.3969/j.issn.1671-5411.2014.02.004
20. Rogers PA, Daye J, Huang H, Blaustein A, Virani S, Alam M, et al. Revascularization improves mortality in elderly patients with acute myocardial infarction complicated by cardiogenic shock. *Int J Cardiol.* (2014) 172:239–41. doi: 10.1016/j.ijcard.2013.12.311
21. Prasad A, Lennon RJ, Rihal CS, Berger PB, Holmes DR. Outcomes of elderly patients with cardiogenic shock treated with early percutaneous revascularization. *Am Heart J.* (2004) 147:1066–70. doi: 10.1016/j.ahj.2003.07.030
22. White HD, Assmann SF, Sanborn TA, Jacobs AK, Webb JG, Sleeper LA, et al. Comparison of percutaneous coronary intervention and coronary artery bypass grafting after acute myocardial infarction complicated by cardiogenic shock: results from the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial. *Circulation.* (2005) 112:1992–2001. doi: 10.1161/CIRCULATIONAHA.105.540948
23. Wolfe JD, Schilling JD. A short bridge over a wide river: the role of extracorporeal membrane oxygenation in older adults with cardiogenic shock. *J Cardiac Fail.* (2020) 261090–2. doi: 10.1016/j.cardfail.2020.09.006

**Conflict of Interest:** MK and JH-M are consultants for Abiomed Inc. CM is a consultant for Abbott Laboratories, Abiomed Inc., Medtronic, and Syncardia. AG is a consultant for Abiomed and NuPulseCV. He has received research support from Abbott and Verantos. DB reports an unrestricted, educational grant from Abiomed Inc. to Cardiovascular Research Foundation. JA was a consultant for Abbott Laboratories, Abiomed Inc. JH-M receives speaker honoraria and a research grant from Abiomed Inc. NK receives consulting/speaker honoraria and institutional grant support from: Abbott Laboratories, Abiomed Inc., Boston Scientific, Medtronic, LivaNova, MDStart, and Precardia.

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# Postcardiotomy Veno-Arterial Extracorporeal Membrane Oxygenation: Does the Cannulation Technique Influence the Outcome?

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**Objectives:** Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) may be cannulated using either central (cannulation of aorta) or peripheral (cannulation of femoral or axillary artery) access. The ideal cannulation approach for postcardiotomy cardiogenic shock (PCS) is still unknown. The aim of this study is to compare the outcome of patients with PCS who were supported with central vs. peripheral cannulation.

**Methods:** This is a single-center retrospective data analysis including all VA-ECMO implantations for PCS from January 2011 to December 2017. The central and peripheral approaches were compared in terms of patient characteristics, intensive care unit (ICU) stay, hospitalization length, adverse event rates, and overall survival.

**Results:** Eighty-six patients met the inclusion criteria. Twenty-eight patients (33%) were cannulated using the central approach, and 58 patients (67%) were cannulated using the peripheral approach. Forty-three patients (50%) received VA-ECMO in the operating room and 43 patients (50%) received VA-ECMO in the ICU. Central VA-ECMO group had higher EuroSCORE II ($p = 0.007$), longer cross-clamp time ($p = 0.054$), higher rate of open chest after the procedure ($p < 0.001$), and higher mortality rate ($p = 0.02$). After propensity score matching, 20 patients in each group were reanalyzed. In the matched groups, no statistically significant differences were observed in the baseline characteristics between the two groups except for a higher rate of open chests in the central ECMO group ($p = 0.02$). However, no significant differences were observed in the outcome and complications between the groups.

**Conclusions:** This study showed that in postcardiotomy patients requiring VA-ECMO support, similar complication rates and outcome were observed regardless of the cannulation strategy.

**Keywords: ECMO, cardiogenic shock, postcardiotomy, cannulation, low cardiac output**

# INTRODUCTION

The application of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in patients with refractory isolated cardiac or cardiopulmonary failure is increasing (1). Among high-risk patient populations requiring VA-ECMO support include patients with postcardiotomy cardiogenic shock (PCS). As all of these patients have open heart surgery, there are two main modalities to implant the VA-ECMO in these patient populations. These modalities include either central cannulation of the right atrium and ascending aorta or peripheral cannulation, most commonly *via* the femoral vein and artery. Alternative approaches may include the placement of a vascular prosthesis in the ascending aorta for central access (2) or, for peripheral access cannulation of the axillary artery, either directly or through a vascular prosthesis.

The optimal cannulation strategy for VA-ECMO, in terms of survival as well as myocardial recovery, management, and complication rates, remains controversial (3). Despite the considerable numbers of studies on VA-ECMO application, only a few have addressed access-related issues as primary focus in their studies (2, 4, 5). In the largest single-center series to date, Rastan et al. (6) reported no advantage of different cannulation sites by means of survival in 517 patients who required VA-ECMO after cardiac surgery, although there has been a general consensus favoring the peripheral approach (2, 6–8). Meanwhile, a recent study demonstrated that a central approach should be considered as a viable alternative in terms of complication rates (9). Based on the controversies above, we aimed to compare the outcomes of the patients with PCS who were mechanically supported with central vs. peripheral VA-ECMO.

# MATERIALS AND METHODS

## Definitions and Data Assessment

### Inclusion and Exclusion Criteria

The inclusion criteria were adult patients (aged > 18 years) who underwent VA-ECMO implantation after elective, urgent, or emergency cardiac surgery either immediately or a few hours after arrival in the intensive care unit (ICU). Exclusion criteria were patients on VA-ECMO prior to index cardiac procedure, patients requiring venovenous (VV)-ECMO, and patients after heart transplantation and/or ventricular assist device implantation. The study protocol was approved from the corresponding institutional ethics committee (Study number: 2018-33-RetroDEuA).

PCS was defined as cardiac failure that results in the inability to wean from cardiopulmonary bypass (CPB) or cardiac failure that appears in early postoperative period under optimized inotropic and vasopressor support. Hypotension, persistent lactatemia as a sign of an end-organ malperfusion, and oliguria were the clinical parameters for the diagnosis, which was supported by an echocardiographic assessment in each patient and hemodynamic monitoring with Swan-Ganz catheterization in most cases.

Central cannulation was defined as the cannulation involving the aorta and right atrium either directly or through percutaneously placed cannula through the femoral veins. Peripheral cannulation was defined as the cannulation of the femoral or subclavian artery and femoral vein.

Bleeding was defined as any bleeding requiring reoperation. Peripheral vascular (PV) complication was defined as any extremity complication involving the vascular access (excluding groin infection). Notably, all patients with peripheral VA-ECMO cannulation technique were supported with distal leg perfusion catheter to avoid limb ischemia. Postoperative gastrointestinal (GI) complication was defined as postoperative new-onset GI bleeding or ischemia requiring surgery. Postoperative neurological injury was defined as any neurological complication including transient ischemic attack, non-disabling or disabling stroke, and global brain ischemia. Postoperative liver failure was defined as an acute increase in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin.

The following data were assessed: patient characteristics, type of the cardiac procedure, urgent or emergency procedure, cross-clamp time, CPB time, EuroSCORE II, VA-ECMO support duration, place of VA-ECMO implantation (intraoperative or in the ICU), and rate of chest being left open at the primary surgery. Furthermore, the following postimplantation data were documented: chest tube output in the first 24 h after implantation, bleeding requiring a reoperation, number of red blood cell (RBC) units given, new onset of renal dialysis, postoperative neurological injury, liver failure, and GI and PV complications. Weaning and explantation rate from ECMO, duration of ICU stay, and mortality rate after ECMO implantation were documented and compared between both groups.

## Statistical Analysis

Using the SPSS statistical package and in order to test the effect of the ICU stay, hospitalization length, adverse event rates, and overall survival on the two groups (central and peripheral approach) of patients, a two-way MANOVA was performed. If the $p$-value is $<0.05$, we reject the null hypothesis that there is no difference between the means and conclude that a significant difference does.

Propensity score (PS) matching was performed as previously reported (10). Briefly, the PSs were computed by binary logistic regression. A 1:1 nearest neighbor matching algorithm with a caliper of 0.1 of the standard deviation of the logit of the PS was chosen to achieve the highest possible representativeness and precision. Risk factors, which were statistically insignificant at baseline, were not considered as confounders and therefore not adjusted by PS matching. As 46 patients did not meet the matching criteria, they were discarded from the final analysis. Finally, the residual imbalances of covariates after matching were assessed by univariate tests, the Hansen–Bowers test and the relative multivariate imbalance measure.

**Abbreviations:** VA-ECMO, veno-arterial extracorporeal membrane oxygenation; PCS, postcardiotomy cardiogenic shock; PV, peripheral vascular; GI, gastrointestinal; PS, propensity score.

**TABLE 1 |** Patient characteristics and demographics.

| | Central (*N* = 28) (*n*, %) Mean ± SD | Peripheral (*N* = 58) (*n*, %) Mean ± SD | *P*-value |
|---|---|---|---|
| Age (years) | 67 ± 11 | 69 ± 10 | 0.540 |
| Body mass index | 27 ± 7 | 27 ± 5 | 0.606 |
| Male (*n*, %) | 17 (61) | 46 (79) | 0.076 |
| EuroSCORE II | 19 ± 14 | 11 ± 10 | 0.007 |
| X-Clamp time (min) | 115 ± 48 | 88 ± 48 | 0.054 |
| CPB time (min) | 229 ± 57 | 180 ± 94 | 0.010 |
| VA-ECMO duration (days) | 7 ± 7 | 7 ± 5 | 0.926 |
| LVEF < 30% | 13 (46) | 17 (29) | 0.150 |
| DM | 10 (36) | 25 (43) | 0.641 |
| AF | 9 (32) | 18 (31) | 1.000 |
| Elective procedure | 10 (36) | 21 (36) | 1.000 |
| Immediate intraoperative VA-ECMO | 16 (57) | 27 (47) | 0.490 |
| Chest left open after surgery | 11 (39) | 3 (5) | <0.001 |
| IABP | 11 (39) | 28 (48) | 0.493 |
| LV venting | 3 (11) | 4 (7) | 0.678 |
| **Primary surgery** | | | |
| CABG | 12 (43) | 33 (57) | 0.255 |
| CABG + AVR | 4 (14) | 5 (9) | 0.465 |
| CABG + MVR ± TVR | 5 (18) | 11 (19) | 1.000 |
| AVR | 0 (0) | 6 (10) | 0.171 |
| Other procedures | 7 (25) | 3 (5) | 0.012 |
| Previous cardiac surgery | 5 (18) | 7 (12) | 0.468 |

*CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; IABP, intra-aortic balloon pump; DM, diabetes mellitus; AF, atrial fibrillation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; MVR, mitral valve replacement; TVR, tricuspid valve repair.*

**TABLE 2 |** Outcome after VA-ECMO implantation.

| | Central (*N* = 28) (*n*, %) Mean ± SD | Peripheral (*N* = 58) (*n*, %) Mean ± SD | *P*-value |
|---|---|---|---|
| Chest tube outcome in first 24 h | 1,251 ± 730 | 1,075 ± 947 | 0.384 |
| RBC units transfused during the stay | 48 ± 27 | 40 ± 29 | 0.226 |
| Resternotomy for bleeding | 13 (46) | 25 (43) | 0.819 |
| Postoperative new-onset renal dialysis | 19 (68) | 39 (67) | 1.000 |
| Postoperative liver failure | 9 (32) | 16 (28) | 0.800 |
| Postoperative neurological injury | 4 (14) | 7 (12) | 0.743 |
| Postoperative GI complications | 2 (7) | 7 (12) | 0.712 |
| Weaning from VA-ECMO | 8 (29) | 30 (52) | 0.063 |
| ICU stay (days) | 16 ± 15 | 19 ± 16 | 0.471 |
| In-hospital mortality | 22 (79) | 30 (52) | 0.020 |
| Peripheral vascular complications | 3 (11) | 16 (28) | 0.100 |

*RBC, red blood cell; GI, gastrointestinal.*

## RESULTS

Eighty-six patients met the inclusion criteria and were included in the analysis. A total of 58 patients (67%) required peripheral cannulation and 28 patients (33%) required central cannulation for VA-ECMO. The majority of patients underwent coronary artery bypass grafting (CABG) (52%). Other primary procedures were mostly combined CABG and valve surgery (29%). The mean age was 68 ± 10 years, and 64 of the patients (73%) were male. The VA-ECMO implantation for PCS took place in 43 patients (50%) in the operating room and 43 patients (50%) in the ICU. In central VA-ECMO group, the aortic cannula was inserted through a Dacron graft, and the chest was closed in 54% of the cases.

Seven (8.1%) patients received left ventricular (LV) venting, which was placed in the right superior pulmonary vein in 71.4%, in the LV apex in 14.3%, and in the pulmonary artery in 14.3% of cases.

**Table 1** demonstrates the patient characteristics and demographics. There were no significant differences between groups except for higher EuroSCORE II (19 ± 14 vs. 11 ± 10, $p = 0.007$) and longer CBP time (229 ± 57 vs.180 ± 94, $p = 0.01$) in the central VA-ECMO group. Moreover, in a greater number of patients was chest left open after surgery in the central cannulation group (11, 39%) than that in the peripheral cannulation group (3, 5%) ($p < 0.001$).

**Table 2** summarizes the outcome after VA-ECMO implantation. There was no significant difference in any of the postoperative parameters except for a significant higher in-hospital mortality rate in the central VA-ECMO group (79 vs. 52%, $p = 0.02$). Moreover, there was a non-significant trend toward a higher rate of weaning in the peripheral VA-ECMO group (29 vs. 52%, $p = 0.063$). There was no statistically significant difference in the resternotomy rates for bleeding between the central and the peripheral group (46 vs. 43%, respectively, $p = 0.819$).

Due to the fact that the groups were not identical, we decided to do a 1:1 PS matching to identify two matched groups. The following factors were included in the matching: EuroSCORE II, cross-clamp time, and type of the cardiac procedure. The PS analysis resulted in 20 patients remaining in each group (**Table 3**). **Table 4** shows the difference in the postimplantation parameters between both groups after PS matching. Interestingly, no significant differences in postoperative bleeding (1,219 ± 651 vs. 1,143 ± 1,317 ml, $p = 0.824$), transfusion (48 ± 29 vs. 45 ± 31, $p = 0.755$), duration of ICU stay (16 ± 14 days vs. 18 ± 19 days, $p = 0.638$), and in-hospital mortality (75 vs. 55%, $p = 0.320$) were observed between the matched groups. Furthermore, the rate of PV complications prior to and after matching remains similar between the groups (11 vs. 28% and 16 vs. 25%, $p = 0.100$ and $p = 0.695$, respectively). **Figures 1A,B** show the Kaplan–Meier survival curve in the unmatched and matched analyses.

## DISCUSSION

The main findings of this single-center study including 86 consecutive patients supported with VA-ECMO in a postcardiotomy setting can be summarized as follows:

**TABLE 3 |** Patient characteristics and demographics after propensity score matching.

| Propensity score | Central (*N* = 20) (*n*, %) Mean ± SD | Peripheral (*N* = 20) (*n*, %) Mean ± SD | *P*-value |
|---|---|---|---|
| Age (years) | 67 ± 10 | 60 ± 10 | 0.738 |
| Body mass index | 26 ± 7 | 27 ± 5 | 0.799 |
| Male (*n*, %) | 14 (70) | 14 (70) | 1.000 |
| EuroSCORE | 15 ± 10 | 16 ± 13 | 0.694 |
| X-Clamp time (min) | 126 ± 44 | 89 ± 53 | 0.062 |
| CPB time (min) | 228 ± 61 | 204 ± 108 | 0.448 |
| VA-ECMO duration (days) | 8 ± 8 | 7 ± 6 | 0.561 |
| LVEF < 30% | 10 (50) | 6 (30) | 0.333 |
| DM | 7 (35) | 7 (35) | 1.000 |
| AF | 7 (35) | 5 (25) | 0.731 |
| Elective procedure | 9 (45) | 8 (40) | 1.000 |
| Immediate intraoperative VA-ECMO | 10 (50) | 9 (45) | 1.000 |
| Chest left open after surgery | 8 (40) | 1 (5) | 0.020 |
| IABP | 8 (40) | 6 (30) | 0.741 |
| LV venting | 2 (10) | 2 (10) | 1.000 |
| **Primary surgery** | | | |
| CABG | 7 (35) | 11 (55) | 0.341 |
| CABG + AKR | 4 (20) | 1 (5) | 0.342 |
| CABG + MKR ± TKR | 5 (25) | 3 (15) | 0.695 |
| AKR | 0 (0) | 3 (15) | 0.231 |
| Other procedures | 4 (20) | 2 (10) | 0.661 |

*CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; IABP, intra-aortic balloon pump; DM, diabetes mellitus; AF, atrial fibrillation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; MVR, mitral valve replacement; TVR, tricuspid valve repair.*

**TABLE 4 |** Outcome after VA-ECMO implantation after propensity score matching.

| | Central (*N* = 20) (*n*, %) Mean ± SD | Peripheral (*N* = 20) (*n*, %) Mean ± SD | *P*-value |
|---|---|---|---|
| Chest tube outcome in first 24 h | 1,219 ± 651 | 1,143 ± 1,317 | 0.824 |
| RBC Units transfused during the stay | 48 ± 29 | 45 ± 31 | 0.755 |
| Resternotomy for bleeding | 9 (45) | 9 (45) | 1.000 |
| Postoperative new onset dialysis | 14 (70) | 15 (75) | 1.000 |
| Postoperative liver failure | 6 (30) | 8 (40) | 0.741 |
| Postoperative neurological injury | 3 (15) | 2 (10) | 0.605 |
| Postoperative GI complications | 2 (11) | 1 (5) | 0.712 |
| Weaning from VA-ECMO | 5 (25) | 9 (45) | 0.320 |
| ICU stay (days) | 16 ± 14 | 18 ± 19 | 0.638 |
| In-hospital mortality | 15 (75) | 11 (55) | 0.320 |
| Peripheral vascular complications | 3 (16) | 5 (25) | 0.695 |

*RBC, red blood cell; GI, gastrointestinal.*

1- In the unmatched group of patients, the central VA-ECMO group tends to have higher mortality rate after the index cardiac procedure.
2- The postimplantation morbidity and mortality remain similar between the groups after PS matching, highlighting the fact that none of the implantation technique is advantageous over the other.
3- The similar bleeding rates in the matched group may be related to chest closure in the majority of the central ECMO group.
4- The rates of PV complications are similar if distal leg perfusion is used in all patients.

The PCS is presumably an annihilating complication after cardiac surgical procedures and correlated with a soaring mortality rate. What seems to be the topmost choice for patients with refractory PCS is the VA-ECMO implantation. The ideal cannulation approach (central vs. peripheral) for PCS is yet to be defined. It was therefore the aim of this study to shed light on the unanswered question in the postcardiotomy setting.

The utilization of VA-ECMO has been increasing during the last decades, and PCS constitutes one of the most common indications (1, 11–14). Although it is considered an ultimate option, the use of VA-ECMO has gradually reduced in-hospital mortality over time as well as remained a resource-consuming treatment (12–14). Despite growing worldwide experience, the overall survival to hospital discharge was 41.4% in adults in a current Extracorporeal Life Support Organization (ELSO) Registry Report (5). Therefore, there are some concerns arising about costs, benefits, and ethics.

Central and peripheral cannulation strategies are both to be utilized habitually on a PCS clinical scenario. The VA-ECMO implantation for PCS according our results took place in 43 patients (50%) in the operating room and 43 patients (50%) in the ICU, as reported in the results of this study. In case of a PCS scenario, failure from CPB weaning regularly requires the implementation of VA-ECMO and usually a central configuration can easily be inaugurated utilizing the already placed cannulas for the previous CPB. A peripheral access can be achieved percutaneously using the femoral or, less frequently, axillary or subclavian (9, 15) artery and femoral or jugular vein (6, 8). Sorokin et al. (3) reported previously the details on appropriate configuration and cannulation strategy for ECMO.

There are both benefits and pitfalls of each cannulation strategy (16): the central cannulation ensures an antegrade flow, which may provide a better LV unloading. The peripheral one directs a retrograde flow toward the aortic valve and causes an increase in LV afterload. Moreover, it is a fundamental issue that the peripheral cannulation leads to Harlequin syndrome. On the other hand, it is a less time-consuming and less invasive technique, which allows sternal closure. Central VA-ECMO might also be initiated with the closed chest in PCS. A Dacron graft can be anastomosed to the ascending aorta, which may be tunneled to exit at the subxiphoid region, allowing patients extubation and mobilization after surgery in case of prolonged support or bridge to destination therapy. However, a potential compression of the graft along its course through the mediastinum toward the subxiphoid exit points may cause an insufficient hemodynamic support. Another possible outlet for the cannulae in closed-chest conditions may be directly through the cranial end of the sternotomy wound. This may avoid a

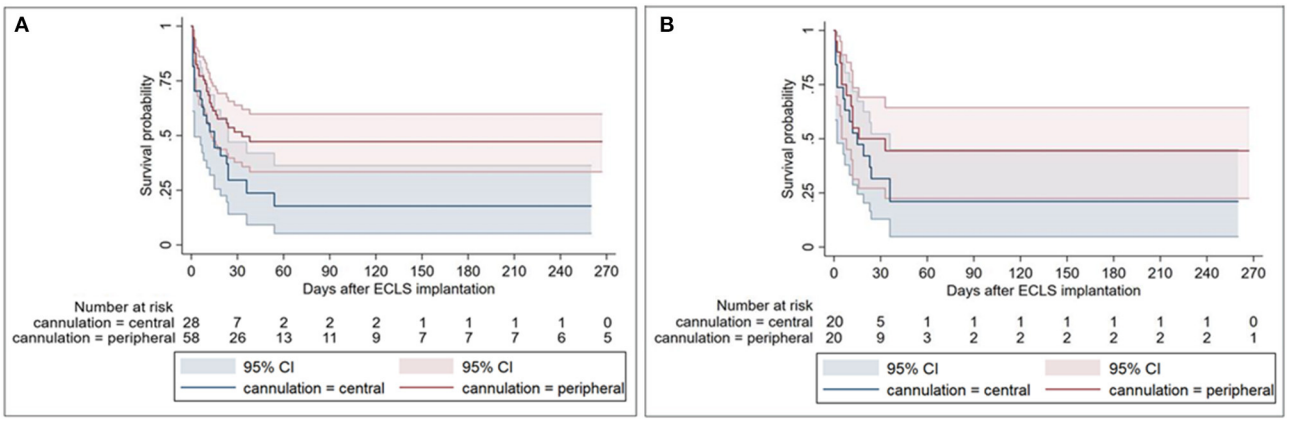


**FIGURE 1 |** Kaplan–Meier survival curves depicting impaired survival in central compared to peripheral cannulation for postcardiotomy extracorporeal life support (ECLS) **(A)**, which attenuates after risk adjustment by propensity score matching **(B)**. The survival difference occurs early after surgery and is maintained in the later postoperative course.

possible cardiac compression by cannulae along their course through the mediastinum.

Mariscalco et al. (17) compared peripheral and central VA-ECMO in a retrospective study of 781 patients with PCS at 19 cardiac surgery centers. This multicenter study showed that central cannulation was associated with greater in-hospital mortality than peripheral cannulation (17). Although our unmatched data support this finding, after PS matching, complication rates and outcome were similar regardless of the cannulation strategy.

The subclavian artery cannulation should provide several advantages by allowing to mimic the blood flow of the central cannulation approach in contrast to femoral artery (9, 18). The advantages include the lack of atherosclerosis, minimizing atherosclerotic embolization, and preferential delivery of oxygenated blood to the heart and brain (19). Therefore, the subclavian approach appears advisable in patients with peripheral arterial occlusive disease because of its lack of atherosclerosis in comparison to the femoral artery. Ranney et al. (9) reported a higher rate of vascular complications (particularly fasciotomy and amputation) and bleeding at the cannulation site (37.5, 30.6, and 13.9%, respectively). In that study, a trend toward a higher incidence of cerebrovascular events was also observed (9). We believe that subclavian cannulation is advantageous when longer support duration is anticipated to allow patients' extubation and mobilization.

The hemodynamic effects and end-organ function regarding cannulation approach is not well-described in the literature. Our group (2) compared the immediate trends in hemodynamics, oxygenation, ventilation, and end-organ function of patients on either peripheral or central VA-ECMO support. No particular advantage of one technique over the other was observed. The course of serum lactate levels under ECMO plays a predictive role in 30-day mortality (20, 21). However, there were no differences between peripheral and central cannulation regarding the mean peak lactate level as a marker of tissue perfusion and end-organ damage (7). In a series of 517 patients reported by Rastan et al. (6), lactate level $>$ 10 mmol/L immediately after ECMO implantation was a significant predictor of mortality. Persistent lactate values $>$ 10 mmol/L were also associated with increased mortality (6). They also found that arterial cannulation site did not significantly influence hospital outcome, but percutaneous venous femoral cannulation was associated with adverse outcomes (6).

Supporting an impaired ventricle with ECMO may lead to LV overload, especially in peripheral configuration due to retrograde flow toward the LV, causing an increased afterload (22). The potential consequences of LV overload are LV dilatation, increased left atrial pressure, blood stasis, and thrombus formation in cardiac chambers and pulmonary edema (22). Despite being adopted in the minority of patients, LV venting is of paramount importance during PCS. However, the optimal method for LV venting is still unclear. Central configuration allows to place an additional cannula in the LV through the right superior pulmonary vein or LV apex. On the other hand, peripheral VA-ECMO in closed-chest conditions may need another method. Intra-aortic balloon pump (IABP), although controversial (22, 23), is still being widely used in clinical practice. In some PCS series, the non-use of IABP was associated with a trend to worse survival (6, 24), whereas the others did not find any differences in survival outcomes (25, 26). Alternative techniques for percutaneous LV venting include Impella® (ABIOMED Inc., Danvers, Massachusetts) or pulmonary artery venting (22, 25, 26). The optimal combination of either peripheral or central cannulation and venting methods needs further research.

Beside its life-saving effect, complications of VA-ECMO are numerous and impair the overall outcomes inevitably (6, 11). Our single-center experience does not favor central or peripheral cannulation in terms of reoperation for bleeding and number of transfused RBC units. Regardless of cannulation strategy, bleeding, transfusion, and revision for bleeding constitute major

problems on VA-ECMO (6). Recently, Djordjevic et al. (27) reported a reexploration rate of 93% of all patients on central VA-ECMO. Central cannulation is opted for by virtue of the following: to leave the chest open to avoid tamponade as well as to allow cardiac edema to resolve, to inherit the previously inserted cannulae for ECMO circuit, and to avoid limb ischemia due to femoral artery cannulation. We expected to see more bleeding complications in the central VA-ECMO group. However, our data support the fact that the bleeding issue in the postcardiotomy setting may be rather derived by the ECMO-related bleeding tendency than the surgical technique implantation. Furthermore, another explanation may be the fact that we tend to use a prosthesis in the majority of central VA-ECMO patients to facilitate chest closure (2). Therefore, the bleeding rate was not significantly higher in the central VA-ECMO group because bleeding from sternal edges was precluded.

The present study showed that PV complications in the peripheral VA-ECMO group exceeded that of the central VA-ECMO group prior to and after matching; however, interestingly, this finding did not reach statistical significance. The main explanation of this finding is the fact that the femoral vein was frequently used as inflow cannula also for central VA-ECMO group and a distal leg perfusion catheter was used in the peripheral VA-ECMO group to avoid limb ischemia. In our study, the majority of the implantation (58.6%) was percutaneous. Loforte et al. (28) showed that central cannulation in PCS resulted in increased bleeding and continuous VV hemofiltration rates compared to peripheral access (62.7 vs. 48.4% and 56.8 vs. 43.6%, respectively). Ko et al. (8) investigated a higher rate of neurologic complication with open femoral ECMO. However, after matching the groups, no significant differences in these morbidities were observed in the present study.

### Limitations

The main limitation of this study is its retrospective single-center nature. However, the majority of the data were already prospectively collected in the hospital databank. Moreover, the implantation approach was not randomized, and the decision regarding central vs. peripheral cannulation was at the discretion of the implanting surgeon in the operating room. However, ECMO implantations in the ICU were performed exclusively peripherally at the bed site. Furthermore, no hemodynamic data or data on vasopressor requirement were available to compare between the groups. After PS matching, a large number of patients were discarded from the analysis, which may potentially influence the results.

## CONCLUSION

This study of a matched group of patients using central vs. peripheral VA-ECMO for postcardiotomy patients showed no advantage of one approach over the other. The high rate of chest closure in the central VA-ECMO group and the exclusive implication of the distal leg perfusion catheter may explain this finding. Decision-making for the cannulation strategy should be individualized and adjusted to the clinical scenario. Further randomized studies are necessary to identify the ideal cannulation strategy in the PCS population.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethic Committee of University Hospital of Düsseldorf. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR'S NOTE

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## AUTHOR CONTRIBUTIONS

NK: conceptualization, data curation, formal analysis, investigation, methodology, and writing—original draft. NS: data curation, supervision, writing—original draft, writing—review and editing, and project administration. GP: formal analysis and writing—review and editing. HA, PA, AA, RW, and AL: writing—review and editing. DS: conceptualization, methodology, supervision, writing—original draft, and writing—review and editing. All authors contributed to the article and approved the submitted version.

## REFERENCES


1. Lawler PR, Silver DA, Scirica BM, Couper GS, Weinhouse GL, Camp PC Jr. Extracorporeal membrane oxygenation in adults with cardiogenic shock. *Circulation.* (2015) 131:676-80. doi: 10.1161/CIRCULATIONAHA.114.006647
2. Saeed D, Stosik H, Islamovic M, Albert A, Kamiya H, Maxhera B, et al. Femoro-femoral versus atrio-aortic extracorporeal membrane oxygenation: selecting the ideal cannulation technique. *Artif Organs.* (2014) 38:549-55. doi: 10.1111/aor.12245
3. Sorokin V, MacLaren G, Vidanapathirana PC, Delnoij T, Lorusso R. Choosing the appropriate configuration and cannulation strategies for extracorporeal membrane oxygenation: the potential dynamic process of organ support and importance of hybrid modes. *Eur J Heart Fail.* (2017) 19:75-83. doi: 10.1002/ejhf.849
4. Biancari F, Perrotti A, Dalén M, Guerrieri M, Fiore A, Reichart D, et al. Meta-analysis of the outcome after postcardiotomy venoarterial extracorporeal membrane oxygenation in adult patients. *J Cardiothorac Vasc Anesth.* (2018) 32:1175–82. doi: 10.1053/j.jvca.2017.08.048

5. Lorusso R, Gelsomino S, Parise O, Mendiratta P, Prodhan P, Rycus P, et al. Venoarterial extracorporeal membrane oxygenation for refractory cardiogenic shock in elderly patients: trends in application and outcome from the Extracorporeal Life Support Organization (ELSO) Registry. *Ann Thorac Surg.* (2017) 104:62–9. doi: 10.1016/j.athoracsur.2016.10.023
6. Rastan AJ, Dege A, Mohr M, Doll N, Falk V, Walther T, et al. Early and late outcomes of 517 consecutive adult patients treated with extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock. *J Thorac Cardiovasc Surg.* (2010) 139:302-11. doi: 10.1016/j.jtcvs.2009.10.043
7. Kanji HD, Schulze CJ, Oreopoulos A, Lehr EJ, Wang W, MacArthur RM. Peripheral versus central cannulation for extracorporeal membrane oxygenation: a comparison of limb ischemia and transfusion requirements. *Thorac Cardiovasc Surg.* (2010) 58:459–62. doi: 10.1055/s-0030-1250005
8. Ko WJ, Lin CY, Chen RJ, Wang SS, Lin FY, Chen YS. Extracorporeal membrane oxygenation support for adult postcardiotomy cardiogenic shock. *Ann Thorac Surg.* (2002) 73:538-45. doi: 10.1016/S0003-4975(01)03330-6
9. Ranney DN, Benrashid E, Meza JM, Keenan JE, Bonadonna DK, Bartz R, et al. Central cannulation as a viable alternative to peripheral cannulation in extracorporeal membrane oxygenation. *Semin Thorac Cardiovasc Surg.* (2017) 29:188-95. doi: 10.1053/j.semtcvs.2017.02.007
10. Petrov G, Kelle S, Fleck E, Wellnhofer E. Incremental cost-effectiveness of dobutamine stress cardiac magnetic resonance imaging in patients at intermediate risk for coronary artery disease. *Clin Res Cardiol.* (2015) 104:401-−9. doi: 10.1007/s00392-014-0793-0
11. Whitman GJ. Extracorporeal membrane oxygenation for the treatment of postcardiotomy shock. *J Thorac Cardiovasc Surg.* (2017) 153:95-101. doi: 10.1016/j.jtcvs.2016.08.024
12. Stretch R, Sauer CM, Yuh DD, Bonde P. National trends in the utilization of short-term mechanical circulatory support: Incidence, outcomes, and cost analysis. *J Am Coll Cardiol.* (2014) 64:1407-15. doi: 10.1016/j.jacc.2014.07.958
13. McCarthy F, McDermott C, Kini V, Gutsche JT, Waldo JW, Xie D, et al. Trend in US extracorporeal membrane oxygenation use and outcomes: 2002–2012. *Semin Thorac Surg.* (2015) 27:81–8. doi: 10.1053/j.semtcvs.2015.07.005
14. Karagiannidis C, Brodie D, Strassmann S, Stoelben E, Philipp A, Bein T, et al. Extracorporeal membrane oxygenation: evolving epidemiology and mortality. *Intensive Care Med.* (2016) 42:889–96. doi: 10.1007/s00134-016-4273-z
15. Javidfar J, Brodie D, Costa J, Miller J, Jurrado J, LaVelle M, et al. Subclavian artery cannulation for venoarterial extracorporeal membrane oxygenation. *ASAIO J.* (2012) 58:494-8. doi: 10.1097/MAT.0b013e318268ea15
16. Raffa GM, Kowalewski M, Brodie D, Ogino M, Whitman G, Meani P, et al. Meta-analysis of peripheral or central ECMO in postcardiotomy and non-postcardiotomy shock. *Ann Thorac Surg.* (2019) 107:311-21. doi: 10.1016/j.athoracsur.2018.05.063
17. Mariscalco G, Salsano A, Fiore A, Dalén M, Ruggieri VG, Saeed D, et al. Peripheral versus central extracorporeal membrane oxygenation for postcardiotomy shock: multicenter registry, systematic review, and meta-analysis. *J Thorac Cardiovasc Surg.* (2020) 160:1207–16. doi: 10.1016/j.jtcvs.2019.10.078
18. Chicotka S, Rosenzweig EB, Brodie D, Bacchetta M. The "Central Sport Model": extracorporeal membrane oxygenation using the innominate artery for smaller patients as bridge to lung transplantation. *ASAIO J.* (2017) 63:e39-44. doi: 10.1097/MAT.0000000000000427
19. Chamogeorgakis T, Lima B, Shafii AE, Nagpal D, Pokersnik JA, Navia JL, et al. Outcomes of axillary artery side graft cannulation for extracorporeal membrane oxygenation. *J Thorac Cardiovasc Surg.* (2013) 145:1088-92. doi: 10.1016/j.jtcvs.2012.08.070
20. Rigamonti F, Montecucco F, Boroli F, Rey F, Gencer B, Cikirikcioglu M, et al. The peak of blood lactate during the first 24h predicts mortality in acute coronary syndrome patients under extracorporeal membrane oxygenation. *Int J Cardiol.* (2016) 221:741-5. doi: 10.1016/j.ijcard.2016.07.065
21. Slottosch I, Liakopoulos O, Kuhn E, Scherner M, Deppe AC, Sabashnikov A, et al. Lactate and lactate clearance as valuable tool to evaluate ECMO therapy in cardiogenic shock. *J Crit Care.* (2017) 42:35-41. doi: 10.1016/j.jcrc.2017.06.022
22. Meani P, Gelsomino S, Natour E, Johnson DM, Rocca H, Pappalardo F, et al. Modalities and effects of left ventricle unloading on extracorporeal life support: a review of the current literature. *Eur J Heart Fail.* (2017) 19:84–91. doi: 10.1002/ejhf.850
23. Cheng R, Hachamovitch R, Makkar R, Ramzy D, Moriguchi JD, Arabia FA, et al. Lack of survival benefit found with use of intraaortic balloon pump in extracorporeal membrane oxygenation: a pooled experience of 1517 patients. *J Invasive Cardiol.* (2015) 27:453-8.
24. Smedira NG, Blackstone EH. Postcardiotomy mechanical support: risk factors and outcomes. *Ann Thorac Surg.* (2001) 71:S60-6. doi: 10.1016/S0003-4975(00)02626-6
25. Distelmaier K, Wiedemann D, Binder C, Haberl T, Zimpfer D, Heinz G, et al. Duration of extracorporeal membrane oxygenation support and survival in cardiovascular surgery patients. *J Thorac Cardiovasc Surg.* (2018) 155:2471-6. doi: 10.1016/j.jtcvs.2017.12.079
26. Mikus E, Tripodi A, Calvi S, Giglio MD, Cavallucci A, Lamarra M. Centri Mag venoarterial extracorporeal membrane oxygenation support as treatment for patients with refractory postcardiotomy cardiogenic shock. *ASAIO J.* (2013) 59:18–23. doi: 10.1097/MAT.0b013e3182768b68
27. Djordjevic I, Eghbalzadeh K, Sabashnikov A, Deppe AC, Kuhn E, Merkle J, et al. Central vs peripheral venoarterial ECMO in postcardiotomy cardiogenic shock. *J Card Surg.* (2020) 35:1037-42. doi: 10.1111/jocs.14526
28. Loforte A, Marinelli G, Musumeci F, Folesani G, Pilato E, Martin Suarez S, et al. Extracorporeal membrane oxygenation support in refractory cardiogenic shock: treatment strategies and analysis of risk factors. *Artif Organs.* (2014) 38:E129-41. doi: 10.1111/aor.12317


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frontiers in Cardiovascular Medicine

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# Unloading in Refractory Cardiogenic Shock After Out-Of-Hospital Cardiac Arrest Due to Acute Myocardial Infarction—A Propensity Score-Matched Analysis

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**Aims:** Unclear neurological outcome often precludes severely compromised patients after out-of-hospital cardiac arrest (OHCA) from mechanical circulatory support (MCS), while it may be considered as rescue therapy for patients with refractory cardiogenic shock (rCS) in the absence of OHCA. This analysis sought to investigate the role of left ventricular (LV) unloading in patients with rCS related to acute myocardial infarction (AMI) after OHCA.

**Methods:** Of 273 consecutive patients receiving microaxial pumps in the Hannover Cardiac Unloading Registry between January 2013 and August 2018, 47 presented with AMI–rCS following successful resuscitation. Subsequently, the patients were compared by propensity score matching to patients with OHCA AMI–rCS without MCS. The patient data for OHCA without LV unloading was available from 280 patients of the Hannover Cooling Registry for the same time period. Furthermore, the patients with OHCA without rCS were compared to the patients with OHCA AMI–rCS and LV unloading.

**Results:** In total, 15 OHCA AMI–rCS patients without MCS were matched to patients with AMI–rCS and Impella. Patients without LV support had a higher proportion of a cardiac cause of death ($n = 7$ vs. $n = 3$; $p = 0.024$). LV unloading with Impella counteract rCS status and was associated with a preferable 30-day survival (66.7 vs. 20%, $p = 0.01$) and a favorable neurological outcome after 30 days (Cerebral Performance Category $\leq 2$, 47 vs. 27%). Impella support is associated with a higher 30-day survival (odds ratio, 2.67; 95% confidence interval, 1.02–13.66).

**Conclusion:** In patients after OHCA with AMI–rCS, Impella support incorporated in a strict standardized treatment algorithm results in a preferable 30-day survival and counteracts severe rCS status.

**Keywords: cardiogenic shock, left ventricular unloading, myocardial infarction, out of hospital cardiac arrest, culprit lesion**

# INTRODUCTION

Acute myocardial infarction (AMI) is a main contributor to out-of-hospital cardiac arrest (OHCA) (1). Despite improvements in diagnosis and treatment, the mortality rates remain high (2). Most patients suffer from post-cardiac arrest syndrome characterized by reduced systemic perfusion due to vasoplegia and adverse metabolism. Therefore, the early recovery of systemic perfusion to prevent end-organ dysfunction is relevant (3), and cardiac revascularization is recommended (1).

In patients with AMI complicated by cardiogenic shock (CS), percutaneous coronary intervention (PCI) of the culprit artery reduced mortality (4, 5). However, despite PCI, decreased cardiac output and metabolic deterioration contribute to end-organ failure, itself leading to a vicious cycle resulting in mortality (6).

Therefore, several percutaneous mechanical circulatory support (MCS) devices attracted attention to rescue patients in refractory cardiogenic shock (rCS) and are recommended by current guidelines (7, 8). In hemodynamically severely compromised patients, the Impella microaxial flow-pump, percutaneously inserted *via* a femoral approach, actively unloads the left ventricle independent of intrinsic left ventricular (LV) function, with the consequence of reduced wall tension and ventricular dimension. The Impella increases myocardial perfusion while maintaining cardiac output and improving end-organ perfusion (9, 10).

However, due to the lack of prospective randomized trials and conflicting results, the efficacy of active LV unloading in patients with OHCA complicated by AMI–rCS has not been determined yet.

We previously demonstrated that an early treatment algorithm (Hannover Cardiac Resuscitation Algorithm, HaCRA) with a multidisciplinary approach, including therapeutic hypothermia, coronary revasularization, and hemodynamic support, in rCS patients after OHCA is associated with lower mortality as described before (11).

Therefore, this analysis sought to investigate whether active LV unloading with Impella in patients after OHCA with AMI–rCS imbedded in a dedicated early in-hospital algorithm (HaCRA) is associated with a preferable outcome.

# METHODS

## Study Design and Participants

The HAnnover Cardiac Unloading REgistry (HACURE) has a prospective and observational design. The HACURE includes all consecutive patients who received an Impella microaxial pump for LV unloading in our department. The HACORE includes all patients admitted after out-of-hospital cardiac arrest and receiving therapeutic hypothermia as part of a standard treatment at the cardiac arrest center at Hannover Medical School. All patients in both registries were treated according to HaCRA. The current analysis is in accordance with the Declaration of Helsinki and approved by the ethics committee at Hannover Medical School (#3566-2017).

We analyzed consecutive patients after OHCA with AMI (either ST segment elevation myocardial infarction or non-ST segment elevation myocardial infarction) and successful PCI of the culprit lesion, complicated AMI–rCS treated with MCS using Impella, and mandatory therapeutic hypothermia who were admitted to the Department of Cardiology at Hannover Medical School between January 2013 and August 2018. In the current analysis, the exclusion criteria were defined as follows: patients without myocardial infarction, mechanical cause of rCS, withdrawal of further life support, isolated right ventricular or biventricular failure at baseline, use of additional MCS (i.e., extracorporeal membrane oxygenation) or unidentifiable culprit lesion or unsuccessful PCI of the culprit lesion. Consecutive patients from the HAnnover COoling REgistry (HACORE, $n = 280$) and HACURE ($n = 273$) were defined as controls and allocated into groups as follows: (1) patients with AMI following OHCA in the absence of CS ($n = 90$) and (2) patients with AMI following OHCA and complicated by rCS without MCS ($n = 23$). Subsequently, to analyze the impact of circulatory support in patients with AMI–rCS after OHCA, a propensity score (PS) matching was considered (OHCA+AMI–rCS without Impella *vs.* OHCA + AMI–rCS + Impella). Furthermore, to verify the applicability of HaCRA to patients after extrahospital resuscitation with refractory cardiogenic shock and support with an Impella, we compared the patients after OHCA without CS and the patients with OHCA AMI–rCS and active LV support by Impella. To avoid unmeasured confounding, these cohorts were not considered for PS matching as described in **Figure 1**. The endpoints were defined as follows: The primary endpoint of this analysis was 30-day mortality in the PS-matched cohorts. The secondary endpoint was defined as 30-day mortality in the group of patients with AMI–rCS and Impella support and patients without CS. Furthermore, the endpoints for the safety outcome in all cohorts are as follows: peripheral ischemic complications forcing vascular surgery or intervention, mild/moderate/severe bleeding assessed by GUSTO, and neurological outcome after 30 days of admission as assessed by cerebral performance category (CPC). We defined a good neurological outcome as CPC $\leq$2, as previously described (12). The detailed study design is provided in the **Supplementary Material**.

## Patient Treatment and Definitions

The patients were treated according to current guidelines (8, 13, 14) and a standardized multidisciplinary local treatment algorithm, HaCRA, for CS and cardiac arrest as previously described (11). Details on patient treatment and clinical follow-up are provided in the **Supplementary Material**.

## Statistical Analysis

The data were analyzed using GraphPad Prism 7.04 (GraphPad Software, San Diego, CA, USA), R program 3.3.3, and SPSS 25 (IBM SPSS Statistics 25). The categorical parameters are presented as counts and percentages. The metric normally distributed variables are presented as mean values ± standard

**Abbreviations:** AMI–rCS, refractory cardiogenic shock owing to myocardial infarction; HaCRA, Hannover Cardiac Resuscitation Algorithm; HACORE, HAnnover COoling Registry; HACURE, HAnnover Cardiac Unloading Registry; LV, left ventricular; MCS, percutaneous mechanical circulatory support; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.

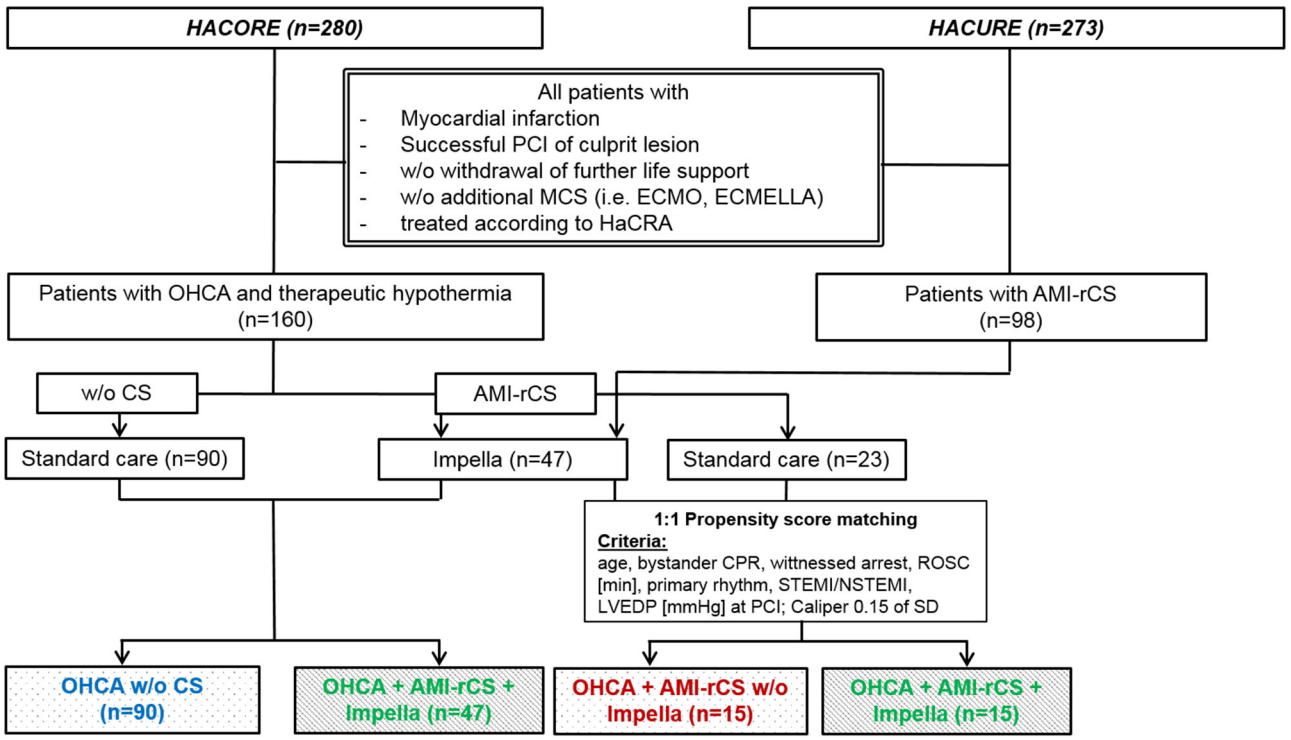


**FIGURE 1 |** Study enrolment. AMI, acute myocardial infarction; CPR, cardio-pulmonary resuscitation; CS, cardiogenic shock; ECMELLA, circulatory support by a combination of Impella and ECMO; ECMO, extracorporeal membrane oxygenation; HACORE, Hannover Cooling Registry; HaCRA, Hannover Cardiac Resuscitation Algorithm; HACURE, Hannover Cardiac Unloading Registry; MCS, mechanical circulatory support; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous intervention; OHCA, out-of-hospital cardiac arrest; rCS, refractory cardiogenic shock; ROSC, return of spontaneous circulation; SD, standard deviation; STEMI, ST elevation myocardial infarction; w/o, without.

deviation and the non-normally as median and interquartile ranges. Normality and variance homogeneity were checked by Shapiro–Wilk and Kolmogorov–Smirnov tests, respectively. The statistical analysis for comparison between PS-matched groups of metric parameters was performed using unpaired *t*-tests as parametric tests and Mann–Whitney tests as non-parametric tests. Chi-square test was applied to compare nominally scaled parameters. In the PS-matched groups, there was no missing data for the documented parameters. The 30-day survival was calculated using Kaplan–Meier curves, and log-rank comparison was performed between the groups. Cox regression analysis was performed to calculate hazard ratios (HR) with 95% confidence intervals (CI). The reported *P*-values are two-sided, with $p < 0.05$ considered statistically significant.

## Propensity Score Matching

To minimize confounder bias and realize a balanced distribution of baseline characteristics to estimate the effects of MCS with Impella in patients after OHCA and AMI complicated by rCS, a PS matching was performed to patients in the control cohort as described above. The propensity scores were estimated using multivariable logistic regression modeling accounting for variables related to the outcome or which are clinically meaningful: age, bystander CPR, witnessed cardiac arrest, ROSC, primary rhythm, STEMI/NSTEMI (11), and LVEDP at the time of PCI. The cases and control groups were matched stepwise on the logit of the estimated propensity score (1:1 propensity score matching) using a nearest-neighbor model using calipers with the width equal to 0.15. A lower caliper width was used to maximize correct matching and to reduce bias.

The baseline balance of parameters used for the matching between patients after OHCA with AMI and successful PCI of the culprit lesion, complicated by rCS treated with MCS using Impella and comparators before and after PS matching, was compared *via* a standardized difference (15). A standardized difference $\leq 0.15$ suggested an appropriate balance between the covariates (**Supplementary Table 1**). To validate the method and perform a sensitivity analysis of the propensity score matching, the primary outcome (30-day survival) was reanalyzed using the entire (unmatched) cohort (**Supplementary Figure 1**).

# RESULTS

## Patient Characteristics

From both registries, HACURE and HACORE, we identified 47 patients between January 1, 2013 and August 31, 2018 treated with an Impella for AMI–rCS following resuscitation (**Figure 1**). After 1:1 PS matching, the patients after OHCA with AMI–rCS without Impella ($n = 15$) were included. The patients with AMI without CS complicated by OHCA

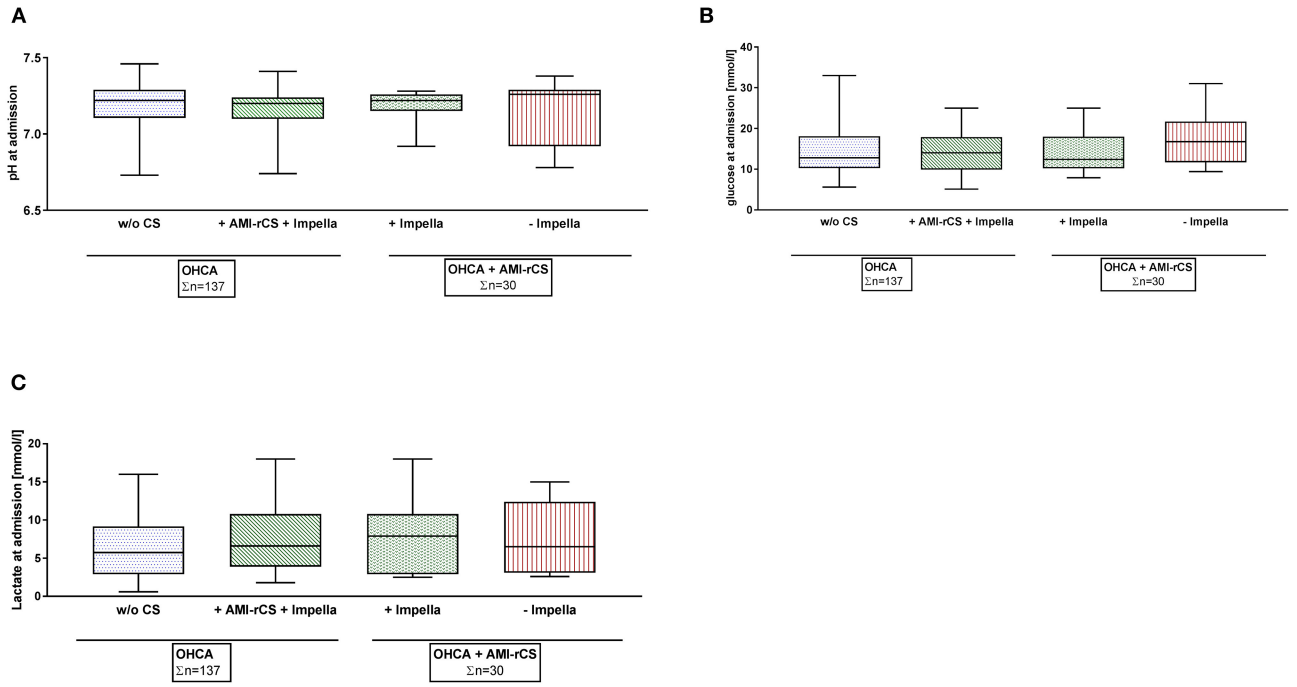


**FIGURE 2 |** Baseline blood gas analysis of propensity score-matched cohorts. AMI, acute myocardial infarction; CS, cardiogenic shock; OHCA, out-of-hospital cardiac arrest; w/o, without; rCS, refractory cardiogenic shock. **(A)** pH at admission. **(B)** Glucose at admission. **(C)** Lactate at admission.

($n = 90$) were compared to patients with AMI–rCS and Impella ($n = 47$). The patients with AMI–rCS and active LV unloading with Impella displayed no statistical significance between pH, glucose, and lactate levels at baseline in comparison to patients with AMI–rCS without Impella support (**Figure 2**). The patients with AMI–rCS after OHCA on Impella support had significantly more vessels treated, longer cumulative stent length, which is explained by standardized complete revascularization in shock at the time of treatment, and higher TIMI risk score. Further patient characteristics are shown in **Table 1**.

## Intensive Care and Safety Outcome

The characteristics of intensive care, MCS, and complications are presented in **Table 2**. Implementing MCS with Impella in resuscitated, ventilated shock patients in clinical routine practice was associated with <10-min delay of wire crossing over the culprit lesion despite the fact that 68% of cases were performed during on-call time. During ICU stay, all patients were mechanically ventilated. The resuscitation and device characteristics did not significantly differ between groups. The patients after OHCA with AMI–rCS more often required renal replacement therapy compared to patients without rCS. Furthermore, hemolysis was significantly increased in patients after OHCA and AMI–rCS when they were treated with Impella. Bleeding complications occurred significantly more frequently in patients with active left ventricular support with Impella. In the PS-matched cohorts, LV unloading with Impella showed a higher number of patients with a good neurological outcome (CPC ≤2) after 30 days. Vascular ischemic events occurred in both PS-matched cohorts. Due to critical peripheral arterial occlusive disease, vascular intervention was performed in one patient in the OHCA AMI–rCS without Impella group. The other patient received vascular surgery due to critical ischemia after prolonged Impella therapy.

## 30-Day Survival in Propensity Score-Matched Groups

Compared to resuscitated shock patients without active LV unloading, the patients after OHCA with AMI–rCS on Impella had a significantly higher survival (**Figure 3A**). During LV support, three patients were deceased due to cardiac deterioration. In the PS-matched groups, patients without LV support had a higher proportion of a cardiac cause of death ($n = 7$ vs. $n = 3$; $p = 0.024$). Furthermore, three additional patients in this group died due to brain damage resulting from extrahospital resuscitation It should be noted that, when the resuscitated patients with AMI–rCS were supported with Impella, they showed no statistical significance for 30-day survival compared to the resuscitated patients without rCS [odds ratio (OR), 0.40; 95% confidence interval (CI), 0.13–1.23; **Figure 3B**]. In summary, LV unloading with Impella was associated with a markedly lower mortality in AMI–rCS patients after OHCA (OR, 2.67; 95%CI, 1.02–13.66) and HR for 30-day mortality of 0.2 (95%CI, 0.05–0.7).

**TABLE 1 |** Baseline characteristics of propensity score-matched cohorts.

| Variable | OHCA | | | OHCA + AMI–rCS | | |
|---|---|---|---|---|---|---|
| | **Without CS, *n* = 90** | **+ AMI–rCS + Impella, *n* = 47** | ***P*** | **+ Impella, *n* = 15** | **Without Impella, *n* = 15** | ***P*** |
| Age (years) | 67 (57–74) | 58 (52–73) | *0.041* | 67 (58–78) | 66 (55–74) | ns |
| Length (cm) | 176 ± 7 | 177 ± 7 | ns | 177 ± 8 | 177 ± 6 | ns |
| Weight (kg) | 82.3 ± 19.3 | 83.9 ± 13.8 | ns | 85.1 ± 14.5 | 67.8 ± 26.9 | ns |
| Gender: male | 76 (84%) | 38 (81%) | ns | 12 (80%) | 14 (93.3%%) | ns |
| Pre-existing disorders | | | | | | |
| Smoking | 45 (50%) | 23 (49%) | ns | 5 (33.3%) | 7 (46.7%) | ns |
| Hypertension | 58 (64.4%) | 28 (59.6%) | ns | 13 (86.7%) | 7 (46.7%) | ns |
| Diabetes | 23 (25.5%) | 8 (17%) | ns | 1 (6.7%) | 2 (13.3%) | ns |
| Cardiogenic shock | 0 | 47 (100%) | *<0.001* | 15 (100%) | 15 (100%) | ns |
| STEMI | 47 (52.2%) | 22 (46.8%) | ns | 9 (60%) | 10 (67%) | ns |
| NSTEMI | 43 (47.8%) | 25 (53.2%) | | 6 (40%) | 4 (26.7%) | |
| Vessels treated (*n*) | 2 (1–3) | 2 (2–3) | ns | 2 (1–2) | 1 (1–2) | *0.013* |
| Cumulative stent length (mm) | 27 (18–45) | 48 (23–74) | *<0.001* | 50 (43–74) | 25 (18–50) | *0.024* |
| Admission lactate (mmol/L) | 6.3 ± 3.9 | 7.3 ± 4.1 | ns | 7.6 ± 4.8 | 6.3 ± 3.8 | ns |
| SAPS II score | 50 ± 12.4 | 50.3 ± 9.4 | ns | 53 ± 14.4 | 51.8 ± 10.5 | ns |
| CardShock score | 4 (3–5) | 5 (5–6) | *0.009* | 5 (5–6) | 5 (5_6) | ns |
| IABP-Shock II score | 3 (1–3) | 3 (3–3) | *<0.001* | 4 (3–5) | 4 (3–5) | ns |
| TIMI risk score | 7 (6–9) | 8 (7–9) | *0.03* | 9 (7–10) | 7 (6–9) | *0.047* |
| In-hospital stay (days) | 14.7 ± 7.1 | 15.6 ± 10.1 | ns | 17 (4–22) | 9 (1–13) | *0.041* |

*AMI, acute myocardial infarction; BL, baseline; CS, cardiogenic shock; NSTEMI, non-ST elevation myocardial infarction; rCS, refractory cardiogenic shock; STEMI, ST elevation myocardial infarction.*

## DISCUSSION

In our PS-matched analysis comparison to medical treatment only, active LV unloading with an Impella in patients after OHCA with AMI–rCS was associated with a significantly higher survival rate: circulatory support with Impella was a factor for survival until 30 days after hospital admission (OR, 2.67; 95%CI, 1.02–13.66) and HR for 30-day mortality was 0.2 (95%CI, 0.05–0.7). The main conclusion is that our approach of active LV unloading with an Impella micro-axial flow-pump as part of an intra-hospital algorithm (HaCRA) for diagnostic and treatment workflow of patients after OHCA antagonized the severe rCS state, resulting in unexpectedly good 30-day survival rates of around 70%, and the survival rate was comparable to patients after OHCA without rCS.

Cardiac arrest and CS are the main causes of mortality in patients with AMI (1, 16). In previous studies of patients with CS after cardiac arrest, mortality was driven by systolic myocardial dysfunction, hemodynamic instability characterized by reduced cardiac output as well as secondary multiorgan failure and was potentially reversible (17). Despite improved PCI strategies (4, 6) and pre-hospital care (18), the persistently high mortality associated with CS led to the development of several percutaneous MCS devices that are increasingly used in CS. The Impella platform reliably provides hemodynamic stabilization, enhances cardiac output, and reduces end-diastolic wall stress in patients with acute coronary syndrome and STEMI (10, 19).

However, investigations leading to evidence-based assessment of the therapeutic efficacy supporting MCS, especially LV unloading with Impella micro-axial flow pumps, in patients after OHCA complicated by rCS are scarce (20–22). It should be noted that randomized prospective studies using MCS, i.e., Impella or intra-aortic balloon pumps, in patients with rCS, incorporating post-cardiac arrest patients, exhibited a dismal mortality rate of these patients (23, 24). This finding was confirmed by a matched pair analysis applying inclusion criteria IABP-SHOCK II trial (Intra-aortic Balloon Pump in Cardiogenic Shock) (24) in patients with AMI-CS (25).

Besides multiorgan failure and post-cardiac arrest metabolism (3), a contributor to mortality is neurological damage due to anoxic cerebral injury provoked prior to hospital admission (26). Hence, puzzling evidence and ambiguous neurological prognosis of patients after OHCA and rCS at admission result in a reserved approach of MCS implantation.

In our analysis, Impella support was associated in patients after OHCA with AMI–rCS, with a significantly higher survival rate in comparison to conservative treatment. Our approach was associated with comparable mortality rates between patients with OHCA without AMI–rCS and patients with OHCA with additional AMI–rCS supported by Impella. In everyday clinical practice, Impella implantation, as a part of HaCRA, by a multiprofession team was associated with a delay of wire crossing of the culprit lesion below 10 min in comparison to patients without active LV unloading. It should be noted that

**TABLE 2 |** ICU course and complications of propensity score-matched cohorts.

| Variable | OHCA | | | OHCA + AMI–rCS | | |
|---|---|---|---|---|---|---|
| | Without CS, *n* = 90 | + AMI–rCS + Impella, *n* = 47 | *P* | + Impella, *n* = 15 | Without Impella, *n* = 15 | *P* |
| Bystander CPR performed | 68 (75.6%) | 37 (78.7%) | ns | 11 (73.3%) | 10 (66.7%) | ns |
| Witnessed arrest | 79 (87.7%) | 39 (83%) | ns | 14 (93.3%) | 14 (93.3%) | ns |
| ongoing CPR at admission | 5 (5.6%) | 6 (65.4%) | ns | 0 | 0 | |
| Out of hospital defibrillation (*n*) | 2.9 ± 2.5 | 3.5 ± 2.9 | ns | 3.8 ± 3.8 | 3.7 ± 2.1 | ns |
| Primary rhythm | | | ns | | | ns |
| Asystole | 18 (20%) | 6 (12.8%) | | 1 (6.7%) | 2 (13.3%) | |
| Ventricular Fibrillation | 72 (80%) | 41 (87.2%) | | 14 (93.3%) | 13 (86.7%) | |
| Time intervals | | | | | | |
| ROSC (min) | 18 (10–30) | 23 (10–31) | ns | 20 (10–30) | 25 (10–35) | ns |
| Duration puncture to wire crossing (min) | 14.3 ± 7.1 | 24.3 ± 9.9 | *<0.001* | 21.5 ± 9.9 | 17.7 ± 5.2 | ns |
| Shock onset to Impella (h) | | 3 (1.5–4) | | 3 (2–4) | | |
| Duration of Impella support (h) | | 89 (46–156) | | 90 (46–216) | | |
| Impella implantation | | | | | | |
| Pre-PCI | | 28 (59.6%) | | 8 (53.3%) | | |
| Post-PCI | | 19 (40.4%) | | 7 (46.7%) | | |
| LVEDP at the time of PCI | 19 ± 6.3 (*n* = 78) | 26.7 ± 6.7 | *<0.001* | 25.5 ± 4.6 | 25.3 ± 4.5 | ns |
| Bridge to | | | | | | |
| Deceased during LV support | | 12 (25.5%) | | 3 (20%) | | |
| Recovery | | 34 (72.3%) | | 12 (80%) | | |
| Durable VAD | | 1 (2.1%) | | 0 | | |
| RRT during ICU stay | 17 (18.9%) | 17 (36.2%) | *0.026* | 6 (40%) | 1 (6.7%) | *0.031* |
| Hemolysis | 0 | 16 (34%) | *<0.001* | 4 (26.7%) | 0 | *0.032* |
| Peripheral ischemic complications forcing vascular surgery or intervention | 2 (2.2%) | 4 (8.5%) | *ns* | 1 (6.7%) | 1 (6.7%) | ns |
| Good neurological outcome after 30 days (CPC ≤2) | 40 (44%) | 24 (51%) | ns | 7 (47%) | 4 (27%) | ns |
| GUSTO bleeding | | | *0.014* | | | *0.039* |
| Mild | 12 (13.3%) | 14 (29.8%) | | 4 (27%) | 2 (13%) | |
| Moderate | 4 (4.4%) | 5 (10.6%) | | 4 (27%) | 0 | |
| Severe | 0 | 1 (2.1%) | | 0 | 0 | |

*AMI, acute myocardial infarction; CPC, cerebral performance category; CPR, cardio-pulmonary resuscitation; ICU, intensive care unit; LV, left ventricular; LVEDP, left ventricular end diastolic pressure; PCI, percutaneous coronary intervention; rCS, refractory cardiogenic shock; ROSC, return of spontaneous circulation; RRT, renal replacement therapy; VAD, ventricular assist device.*

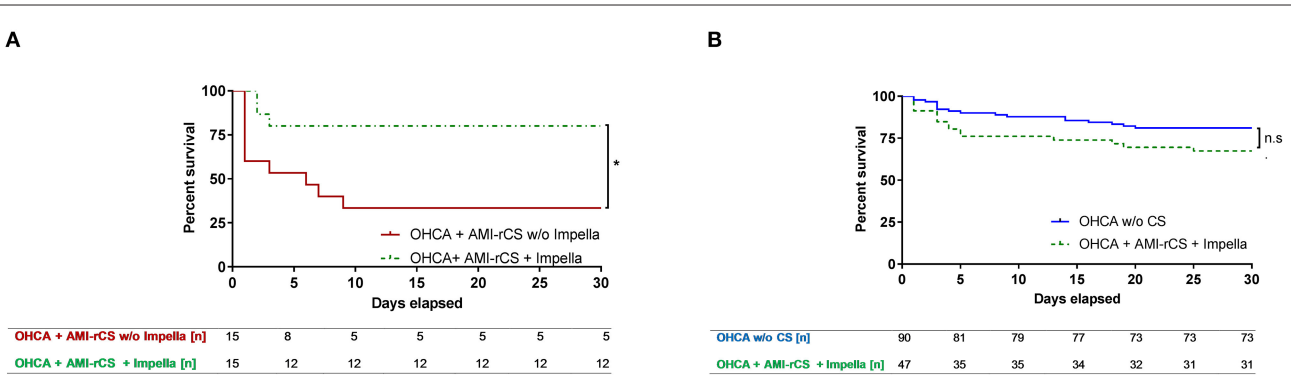


**FIGURE 3 |** 30-day survival after propensity score matching. AMI, acute myocardial infarction; CI, confidence interval; CS, cardiogenic shock; HR, hazard ratio; OHCA, out-of-hospital cardiac arrest; rCS, refractory cardiogenic shock. **(A)** Kaplan–Meier curves of AMI–rCS after OHCA with or without active left ventricular unloading by Impella, $^*p < 0.05$. **(B)** Kaplan–Meier curves of AMI–rCS patients after OHCA without CS or with AMI–rCS supported by Impella.

all groups with applied HaCRA algorithm in this analysis have higher survival rates than previously reported or predicted. In detail, patients with OHCA and AMI–rCS supported with Impella had a better in-hospital survival than predicted by Card Shock score [Card Shock Score: 5 (5, 6), ∼70% in-hospital mortality; OHCA AMI–rCS with Impella: 38.5% in-hospital mortality]. In the IMPRESS-in-SEVERE-Shock trial (23), all patients randomized to Impella support had cardiac arrest before implantation ($n = 24$). These patients had a 30-day mortality rate of 46%. In contrast, our analysis of OHCA AMI–rCS patients supported by Impella displayed a 30-day mortality rate of 32%. As opposed to our analysis, in the IMPRESS-in-SEVERE-Shock trial, no standardized algorithm for early diagnosis and treatment of rCS was applied, and Impella implantation was frequently performed after coronary intervention (IMPRESS-in-SEVERE-Shock trial, 80 vs. 39%).

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) maintains end-organ perfusion and has been conventionally considered after OHCA and rCS. In particular, the use of VA-ECMO during resuscitation as extracorporeal cardio-pulmonary resuscitation (eCPR) recently showed exceptionally good results. In the recently published ARREST trial, early eCPR with VA-ECMO in patients with OHCA and refractory ventricular fibrillation resulted in significant survival to hospital discharge compared with standard therapy (27). Nevertheless, in broader every-day patient cohorts, other groups have reported much lower survival rates sometimes indistinguishable from conventional CPR (28, 29). In rCS without refractory cardiac arrest, however, VA-ECMO increases LV afterload with the consequence of increased filling pressures, pulmonary congestion, and restricted LV recovery (30). Therefore, when treating rCS in stable ROSC after OHCA, we favor the use of the MCS, taking into account its individual characteristics and disadvantages. The DTU-STEMI pilot trial showed that the initiation of active LV unloading by Impella CP in patients with anterior STEMI is feasible and safe (31). Active cardiac support by Impella was associated with a reduced infarct size, increased collateral blood flow to the ischemic myocardium, and reduction of reperfusion injury in a preclinical study (32).

In a recently published analysis of a multicenter registry, 49 patients with acute coronary syndrome-related cardiogenic shock following OHCA were actively supported by Impella (33). The applied treatment protocol, like HaCRA, included an early evaluation of the mechanical circulatory support and prompt coronary angiography. However, the patient characteristics and the post-resuscitation management of the National Cardiogenic Shock Initiative were different to our current analysis. rCS was present in 19 patients (39 vs. 100%), and 19 patients received therapeutic hypothermia after extrahospital resuscitation (39 vs. 100%). The authors displayed a survival rate to hospital discharge of 85.7%.

Further evidence for LV support by Impella in patients with AMI-CS without OHCA will be provided by the ongoing DanGer-SHOCK (Danish–German cardiogenic shock; https://clinicaltrials.gov/ct2/show/NCT01633502?cond=01633502&draw=2&rank=1~NCT01633502) trial (34).

Overall, we strongly believe that HaCRA, as a multidisciplinary early treatment algorithm, supports the early recognition of shock states, initiation of MCS, PCI of the culprit lesion, and mandatory therapeutic hypothermia, resulting in a higher survival rate than that reported and predicted by scores in patients after OHCA complicated by AMI–rCS.

## Limitations

HACURE and HACORE are prospective and observational monocentric registries. Therefore, no randomized control group of the treatment is allocable. HaCRA was performed in a tertiary university hospital setting and was optimized to local conditions. However, applying a standardized protocol, bias cannot be excluded as the decision of indication and the timing of the Impella insertion were done by the physician in charge. This PS analysis included a small series of patients. As a consequence of PS matching with the aim of reducing influencing variables, only a few patients were included in each group. Therefore, the results should be carefully extrapolated owing to potentially unknown covariates and subsequent biases. Furthermore, despite the efforts to form comparable cohorts using a strict post-resuscitation management protocol and PS matching, a possible influence of bias cannot be excluded in this retrospective analysis with a small patient cohort. Overall, the presented results from this non-randomized single-center registry with PS matching have to be considered as hypothesis-generating. However, MCS in rCS and after OHCA is expertise dependent, and patient selection is critical; thus, multi-center studies may be difficult to conduct.

# CONCLUSION

The results of our analysis suggest that Impella support included in an early intrahospital algorithm (HaCRA) with a multidisciplinary approach and structured diagnostic and therapeutic assessment in patients after OHCA complicated by AMI–rCS and PCI of the culprit lesion is associated with a higher survival rate.

# DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

# ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethics committee at Hannover Medical School #3566-2017. The patients/participants provided their written informed consent to participate in this study.

# AUTHOR CONTRIBUTIONS

J-TS, AS, and JB designed the Hannover Cardiac Unloading Registry. AS, MA, and JB designed the Hannover Cooling Registry. J-TS, MA, J-AB, and UF recruited patients and collected

data. J-TS, MA, and J-AB analyzed and interpreted the data. J-TS, MA, JB, and AS wrote the manuscript. JB and AS accurately approved the manuscript. All the authors critically revised and finally approved the manuscript. All the authors agree to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work will be appropriately investigated and resolved.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.704312/full#supplementary-material

## REFERENCES

1. Dumas F, Cariou A, Manzo-Silberman S, Grimaldi D, Vivien B, Rosencher J, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. *Circ Cardiovasc Interv.* (2010) 3:200–7. doi: 10.1161/CIRCINTERVENTIONS.109.913665
2. Wong MK, Morrison LJ, Qiu F, Austin PC, Cheskes S, Dorian P, et al. Trends in short- and long-term survival among out-of-hospital cardiac arrest patients alive at hospital arrival. *Circulation.* (2014) 130:1883–90. doi: 10.1161/CIRCULATIONAHA.114.010633
3. Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, et al. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. *Eur J Heart Fail.* (2015) 17:544–58. doi: 10.1002/ejhf.289
4. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med.* (2017) 377:2419–32. doi: 10.1056/NEJMoa1710261
5. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med.* (1999) 341:625–34.
6. Bangalore S, Gupta N, Guo Y, Lala A, Balsam L, Roswell RO, et al. Outcomes with invasive vs conservative management of cardiogenic shock complicating acute myocardial infarction. *Am J Med.* (2015) 128:601–8. doi: 10.1016/j.amjmed.2014.12.009
7. Reyentovich A, Barghash MH, Hochman JS. Management of refractory cardiogenic shock. *Nat Rev Cardiol.* (2016) 13:481–92. doi: 10.1038/nrcardio.2016.96
8. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis treatment of acute chronic heart failure: the Task Force for the diagnosis treatment of acute chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* (2016) 18:891–975. doi: 10.1002/ejhf.592
9. Schafer A, Werner N, Westenfeld R, Moller JE, Schulze PC, Karatolios K, et al. Clinical scenarios for use of transvalvular microaxial pumps in acute heart failure and cardiogenic shock - A European experienced users working group opinion. *Int J Cardiol.* (2019) 291:96–104 S0167–5273(19)31855–8. doi: 10.1016/j.ijcard.2019.05.044
10. Schafer A, Burkhoff D, Bauersachs J. Haemodynamic simulation and the effect of early left ventricular unloading in pre-shock acute coronary syndrome. *ESC Heart Fail.* (2019) 6:457–63. doi: 10.1002/ehf2.12417
11. Akin M, Sieweke JT, Zauner F, Garcheva V, Tongers J, Napp LC, et al. Mortality in patients with out-of-hospital cardiac arrest undergoing a standardized protocol including therapeutic hypothermia and routine coronary angiography: experience from the HACORE registry. *JACC Cardiovasc Interv.* (2018) 11:1811–20. doi: 10.1016/j.jcin.2018.06.022
12. Akin M, Garcheva V, Sieweke JT, Adel J, Flierl U, Bauersachs J, et al. Neuromarkers and neurological outcome in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia-experience from the HAnnover COoling REgistry (HACORE). *PLoS ONE.* (2021) 16:e0245210. doi: 10.1371/journal.pone.0245210
13. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* (2018) 39:119–77. doi: 10.1093/eurheartj/ehx393
14. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J.* (2016) 37:267–315. doi: 10.1093/eurheartj/ehv320
15. Heinze G, Juni P. An overview of the objectives of and the approaches to propensity score analyses. *Eur Heart J.* (2011) 32:1704–8. doi: 10.1093/eurheartj/ehr031
16. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. *Circulation.* (2009) 119:1211–9. doi: 10.1161/CIRCULATIONAHA.108.814947
17. Laurent I, Monchi M, Chiche JD, Joly LM, Spaulding C, Bourgeois B, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. *J Am Coll Cardiol.* (2002) 40:2110–6. doi: 10.1016/S0735-1097(02)02594-9
18. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* (2014) 35:2541–619. doi: 10.1093/eurheartj/ehu278
19. Ouweneel DM, Henriques JP. Percutaneous cardiac support devices for cardiogenic shock: current indications and recommendations. *Heart.* (2012) 98:1246–54. doi: 10.1136/heartjnl-2012-301963
20. Manzo-Silberman S, Fichet J, Mathonnet A, Varenne O, Ricome S, Chaib A, et al. Percutaneous left ventricular assistance in post cardiac arrest shock: comparison of intra aortic blood pump and IMPELLA Recover LP2.5. *Resuscitation.* (2013) 84:609–15. doi: 10.1016/j.resuscitation.2012.10.001

21. Mukku VK, Cai Q, Gilani S, Fujise K, Barbagelata A. Use of impella ventricular assist device in patients with severe coronary artery disease presenting with cardiac arrest. *Int J Angiol.* (2012) 21:163–6. doi: 10.1055/s-0032-1324736
22. Karatolios K, Chatzis G, Markus B, Luesebrink U, Ahrens H, Dersch W, et al. Impella support compared to medical treatment for post-cardiac arrest shock after out of hospital cardiac arrest. *Resuscitation.* (2018) 126:104–10. doi: 10.1016/j.resuscitation.2018.03.008
23. Ouweneel DM, Eriksen E, Sjauw KD, van Dongen IM, Hirsch A, Packer EJ, et al. Impella CP versus intra-aortic balloon pump in acute myocardial infarction complicated by cardiogenic shock: the IMPRESS trial. *J Am Coll Cardiol.* (2017) 69:278–87. doi: 10.S0735-1097(16)36767-5 [pii].
24. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet.* (2013) 382:1638–45. doi: 10.1016/S0140-6736(13)61783-3
25. Schrage B, Ibrahim K, Loehn T, Werner N, Sinning JM, Pappalardo F, et al. Impella support for acute myocardial infarction complicated by cardiogenic shock: a matched-pair IABP-SHOCK II trial 30-day mortality analysis. *Circulation.* (2019) 139:1249–58. doi: 10.1161/CIRCULATIONAHA.119.041637
26. Paul M, Bougouin W, Geri G, Dumas F, Champigneulle B, Legriel S, et al. Delayed awakening after cardiac arrest: prevalence and risk factors in the Parisian registry. *Intensive Care Med.* (2016) 42:1128–36. doi: 10.1007/s00134-016-4349-9
27. Yannopoulos D, Bartos J, Raveendran G, Walser E, Connett J, Murray TA, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. *Lancet.* (2020) 396:1807–16. doi: 10.1016/S0140-6736(20)32338-2
28. Bougouin W, Dumas F, Lamhaut L, Marijon E, Carli P, Combes A, et al. Extracorporeal cardiopulmonary resuscitation in out-of-hospital cardiac arrest: a registry study. *Eur Heart J.* (2020) 41:1961–71. doi: 10.1093/eurheartj/ehaa626
29. Napp LC, Sanchez Martinez C, Akin M, Garcheva V, Kuhn C, Bauersachs J, et al. Use of extracorporeal membrane oxygenation for eCPR in the emergency room in patients with refractory out-of-hospital cardiac arrest. *PLoS ONE.* (2020) 15:e0239777. doi: 10.1371/journal.pone.0239777
30. Burkhoff D. Device therapy: where next in cardiogenic shock owing to myocardial infarction? *Nat Rev Cardiol.* (2015) 12:383–4. doi: 10.1038/nrcardio.2015.81
31. Kapur NK, Alkhouli MA, DeMartini TJ, Faraz H, George ZH, Goodwin MJ, et al. Unloading the left ventricle before reperfusion in patients with anterior ST-segment-elevation myocardial infarction. *Circulation.* (2019) 139:337–46. doi: 10.1161/CIRCULATIONAHA.118.038269
32. Briceno N, Annamalai SK, Reyelt L, Crowley P, Qiao X, Swain L, et al. Left ventricular unloading increases the coronary collateral flow index before reperfusion and reduces infarct size in a swine model of acute myocardial infarction. *J Am Heart Assoc.* (2019) 8:e013586. doi: 10.1161/JAHA.119.013586
33. Goldsweig AM, Tak HJ, Alraies MC, Park J, Smith C, Baker J, et al. Mechanical circulatory support following out-of-hospital cardiac arrest: insights from the National Cardiogenic Shock Initiative. *Cardiovasc Revasc Med.* (2020). doi: 10.1016/j.carrev.2020.12.021. [Epub ahead of print].
34. Udesen NJ, Moller JE, Lindholm MG, Eiskjaer H, Schafer A, Werner N, et al. Rationale and design of DanGer shock: Danish-German cardiogenic shock trial. *Am Heart J.* (2019) 214:60–8. doi: 10.1016/j.ahj.2019.04.019


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REVIEW
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# Systems of Care in Cardiogenic Shock

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Outcomes for cardiogenic shock (CS) patients remain relatively poor despite significant advancements in primary percutaneous coronary interventions (PCI) and temporary circulatory support (TCS) technologies. Mortality from CS shows great disparities that seem to reflect large variations in access to care and physician practice patterns. Recent reports of different models to standardize care in CS have shown considerable potential at improving outcomes. The creation of regional, integrated, 3-tiered systems, would facilitate standardized interventions and equitable access to care. Multidisciplinary CS teams at Level I centers would direct care in a hub-and-spoke model through jointly developed protocols and real-time shared decision making. Levels II and III centers would provide early access to life-saving therapies and safe transfer to designated hub centers. In regions with large geographical distances, the implementation of telemedicine-cardiac intensive care unit (CICU) care can be an important resource for the creation of effective systems of care.

**Keywords: cardiogenic shock, systems of care, AMI-CS, AHF-CS, shock team, hub and spoke**

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## INTRODUCTION

Cardiogenic shock (CS) is a life-threatening condition that begins with an initial insult leading to hypoperfusion and can progress to multiorgan failure and death. Effective treatment requires early recognition and time-sensitive interventions to restore perfusion. Despite the widespread adoption of primary percutaneous coronary interventions (PCI) and the technological advancements made in temporary circulatory support (TCS), mortality for CS patients has remained largely unabated over the last decade (1). Today, 30-day mortality for CS due to any etiology is close to 40–47% in clinical trials and 30–51% in registry studies (2).

Large disparities in outcomes exist, however, across different care environments. In the United States (US), CS patients treated in large, urban and left ventricular assist device (LVAD)-capable centers, have the lowest mortality rates (3, 4) while those in smaller, rural hospitals have the highest mortality rates, along with the lowest rates of early angiography, PCI and access to TCS (5). Notably, current data shows that nearly half of patients with acute myocardial infarction and cardiogenic shock (AMI-CS) are being treated in low volume centers (6).

Recently published studies have demonstrated that initiatives to standardize care for CS patients within integrated care systems can lead to large improvements in clinical outcomes (7, 8). These models, akin to those adopted in other time-sensitive conditions, can facilitate efficient access to different tiers of care for patients with different severities of CS, which could improve the existing disparities. Herein, we describe the current state of systems of care in CS and propose what an ideal system might look like.

## CURRENT LANDSCAPE

CS remains the main cause of death among patients with acute myocardial infarction (AMI), and now complicates close to 10% of cases (9). Currently, inpatient mortality for AMI-CS is estimated between 31 and 41%. Patients are increasingly presenting with higher clinical complexity, older age, greater comorbid burden and more complex culprit lesions (6). Higher overall use of primary PCI has not sustainably decreased mortality (10), but shorter times between first medical contact and PCI do seem to improve survival in AMI-CS patients (11). In the US, the number of PCI-capable centers has grown at a faster rate than the population growth, but these centers are unequally distributed, ranging between per capita 3–4/1 to 12/1 million. Distance between centers also varies greatly, reaching as far as 150 miles in some regions (12).

Between 2011 and 2013, PCI centers classified as suburban and rural performed 49% of all PCIs for AMI-CS in the US. Private and community hospitals performed 90% of these PCIs, while tertiary care centers performed only 10%. Data from the National Cardiovascular Data Registry indicates that in-hospital mortality as a whole is rising for this patient population, regardless of the treating center's characteristics (6). However, other large registry-based analyses suggest there may be higher survival for AMI-CS patients treated in large, urban or LVAD-capable centers (3, 6, 13).

Acute heart failure CS (AHF-CS), is increasingly recognized as a common etiology for CS, now accounting for 30–50% of cases depending on the hospital setting (14, 15). Reported mortality for these patients varies widely depending on the data source, likely reflecting important disparities in care. In a recent report from the Cardiogenic Shock Working Group, a research consortium of large academic centers, in-hospital mortality for AHF-CS was 26% (13), while in a contemporary analysis of the National Inpatient Sample (NIS) including all hospital types, mortality was 48% (15).

Access to TCS and physician patterns of device use also show wide variations. In a recent survey study of cardiac surgery centers, the IABP was offered in 92% of centers, followed by the Impella (Abiomed, Danvers, MA) in 78% and VA-ECMO in 66%. This survey also indicates that nearly one-third of physicians consider TCS before PCI in AMI-CS patients, and two-thirds do so after PCI (5). Patients admitted to larger hospitals ($\geq$600 beds) are more likely to receive TCS than those admitted to smaller ones ($\leq$200 beds) (16). Accordingly, in the United States, over 80% of VA-ECMO cases are performed in large, urban, teaching institutions (17). Use of MCS is also lower in patients older than 65 (15), women, African Americans, non-privately insured patients, and patients with low-income status (18).

Disparities in outcomes for CS patients seem to reflect these differences in management. In the US, patients in the Midwest and West have significantly lower in-hospital mortality than those in the Northeast, where lower rates of primary PCI and TCS are also noted. Meanwhile, patients in the South have the highest mortality of any region (4, 19). Patients admitted to urban and larger hospitals, with higher resource availability, have better outcomes than those in rural and smaller hospitals (4). Although in-hospital mortality is higher amongst Hispanics (74%) and African Americans (65%), these differences disappear when controlled for access to primary PCI (20). Similarly, the higher mortality observed amongst women with AMI-CS (21), is reduced with the use of standardized management algorithms (22).

## DEVELOPING SYSTEMS OF CARE IN CS

The above data support the notion that creating multi-tier systems that allow for timely and equal access to standardized care for patients with CS, would improve outcomes. As an initial step, an effort has been made in recent years to identify CS "centers of excellence" that could serve as hubs to receive patients within a larger conglomerate of hospitals.

According to an American Heart Association scientific statement on CS management, designated CS hospitals should have access to a critical care unit, 24/7 PCI capability, support from cardiac surgery and access to TCS including VA-ECMO as well as durable LVADs (2). Notably, in a survey from 2019, only 40% of the 6,000 responding centers have access to all TCS support modalities, 20% report access to PCI only, 16% do not have Cardiac Surgery programs, and 6% do not have 24/7 access to PCI (5). This highlights the current existence of different tiers of care for CS patients. A regional system should be designed to stabilize patients in lower-level centers and provide timely transfer to larger center with access to higher care for those who are most severely ill (5, 23).

### Barriers

Several key issues should be considered in the creation of effective systems of care for CS (**Table 1**). First, timely diagnosis and identification of patients is problematic. Currently, there is no universally accepted definition of CS, as none seem to effectively identify all cases (2). Using hard cut-points in objective clinical and laboratory parameters is limited by the variety of presentations seen with the different etiologies. A highly sensitive definition can identify more patients earlier, but depending on the adopted model of care, it could also result in the unnecessarily frequent mobilization of large amounts of resources. The definition of the CS stages by the Society of Cardiovascular Angiography and Interventions (SCAI) has provided a classification of shock that contemplates pre-shock stages that can help in early diagnosis (24). A recent study using machine learning technology was able to further stratify patient risk by identifying three distinct CS phenotypes upon presentation: "Non-congested," "Cardiorenal,"

**Abbreviations:** ACLS, advanced cardiovascular life support; AHF, acute heart failure; AHF-CS, acute heart failure cardiogenic shock; AMI, acute myocardial infarction; AMI-CS, acute myocardial infarction—cardiogenic shock; CICU, cardiac intensive care unit; CS, cardiogenic shock; DSI, Detroit shock initiative; HD, hemodynamics; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; MCS, mechanical circulatory support; NCSI, National cardiogenic shock initiative; OHCA, out of hospital cardiac arrest; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TCS, temporary circulatory support; TTE, transthoracic echocardiogram; US, United States; VA-ECMO, venoarterial—extracorporeal membrane oxygenation.

**TABLE 1 |** Current Barriers to the creation of effective regional systems of care for CS.

| Current barriers | Potential solutions |
|---|---|
| No standard definition of CS | Convened definition developed within the region and accepted by all three hospital levels |
| Gaps in standard of care for CS | Jointly developed regional management protocol with distinct pathways for AMI-CS and AHF-CS |
| Long geographical distances between spokes and hub | Three-tier system with CCL serving as base for initiation of monitoring and care in Level II centers<br>Development of tele-CCU system to guide care from Level I centers |
| No definition for CS centers of excellence | Development of a three-tiered system supported by national or international professional societies |

*AHF-CS, acute heart failure—cardiogenic shock; AMI-CS, acute myocardial infarction—cardiogenic shock; CCL, cardiac catheterization lab; CCU, coronary care unit; CS, cardiogenic shock.*

and "Cardiometabolic" among patients with both, AMI-CS and AHF-CS (25). These classifications represent important steps toward guiding early therapeutic interventions.

Second, important inconsistencies exist in current guidelines addressing the management of CS patients. For instance, early revascularization in AMI-CS is the only therapeutic intervention that receives a class I indication in both ACC/AHA and ESC guidelines. Meanwhile the use of a pulmonary artery catheter receives no grade in the ACC/AHA STEMI guidelines, but a class I recommendation in American heart failure guidelines and a class IIb grading in European guidelines. Larger discrepancies are seen in the recommendations for IABP use. The American guidelines give IABP a class IIa recommendation in STEMI, and European guidelines consider it a Class III indication in STEMI and HF guidelines. The use of other TCS devices is graded as class IIb by ESC guidelines and ACC/AHA STEMI guidelines, but a class IIa in the American HF guidelines. These discrepancies reflect the low level of evidence underpinning most of these recommendations, as well as differences in publication timing (2013 for ACC/AHA STEMI and HF guidelines vs. 2016 and 2017 for ESC HF and STEMI guidelines) (26).

Moreover, the majority of existing clinical trials in CS were done in AMI-CS patients. However, depending on the hospital setting, AHF-CS is potentially as frequent as AMI (27–29). Patients with AHF-CS have a distinct clinical phenotype and also respond differently to TCS than AMI-CS patients do, and often present to all hospital types (30, 31). Hence, a multi-tiered system needs to develop shared management algorithms with distinct pathways for these different patient phenotypes.

Third, geographical distance can have a negative impact in certain regions. A careful balance is needed between the institution of early therapeutic interventions and the transfer of patients to higher level of care centers where therapy can be escalated. For example, short first-medical-contact to balloon times in AMI-CS (11) should be prioritized, but protocolized institution of hemodynamic support should also occur as early as possible in selected patients. Lower-level hospitals should have streamlined access to designated teams in larger centers who can aid with early management decisions, coordinate transfer and deploy to these smaller centers as needed. Emergency medical services available in the region will obviously play an important role in this effort.

Finally, an established definition for "CS centers of excellence" is needed to help with the appropriate identification of hub centers within a region. Clear identification of these centers would not only help standardize access to care, but could also garner strong support from governing bodies to facilitate issues like sharing of physician credentialing across hospitals and state lines, and sharing of costs between transferring and receiving centers.

# CURRENT INITIATIVES

## Hub and Spoke Model

The Hub-and-Spoke model is based on the current model for STEMI, trauma and stroke referral systems (23). The original hub-and-spoke model for CS was implemented in New York for patients for treatment of post-cardiotomy CS. Each spoke site was within 250 miles of the hub. The hub center was contacted when a patient was in refractory shock for over 12 h following surgery. This model was successful in increasing the survival rate by 66% (2).

Hospitals within such networks are organized into 3 levels: Level I centers act as dedicated shock hubs with access to advanced TCS, cardiothoracic surgery, durable LVAD, hypothermia protocols and a robust multidisciplinary team culture in place. They accept transfers from both level II and level III hospitals, which differ in their ability to perform PCI and institute IABP or Impella support. Level II and III hospitals need to have protocols in place for out of hospital cardiac arrest (OHCA) and advanced cardiac life support (ACLS), as well as the ability to rapidly identify and transfer CS patients safely. Emergency Department staff in levels II and III centers should have access to bedside transthoracic echo (TTE) (7). Published data from formally established models in Spain and in the Mayo Clinic in Arizona showed increased survival rates using this approach (14, 31). Distances between spokes and hub centers can be a limitation in certain areas like the rural United States, where immediate transfer may require a large amount of resources (14, 32).

The hub and spoke model effectively centralizes the management of the most complex patients in level I centers with higher use of TCS and higher volumes of CS (2). Studies performed in patients receiving ECMO (33), PCI, CABG (2), and LVADs (3) have all demonstrated better outcomes in the facilities with the highest volume. This model can hence serve to concentrate scarce resources in a given region.

The Cardiac-RESCUE trial identified that only one sixth of the 1,000 ICU beds in the Paris region were able to provide ECMO support. Their mobile hub shock team quadrupled the number of ICU beds able to provide this therapy (34) and served as a solution to the geographic disparities. A similar mobile team was used in a network of hospitals in Spain (14) where a

shock team could travel to level II and III hospitals to evaluate patients and provide MCS as needed. They eventually transferred 42% of patients to their level I center, improving survival to discharge from 51 to 64%. Arizona had similar outcomes, with 25 of 27 patients transferred, 55% of which had MCS placed prior to transfer (35). Key to the hub and spoke model's success is the close collaboration between the hub and the spoke sites to develop joint protocols and provide training for the effective implementation of these protocols at each site (36).

Based on experiences from the development of STEMI systems, the ability for facilities to carry this out depends on geography (rural vs. urban), regional resources, and state lines. The transition to a hub and spoke model can be complicated by misaligned existing referral patterns and lack of funding and supplies for mobile teams (2). The development of a national CS database will be important to developing regionalized care guidelines and improving outcomes (2).

## Cardiogenic Shock Protocols

The Detroit Cardiogenic Shock Initiative (DCSI) evaluated the use of early MCS in patients with AMI-CS that were undergoing PCI. Four Detroit hospitals participated with adherence to the protocol which included: early PCI with invasive assessment of HD and use of Impella based on established criteria, aim for TIMI III flow with use of vasodilators as needed, and post intervention assessment of invasive hemodynamics with escalation or de-escalation in support as needed. Forty-one patients were included in the initial study, with 85% surviving until device removal, and 76% surviving until discharge (37). The DCSI has been expanded to become the National Cardiogenic Shock Initiative (NCSI) with over 80 institutions adopting the initial DCSI protocol by December 2020. Preliminary data has been made available on their latest report, which included 406 patients enrolled at 80 sites with a 71% survival to discharge between 2016 and 2020 (38).

Consistent with prior data emphasizing the importance of early interventions in AMI-CS patients, the DCSI found that with every 60 min delay to MCS, there was a 9.9% increase in mortality (7, 37). Their protocol enabled early identification of patients with a documented plan of action, which drastically improved time to MCS ($85 \pm 63$ min) without significantly delaying revascularization. This is an example of how the incorporation of shock protocols into regionalized care systems has the potential to uniformly improve outcomes.

## Shock Teams

Based off of the success seen with team-based care for STEMIs, in-hospital cardiac arrest and rapid response teams, some hospitals have developed CS teams (7). These generally consist of physicians with backgrounds in Critical Care, Interventional Cardiology, Heart Failure, and Cardiothoracic Surgery. The team is activated with a single phone call when a patient with CS is identified (31, 39, 40) This multidisciplinary team can assess the patient at the bedside or through chart review, and make decisions on different therapeutic interventions. Some shock teams are mobile and can move to the referring hospital for support, while other models stay in the hospital and coordinate urgent transfers to their center. After initial stabilization or clarification of the goals of care, involvement of the shock team can be de-escalated (41).

The University of Utah Shock Team approach, the INOVA team-based care model, the Canadian shock team and the French Cardiac-RESCUE study, all used versions of shock teams for the identification and treatment of patients with CS. These studies often blend the use of a shock team with a hub-and-spoke model as described above. In the Utah experience, 67.5% of patients were transferred to the hub hospital (31% of them after TCS institution at the referring hospital) (39). Fifty-two percent were transferred to the tertiary center in the INOVA experience, 74% in the Canadian shock team publication (29) and 84% were successfully transferred to the main VA-ECMO centers in the Cardiac-RESCUE study (34).

At the University of Utah, the shock team decreased in-hospital and 30-day mortality from 61 to 48% between 2015 and 2018 (39). Patients with post-cardiotomy shock were not included in this initiative. The Utah CS team was activated using criteria defined as "CS suspected by the treating physician." Activation occurred via a 24/7 on-call heart failure specialist who would initially assess the case and then coordinate and organize the team's response. A protocolized early escalation to TCS was favored for patients who remained hypoperfused and refractory to medical therapy. Notably, TCS device type did not predict survival and involvement of the CS team did not delay the time to institution of TCS. This initiative has been sustainable, and the shock team remained active 4 years after its creation (39).

The INOVA model consists of a multidisciplinary shock team in which all members are contacted simultaneously via a single phone call after CS is identified using simple clinical parameters (hypotension, hypoperfusion, elevated lactate). Specific pathways are defined for patients with AMI-CS and patients with AHF-CS. Their management strategy has five key areas of focus: early identification of CS, early universal right heart catheterization (RHC) to guide tailored treatment, early TCS institution, limiting inotropic and vasopressor use, and patient recovery and survival. A continued improvement in survival was seen with this approach as survival rates increased from 47% in 2016, to 58% in 2017, and 77% in 2018 (42). This system combines the use of a basic protocol with a shock team and a hub-and-spoke model with over half of patients transferred to their tertiary care center from smaller hospitals (40).

CS teams highlight the value of the simultaneous bedside assessment by specialists from different disciplines in improving management decisions. But, given the wide variations in access and practice patterns mentioned above, these models are not feasible for study in a RCT setting. CS teams are also highly resource intensive. They require the creation and maintenance of an on-call team as well as a parallel track for 24/7 activation of the cardiac catheterization laboratory (41). With less stringent activation criteria, a high incidence of false calls and inappropriate use of resources can lead to increased costs and compromise the program's sustainability. This effect has been studied previously in STEMI systems (43). A tiered activation model, where cases are first filtered through an on-call intensivist or HF specialist as seen in the Utah experience after hours and with the Canadian shock team during all activations, could limit

resource exhaustion (29, 39). This did not increase time to TCS in the Utah experience, but it was not directly measured in the Canadian report (29).

# DISCUSSION

## Integration of Hub-and-Spoke Models, Protocols, and CS Teams: What Should the System of Care Look Like?

The ideal system of care for CS would integrate elements from all three models described above (**Table 2**). Within a region, hospitals would be aligned within a hub-and-spoke model. Care at the spoke sites would be guided by established protocols and supported by a CS team at the hub center.

**TABLE 2 |** Basic characteristics of a cardiogenic shock protocol.

| |
|---|
| Jointly developed by collaboration between hubs-and-spokes within a region |
| Adapted for each region's resources and characteristics |
| Distinct pathways for AMI-CS and AHF-CS |
| Provides guidance on appropriate initial testing and hemodynamic monitoring |
| Provides guidance for care at each tier of the system |
| Provides guidelines for triage and safe transfer of patients |

*AHF-CS, acute heart failure—cardiogenic shock; AMI-CS, acute myocardial infarction—cardiogenic shock.*

A uniform definition of CS would be shared across all three levels of care in the system. In our opinion this definition should be sensitive enough to identify early cases but should also be able to discriminate between patients in different risk groups. The early recognition of CS in our institution is based on the early identification of the following data:

1. Patient's risk of CS: Does the patient have an acute or recent MI? Does the patient have known cardiomyopathy?
2. Is the patient exhibiting signs of hypoperfusion, congestion and/or hypotension? Cool skin, pulmonary edema, peripheral edema or altered mental status regardless of systemic BP?
3. Does the patient have laboratory evidence of end-organ dysfunction such as new or worsening renal failure, elevated transaminases or elevated lactic acid?

Using these three points, patients can be identified either in the emergency department or in the CCL. After diagnosis, the algorithm in **Figure 1** should be followed. At our institution the HF attending on service in the CCU serves as the first point of contact for calls regarding CS patients. The HF attending collects relevant initial data and recommends initial steps in treatment. The surgical and critical care teams are then activated as needed.

Our preferred initial vasopressor is norepinephrine and care is taken to avoid doses above 15 mcg/min. Vasopressin is

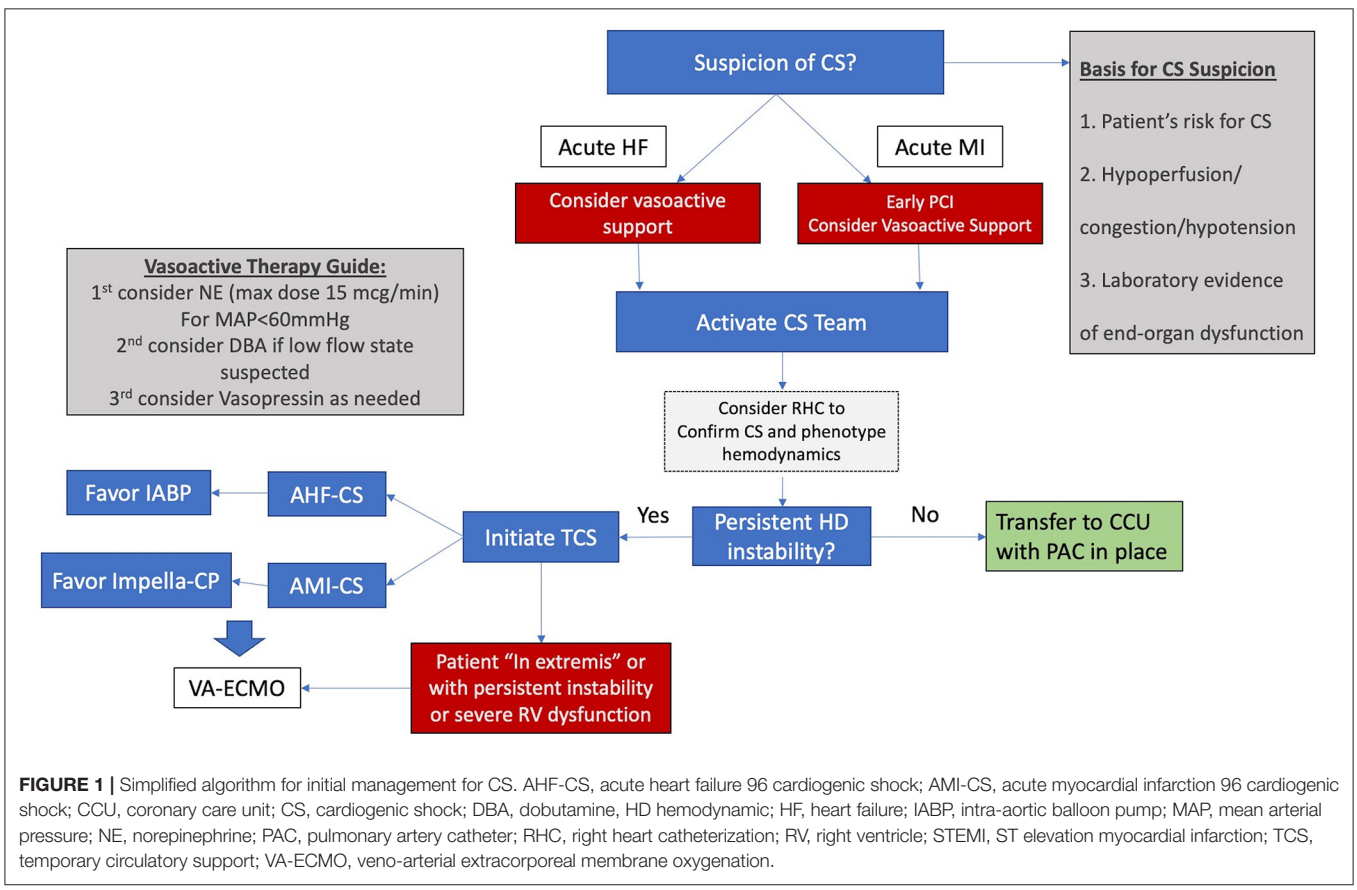


**FIGURE 1 |** Simplified algorithm for initial management for CS. AHF-CS, acute heart failure 96 cardiogenic shock; AMI-CS, acute myocardial infarction 96 cardiogenic shock; CCU, coronary care unit; CS, cardiogenic shock; DBA, dobutamine, HD hemodynamic; HF, heart failure; IABP, intra-aortic balloon pump; MAP, mean arterial pressure; NE, norepinephrine; PAC, pulmonary artery catheter; RHC, right heart catheterization; RV, right ventricle; STEMI, ST elevation myocardial infarction; TCS, temporary circulatory support; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

our next vasopressor of choice, usually at a dose of 0.04 mcg/kg/min. Dobutamine and Milrinone are used as inotropes and an early RHC is encouraged either in the CCU or the CCL.

For patients with AHF-CS our initial TCS of choice is the IABP and for patients with AMI-CS, our initial device of choice is the Impella CP. When hemodynamic instability persists or severe RV failure is present, our choice is commonly to proceed with VA-ECMO in order to restore end-organ perfusion and prevent further deterioration. VA-ECMO in our institution is implanted by the cardiac surgery team who is deployed to smaller hospitals within our system for implant and transfer of unstable patients to our main hospital in the "Moses Campus." This hospital houses our cardiac transplantation and LVAD program and serves as the hub within our referral network.

**TABLE 3 |** Basic characteristics of a hub cardiogenic shock team.

| |
|---|
| Multidisciplinary: Interventional cardiology, cardiac intensive care, cardiac surgery, heart failure |
| Guides care at a system level by proposing protocols and aiding in organization of resources |
| Provides ongoing education to staff at the spoke level |
| Available for consultation 24/7 via single phone call |
| Has a mobile unit capable of deploying from Level I to Levels II and III centers |

To become a hub within a CS system, a hospital would ideally obtain accreditation as a "Level I" center through a certification process sponsored by a professional society or a pertinent governing body. This process would ensure that these centers have the necessary resources for this role, including 24/7 PCI capability and dedicated CCU care, access to all modalities of TCS including VA-ECMO, cardiac surgery support, a multi-disciplinary cardiogenic shock team and access to advanced cardiac therapies like LVAD and transplant (**Table 3**).

Through the same process, spoke hospitals would obtain accreditation as Level II and Level III centers. This 3-tiered system, similar to what is seen in trauma care, has been previously proposed by some authors (2, 7, 32). In this model, a Level III center would identify patients in or at risk of CS and triage them to a Level II or I center within the region depending on the patient's needs. Level II centers, more widely available than Level I centers, would have 24/7 PCI capability. At this level, the cardiac catheterization laboratory (CCL) would serve as the base for initial interventions, including early angiography and PCI for AMI-CS patients, but also RHC and TCS institution for patients with all etiologies of CS (**Figure 2**).

The availability of MCS at spoke centers is rapidly changing. Although the IABP is currently the most widely available TCS modality across would-be Level II centers, the Impella is gaining wide availability in certain regions. The advent of newer technologies like the LifeSparc system (TandemLife, Pittsburgh) could also facilitate the more widespread access to VA-ECMO

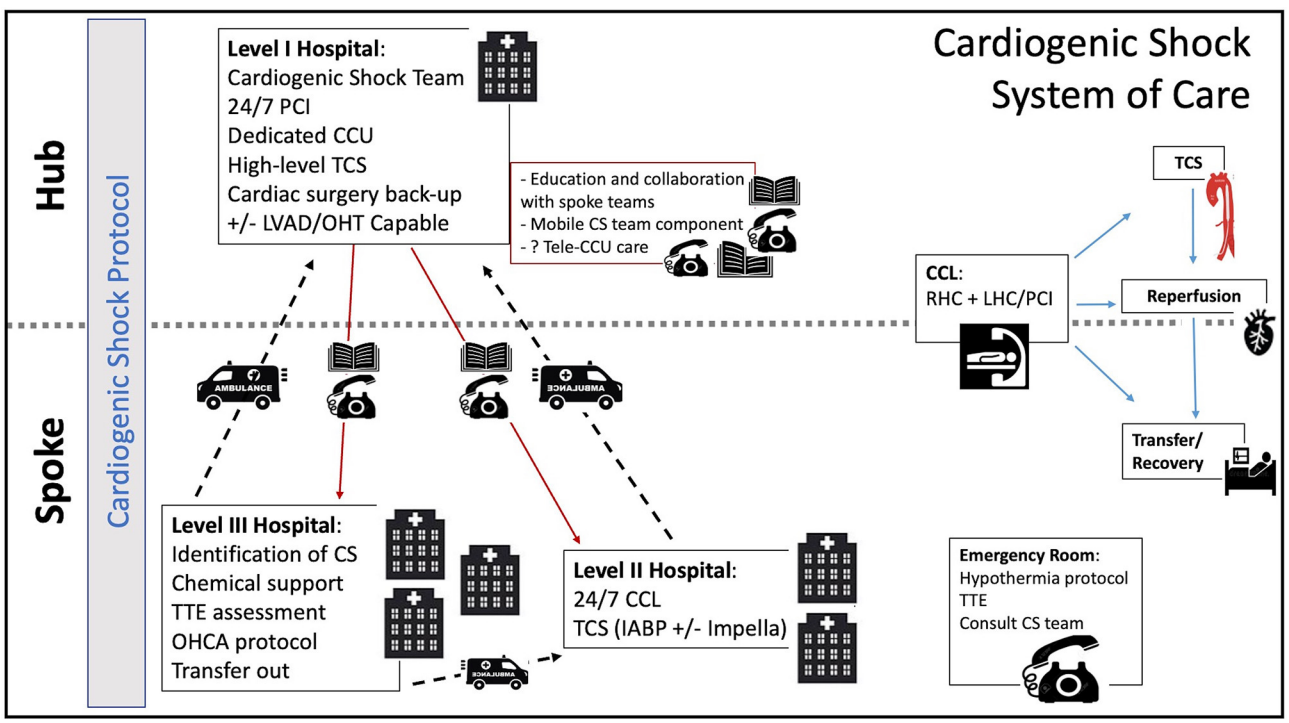


**FIGURE 2 |** Cardiogenic Shock System of Care. CCU, coronary care unit; CCL, cardiac catheterization lab; CS, cardiogenic shock; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; OHCA, out of hospital cardiac arrest; OHT, orthotropic heart transplant; PCI, percutaneous coronary intervention; RHC, right heart catheterization; TCS, temporary circulatory support; TTE, transthoracic echocardiogram.

in a CCL setting without the need for an on-site perfusionist or cardiac surgery support. Patients supported with higher level TCS would be immediately transferred to the Level I center.

Level II and III centers would operate based on a clear algorithm focused on best practices developed with their designated hub center. Clear pathways would be provided for patients with AMI-CS and AHF-CS. This CS protocol would also include guidance on early institution of hemodynamic monitoring, preferred initial pharmacologic support, and the early identification of patients needing escalation to TCS. This protocol would be coupled with an intensive training and awareness campaign for the early identification of CS patients in all hospital departments. In addition, the emergency department would be able to perform rapid and reliable bedside TTE assessment. Our institutional protocol for the early management of CS is outlined as an example in **Figure 1**.

At the designated Level I center, a CS team would be available via a single phone call on a 24/7 basis to provide early consultation and assist in shared decision making. Access to the spoke hospital's electronic health records could help the CS team have direct access to the patient's primary data. In areas where centers are spread over large geographical distances and immediate transfers may not be feasible, an intensive care telemedicine model could be adopted. This model has shown promise in adult critical care, reducing mortality and improving adherence to best practices (40). A robust telemedicine model could eventually offload the need for beds at the hub center, allowing for ongoing care of appropriately selected patients at Level II centers. Such telemedicine systems can be financially sustainable if compensation models are properly aligned (44). As greater capacity develops in Level II and III hospitals, patients could be transferred back to these centers to alleviate the demand for beds in the hub centers.

Ideally, a component of the hub's CS team should be mobile, able to deploy to the spoke sites to aid in management and institute higher levels of TCS not primarily available at the local level. As mentioned above, mobile teams have been successful in improving access to care and reducing mortality in France and Spain (14, 34).

## CONCLUSIONS

The current landscape in CS is characterized by a persistently high mortality along with important variations in access to care and physician practice patterns. While most of the data guiding CS care comes from studies performed in AMI-CS, the relative incidence of AHF-CS is growing. A universal definition for CS remains elusive and important gaps in knowledge limit the adoption of standards of care. The implementation of hub-and spokes models, CS protocols, and CS teams have all shown promising results at improving access to high-level care and improved short-term survival. The creation of accredited 3-tiered hospital systems within defined geographical regions can serve to direct care through ongoing education, the development of protocols, and shared patient management through a centralized multi-disciplinary CS team.

## AUTHOR CONTRIBUTIONS

MA: contributed to design of paper and wrote first draft. RC: assisted in writing first draft, organizing references, and designed the figure. PW, DS, and UJ: reviewed manuscript and provided editorial comments, adding additional references, and editing figures and tables. All authors contributed to manuscript revision, read, and approved the submitted version.

## REFERENCES


1. Vallabhajosyula S, Dunlay SM, Prasad A, Kashani K, Sakhuja A, Gersh BJ, et al. Acute noncardiac organ failure in acute myocardial infarction with cardiogenic shock. *J Am Coll Cardiol.* (2019) 73:1781–91. doi: 10.1016/j.jacc.2019.01.053
2. Van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation.* (2017) 136:e232–68. doi: 10.1161/CIR.0000000000000525
3. Wang JI, Lu DY, Mhs Feldman DN, McCullough SA, Goyal P, Karas MG, et al. Outcomes of hospitalizations for cardiogenic shock at left ventricular assist device versus non-left ventricular assist device centers. *J Am Heart Assoc.* (2020) 9:e017326. doi: 10.1161/JAHA.120.017326
4. Vallabhajosyula S, Dunlay SM, Barsness GW, Rihal CS, Holmes DR Jr, Prasad A. Hospital-level disparities in the outcomes of acute myocardial infarction with cardiogenic shock. *Am J Cardiol.* (2019) 124:491–8. doi: 10.1016/j.amjcard.2019.05.038
5. Lobo AS, Sandoval Y, Henriques JP, Drakos SG, Taleb I, Bagai J, et al. Cardiogenic shock management: international survey of contemporary practices. *J Invasive Cardiol.* (2020) 32:371–4.
6. Wayangankar SA, Bangalore S, McCoy LA, Jneid H, Latif F, Karrowni W, et al. Temporal trends and outcomes of patients undergoing percutaneous coronary interventions for cardiogenic shock in the setting of acute myocardial infarction: a report from the CathPCI registry. *JACC Cardiovasc Interv.* (2016) 9:341–51. doi: 10.1016/j.jcin.2015.10.039
7. Rab T, Ratanapo S, Kern KB, Basir MB, McDaniel M, Meraj P, et al. Cardiac shock care centers: JACC review topic of the week. *J Am Coll Cardiol.* (2018) 72:1972–80. doi: 10.1016/j.jacc.2018.07.074
8. Tehrani B, Truesdell A, Singh R, Murphy C, Saulino P. Implementation of a cardiogenic shock team and clinical outcomes (INOVA-SHOCK Registry): observational and retrospective study. *JMIR Res Protoc.* (2018) 7:e160. doi: 10.2196/resprot.9761
9. Kolte D, Khera S, Aronow WS, Mujib M, Palaniswamy C, Sule S, et al. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. *J Am Heart Assoc.* (2014) 3:e000590. doi: 10.1161/JAHA.113.000590
10. Redfors B, Angeras O, Ramunddal T, Dworeck C, Haraldsson I, Ioanes D, et al. 17-year trends in incidence and prognosis of cardiogenic shock in patients with acute myocardial infarction in western Sweden. *Int J Cardiol.* (2015) 185:256–62. doi: 10.1016/j.ijcard.2015.03.106
11. Scholz KH, Maier SKG, Maier LS, Lengenfelder B, Jacobshagen C, Jung J, et al. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. *Eur Heart J.* (2018) 39:1065–74. doi: 10.1093/eurheartj/ehy004
12. Langabeer JR, Henry TD, Kereiakes DJ, Dellifraine J, Emert J, Wang Z, et al. Growth in percutaneous coronary intervention capacity

relative to population and disease prevalence. *J Am Heart Assoc.* (2013) 2:e000370. doi: 10.1161/JAHA.113.000370
13. Thayer KL, Zweck E, Ayouty M, Garan AR, Hernandez-Montfort J, Mahr C, et al. Invasive hemodynamic assessment and classification of in-hospital mortality risk among patients with cardiogenic shock. *Circ Heart Fail.* (2020) 13:e007099. doi: 10.1161/CIRCHEARTFAILURE.120.007099
14. Hernandez-Perez FJ, Alvarez-Avello JM, Forteza A, Gomez-Bueno M, Gonzalez A, Lopez-Ibor JV, et al. Initial outcomes of a multidisciplinary network for the care of patients with cardiogenic shock. *Rev Esp Cardiol.* (2021) 74:33–43. doi: 10.1016/j.rec.2020.03.010
15. Shah M, Patnaik S, Patel B, Ram P, Garg L, Agarwal M, et al. Trends in mechanical circulatory support use and hospital mortality among patients with acute myocardial infarction and non-infarction related cardiogenic shock in the United States. *Clin Res Cardiol.* (2018) 107:287–303. doi: 10.1007/s00392-017-1182-2
16. Dhruva SS, Ross JS, Mortazavi BJ, Hurley NC, Krumholz HM, Curtis JP, et al. Use of mechanical circulatory support devices among patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA Netw Open.* (2021) 4:e2037748. doi: 10.1001/jamanetworkopen.2020.37748
17. Sanaiha Y, Bailey K, Downey P, Seo YJ, Aguayo E, Dobaria V, et al. Trends in mortality and resource utilization for extracorporeal membrane oxygenation in the United States: 2008-2014. *Surgery.* (2019) 165:381–8. doi: 10.1016/j.surg.2018.08.012
18. Thangam M, Luke A, Amin AP, Lasala JM, Maddox KEJ. Disparities in the implantation of mechanical circulatory support for cardiogenic shock. *J Am Coll Cardiol.* (2020) 75(11_Suppl._1):1325. doi: 10.1016/S0735-1097(20)31952-5
19. Vallabhajosyula S, Patlolla SH, Dunlay SM, Prasad A, Bell MR, Jaffe AS, et al. Regional variation in the management and outcomes of acute myocardial infarction with cardiogenic shock in the United States. *Circ Heart Fail.* (2020) 13:e006661. doi: 10.1161/CIRCHEARTFAILURE.119.006661
20. Palmeri ST, Lowe AM, Sleeper LA, Saucedo JF, Desvigne-Nickens P, Hochman JS, et al. Racial and ethnic differences in the treatment and outcome of cardiogenic shock following acute myocardial infarction. *Am J Cardiol.* (2005) 96:1042–9. doi: 10.1016/j.amjcard.2005.06.033
21. Vallabhajosyula S, Ya'Qoub L, Singh M, Bell MR, Gulati R, Cheungpasitporn W, et al. Sex Disparities in the management and outcomes of cardiogenic shock complicating acute myocardial infarction in the young. *Circ Heart Fail.* (2020) 13:e007154. doi: 10.1161/CIRCHEARTFAILURE.120.007154
22. Jerónimo A, Ferrández-Escarabajal M, Ferrera C, Noriega FJ, Diz-Díaz J, Fernández-Jiménez R, et al. Cardiogenic shock clinical presentation, management, and in-hospital outcomes in patients admitted to the acute cardiac care unit of a tertiary hospital: does gender play a role? *J Clin Med.* (2020) 9:3117. doi: 10.3390/jcm9103117
23. Samsky M, Krucoff M, Althouse AD, Abraham WT, Adamson P, Aguel F, et al. Clinical and regulatory landscape for cardiogenic shock: a report from the Cardiac Safety Research Consortium ThinkTank on cardiogenic shock. *Am Heart J.* (2020) 219:1–8. doi: 10.1016/j.ahj.2019.10.006
24. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock. *Catheter Cardiovasc Intervent.* (2019) 94:29–37. doi: 10.1002/ccd.28329
25. Zweck E, Thayer KL, Helgestad OK, Kanwar M, Ayouty M, Garan AR, et al. Phenotyping cardiogenic shock. *J Am Heart Assoc.* (2021) 2021:e020085. doi: 10.1161/JAHA.120.020085
26. van Diepen S, Thiele H. An overview of international cardiogenic shock guidelines and application in clinical practice. *Curr Opin Crit Care.* (2019) 25:365–70. doi: 10.1097/MCC.0000000000000624
27. Berg DD, Bohula EA, van Diepen S, Katz JN, Alviar CL, Baird-Zars VM, et al. Epidemiology of shock in contemporary cardiac intensive care units. *Circ Cardiovasc Qual Outcomes.* (2019) 12:e005618. doi: 10.1161/CIRCOUTCOMES.119.005618
28. Ueki Y, Mohri M, Matoba T, Tsujita Y, Yamasaki M, Tachibana E, et al. Characteristics and predictors of mortality in patients with cardiovascular shock in Japan- results from the japanese circulation society cardiovascular shock registry. *Circ J.* (2016) 80:852–9. doi: 10.1253/circj.CJ-16-0125
29. Lee F, Hutson JH, Boodhwani M, McDonald B, So D, De Roock S, et al. Multidisciplinary code shock team in cardiogenic shock: a canadian centre experience. *CJC Open.* (2020) 2:249–57. doi: 10.1016/j.cjco.2020.03.009
30. Lim HS, Howell N. Cardiogenic shock due to end-stage heart failure and acute myocardial infarction: characteristics and outcome of temporary mechanical circulatory support. *Shock.* (2018) 50:167–72. doi: 10.1097/SHK.0000000000001052
31. Malick W, Fried JA, Masoumi A, Nair A, Zuver A, Huang A, et al. Comparison of the hemodynamic response to intra-aortic balloon counterpulsation in patients with cardiogenic shock resulting from acute myocardial infarction versus acute decompensated heart failure. *Am J Cardiol.* (2019) 124:1947–53. doi: 10.1016/j.amjcard.2019.09.016
32. Patarroyo Aponte MM, Manrique C, Kar B. Systems of care in cardiogenic shock. *Methodist Debakey Cardiovasc J.* (2020) 16:50–6. doi: 10.14797/mdcj-16-1-50
33. Becher PM, Gossling A, Schrage B, Twerenbold R, Fluschnik N, Seiffert M, et al. Procedural volume and outcomes in patients undergoing VA-ECMO support. *Crit Care.* (2020) 24:291. doi: 10.1186/s13054-020-03016-z
34. Beurtheret S, Mordant P, Paoletti X, Marijon E, Celermajer DS, Leger P, et al. Emergency circulatory support in refractory cardiogenic shock patients in remote institutions: a pilot study (the cardiac-RESCUE program). *Eur Heart J.* (2013) 34:112–20. doi: 10.1093/eurheartj/ehs081
35. Jaroszewski DE, Kleisli T, Staley L, Pierce C, Scott R, Steidley DE, et al. A traveling team concept to expedite the transfer and management of unstable patients in cardiopulmonary shock. *J Heart Lung Transplant.* (2011) 30:618–23. doi: 10.1016/j.healun.2010.11.018
36. Rab T. "Shock teams" and "shock docs". *J Am Coll Cardiol.* (2019) 73:1670–2. doi: 10.1016/j.jacc.2019.01.039
37. Basir MB, Schreiber T, Dixon S, Alaswad K, Patel K, Almany S, et al. Feasibility of early mechanical circulatory support in acute myocardial infarction complicated by cardiogenic shock: the Detroit cardiogenic shock initiative. *Catheter Cardiovasc Interv.* (2018) 91:454–61. doi: 10.1002/ccd.27427
38. Basir MB, O'Neill W. "Final results from the national cardiogenic shock initiative." Society of cardiovascular angiography and interventions scientific sessions. In: *Virtual Meeting*. Washington, DC: (2021).
39. Taleb I, Koliopoulou AG, Tandar A, McKellar SH, Tonna JE, Nativi-Nicolau J, et al. Shock team approach in refractory cardiogenic shock requiring short-term mechanical circulatory support: a proof of concept. *Circulation.* (2019) 140:98–100. doi: 10.1161/CIRCULATIONAHA.119.040654
40. Tehrani BN, Truesdell AG, Sherwood MW, Desai S, Tran HA, Epps KC, et al. Standardized team-based care for cardiogenic shock. *J Am Coll Cardiol.* (2019) 73:1659–69. doi: 10.1016/j.jacc.2018.12.084
41. Doll JA, Ohman EM, Patel MR, Milano CA, Rogers JG, Wohns DH, et al. A team-based approach to patients in cardiogenic shock. *Catheter Cardiovasc Interv.* (2016) 88:424–33. doi: 10.1002/ccd.26297
42. Truesdell AG, Tehrani B, Singh R, Desai S, Saulino P, Barnett S, et al. 'Combat' approach to cardiogenic shock. *Interv Cardiol.* (2018) 13:81–6. doi: 10.15420/icr.2017:35:3
43. Barnes GD, Katz A, Desmond JS, Kronick SL, Beach J, Chetcuti SJ, et al. False activation of the cardiac catheterization laboratory for primary PCI. *Am J Manag Care.* (2013) 19:671–5. doi: 10.1177/2048004019836365
44. Lilly CM, McLaughlin JM, Zhao H, Baker SP, Cody S, Irwin RS, et al. A multicenter study of ICU telemedicine reengineering of adult critical care. *Chest.* (2014) 145:500–7. doi: 10.1378/chest.13-1973

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# Lingua Franca of Cardiogenic Shock: Speaking the Same Language

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Cardiogenic shock has remained a vexing clinical problem over the last 20 years despite progressive development of increasingly capable percutaneous mechanical circulatory support devices. It is increasingly clear that the published trials of various percutaneous mechanical circulatory support devices have compared heterogenous populations of cardiogenic shock patients, and therefore have not yielded a single result where one approach improved survival. To classify patients, various risk scores such as the CARDSHOCK and IABP-Shock-II scores have been developed and validated but they have not been broadly applied. The Society for Cardiac Angiography and Intervention Expert Consensus on Classification of Cardiogenic Shock has been widely studied since its publication in 2019, and is reviewed at length. In particular, there have been numerous validation studies done and these are reviewed. Finally, the directions for future research are reviewed.

**Keywords: risk score, cardiogenic shock, mechanical circulatory (MCS) support, intraaortic balloon counter pulsation, Impella®, classification**

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## INTRODUCTION

Shock is a life threatening condition with circulatory failure leading to inadequate delivery of oxygen to tissues, leading to ischemic dysfunction and injury. This can occur from a variety of causes, including hypovolemia, hemorrhage, or severe infection associated with sepsis. As well, it may occur with pump failure as a primary event. This may occur suddenly such as patients with acute myocardial infarction, or sub acutely such as is seen with acutely decompensated states of chronic heart failure, Cardiogenic shock (CS) is defined as a complex physiological state involving tissue hypoxia and end-organ damage secondary to a failure of the heart to provide adequate systemic perfusion. It remains a significant cause of mortality and morbidity, despite advancing techniques in management (1). The management of cardiogenic shock is complex and beyond the scope of the current work but several recent reviews are available to guide the reader (2–5).

The last significant improvement in survival occurred following the SHOCK trial (more than 20 years ago) and use of immediate revascularization for acute myocardial infarction with CS (6). Compounding this is the lack of consensus regarding degrees of CS severity with related management recommendations. Prior CS trials have enrolled a mixture of patients of various grades of severity. Some, such as patients who are survivors of out of hospital cardiac arrest, may have significant neurologic impairment which determines their outcome, regardless of treatment. Some patients have modest signs of CS vs. others who are on numerous pressors, yet most trials do not distinguish between groups.

## MORTALITY RISK PREDICTION SCORES

Early assessment of shock severity is critical to identifying patients at the highest risk of mortality and those most likely to benefit from intervention. Previously established cardiogenic shock risk score paradigms include CARD-SHOCK (7), and IABP-SHOCK 2 scores (8). These were derived from prior studies and then subsequently validated. Both demonstrate nearly equivalent predictive ability for intra-hospital, short term mortality, even when accounting for operator experience (9). For both scores however, comparative assessments have shown that predictive accuracy is acceptable with CS secondary to Acute Coronary Syndrome (ACS), but not other causes (9, 10). Additionally, neither score was designed to accommodate serial assessments, or deteriorating clinical status.

## USE OF SUPPORT DEVICES

Currently there is little data to guide the evidence-based use of mechanical support devices in cardiogenic shock, though multiple trials have been performed in the last two decades. One of the largest trials was the multicenter, randomized trial, the IABP-SHOCK 2 study (11, 12). This trial studied utility of mechanical hemodynamic support with Intra-aortic balloon pump counter pulsation (IABP), a circulatory support device which increases myocardial perfusion directly, and indirectly increases cardiac output through afterload reduction. Here, IABP use for hemodynamic support vs. control was assessed in patients with ACS and CS undergoing revascularization. IABP was typically placed following revascularization. With a sample of size of 600 patients followed to 6 years post study enrollment, there was no difference in mortality rate noted between those receiving IABP and those in the control arm of the study at any time point assessed (12).

The IMPRESS CP trial was a randomized comparison of IABP vs. Impella CP in patients with AMI-CS and receiving mechanical ventilation (13). The timing of device placement was left to the discretion of the operator, with more than 80% of patients having a support device placed after PCI. Interestingly, there was no difference in mortality noted in either arm at 30 days or 6 months. In both trial arms reduced mortality was noted when mechanical support devices were placed early, typically prior to PCI. This was a surprising result since the patients were critically ill, all receiving mechanical ventilation and unable to consent. Furthermore, the Impella CP device clearly provides much more cardiac flow than an IABP. However, the trial didn't measure shock severity or resolution of shock but mortality which can be greatly influenced by neurological status. Whether any device would successfully salvage such patients remains an open question.

Noting the lack of a "lingua franca" for CS, the Society for Cardiac Angiography and Intervention convened an expert group and released a proposed classification in 2019 (14). This was the result of a multi-disciplinary writing group and sought to provide a common framework for use by clinicians and researchers alike. This classification scheme emphasizes ease of use across the spectrum of care, from pre-hospital to intensive care and catheterization laboratory and the facilitation of communication between all members of the treatment team. It was hoped that this framework would create a standardized platform to be used for clinical trials and research going forward.

This expert consensus document was endorsed by the American College of Cardiology, the American Heart Association, the Society of Critical Care Medicine, and the Society of Thoracic Surgeons (14). As shown in **Figure 1**, there are five stages "A–E," with each increasing stage indicative of deterioration in the patient's clinical and hemodynamic status. Stage A is "at risk" for CS, stage B is "beginning" shock, stage C is "classic" CS, stage D is "deteriorating", and E is "extremis". The criteria are also meant to alert providers regarding changes in the patient's clinical status. The staging system was developed without any preceding evidence that it would accurately predict outcomes or prove to be valid. Given the broad multidisciplinary representation, the goal of implementing a widespread validation and use of the staging system seemed reasonable, and the hope was that it might lead to improvements in design of future trials.

## VALIDATION OF SCAI SHOCK CLASSIFICATION

There have been several large retrospective analyses (15–23) and one prospective study (24) since the SCAI shock stages were published in 2019. This framework has been shown to predict mortality when applied across multiple categories and in different scenarios. These included SCAI classifications made at time of initial triage or during inpatient ICU admissions (16, 18, 19), and those with out of hospital cardiac arrest (17, 21). The SCAI shock stage was also associated with prognosis in patients with acute coronary syndrome or decompensated heart failure (15, 22, 23).

Additionally, the first prospective validation of the SCAI shock criteria was recently published, which demonstrated that initial SCAI Stage was a strong predictor of survival, with thirty-day survival strongly correlated with initial SCAI shock stage 100, 65.4, 44.2, and 60% for patients with initial SCAI shock stage B, C, D, and E respectively ($p = 0.0004$) (24). Age and initial SCAI Shock Stage were shown to be the strongest predictors of survival by Cox proportional hazards. In addition, the group showed that 24-h re-assessment was critically important. If a patient improved in SCAI stage (lower degree of CS), then the mortality was significantly lower. Conversely, if SCAI stage is not changed or worsens at 24 h, the survival is much worse. These findings have great practical importance. If a patient is in a hospital without access to the full breadth of support strategies but is improving with management of cardiogenic shock, the outlook is positive. However, if the patient is not improving at 24 h, it serves as a strong indicator to alter the course of care, if appropriate as the predicted outcome is not good.

## IMPLEMENTATION OF STAGING SYSTEM BY ALL CARE TEAM MEMBERS

The simplicity of the SCAI criteria facilitates its use by any member of the patient's care team, from initial assessment and

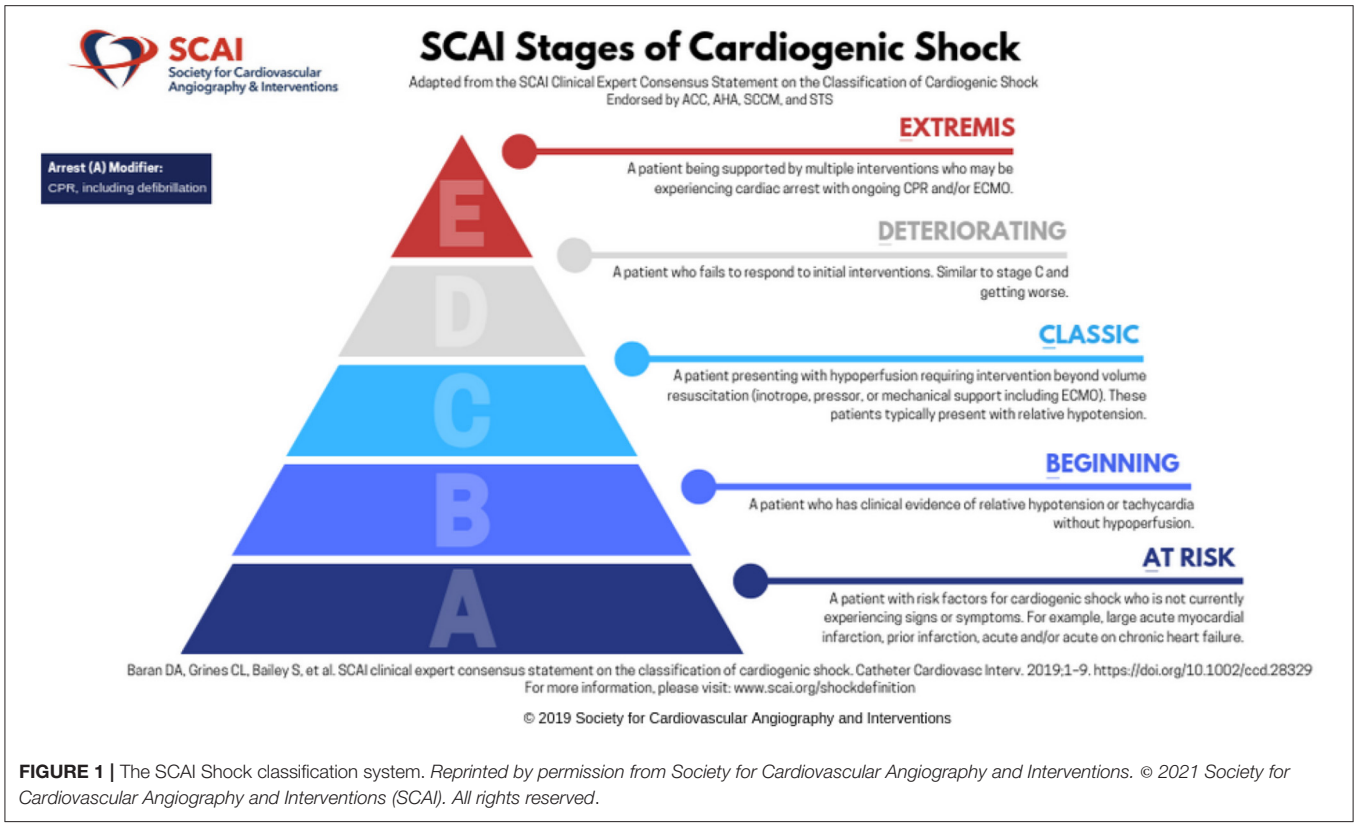


**FIGURE 1 |** The SCAI Shock classification system. *Reprinted by permission from Society for Cardiovascular Angiography and Interventions. © 2021 Society for Cardiovascular Angiography and Interventions (SCAI). All rights reserved*.

triage by Shock team responders and emergency department staff, to extracting objective data from the patient's electronic medical record (EMR) after admission. In fact, the SCAI classification system could potentially be integrated into an EMR to facilitate awareness of a patient's clinical status for the entire care team, and to alert providers of deteriorating clinical status, which may require associated escalating interventions. This wouldn't be perfect, but could be based on vital signs, changes in laboratories and urine output, since most of these factors are integrated into the system already.

## FUTURE DIRECTIONS

The SCAI Shock classification has been validated in retrospective as well as prospective cohorts and has gained traction since it filled a void which had existed. Future directions include refinements to the classification to guide clinicians and increase uniformity of assignment of SCAI stage. The writing committee which created the SCAI Shock Staging is currently working on an updated guidance document which will offer more concrete definitions of the various SCAI stages, while maintaining the simplicity and utility which the system enjoys currently. It is notable that the SCAI staging has been found to be predictive with a variety of populations and ways of retrospectively and prospectively defining it. The key elements appear to be hypoperfusion at the gateway to SCAI Stage C, and the element of time indicating that a patient is deteriorating (stage D). The specific laboratory or hemodynamic values seem less important than the clinical gestalt, as shown by the prospective experience.

Studying CS patients in the setting of prospective randomized trials is challenging for a number of reasons. First, these patients have poor perfusion by definition so obtaining informed consent is problematic. Given the patient acuity, it is often not practical to wait for prolonged periods of time to find designated family representatives and surrogate consent is not always acceptable. In addition, depending on the study entry criteria, patients may be excluded due to lack of a catheter or other datapoint despite the presence of CS. Furthermore, despite few proven therapies, there is a frequent lack of equipoise. Investigators often believe that mechanical pumps must be better given the increase in cardiac output, and may be unwilling to randomize some patients. Lastly, prior to the SCAI Shock classification, all patients with CS were "lumped together" leading to a mix of outcomes.

Another way to study CS is through registry studies. The American Heart Association is exploring the possibility of a large nationwide registry of CS patients which would gather broad data across a variety of centers of varying size and experience across the United States and give unique insights. The focused Cardiogenic Shock Working Group has utilized their registry to generate insights into CS outcomes (15, 23).

Perhaps the most impactful change would be the use of the SCAI stages as part of prospective, randomized clinical trials of treatments for CS. As stated earlier, trials which include extremely heterogeneous populations have not shown superiority of any device to modify survival in patients with cardiogenic shock.

Either that means that cardiogenic shock is not a modifiable condition (which is unlikely), or that the different subgroups of patients behave differently. Designing future clinical trials and large prospective studies where the SCAI classification system is used to define patient responder subgroups is a tangible goal for the imminent future. Conceivably this would lead to further refinements of the SCAI criteria, with specific algorithms for management by patient responder group, and new systems for cardiogenic shock management.

## CONCLUSION

A small fire is easier to quell than a massive blaze, and treating all shock in a similar fashion is like using a fire extinguisher to put out all fires: Doomed to failure! Hopefully, the lingua franca of shock (the SCAI Shock classification) will lead to a new chapter being written where we find effective treatments to reduce the mortality of this devastating illness. After more than 20 years of trying, we owe our patients nothing less than persistence and to find treatments that work.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

DB conceived of the paper and edited and revised manuscript. AL wrote the first draft and edited for clarity and content. Both authors contributed to the article and approved the submitted version.

## REFERENCES


1. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, et al. Contemporary management of cardiogenic shock: a scientific statement from the american heart association. *Circulation.* (2017) 136:e232–68. doi: 10.1161/CIR.0000000000000525
2. De Backer D, Arias Ortiz J, Levy B. The medical treatment of cardiogenic shock: cardiovascular drugs. *Curr Opin Crit Care.* (2021) 27:426–32. doi: 10.1097/MCC.0000000000000822
3. Kunkel KJ, Fuller B, Basir MB. Management of cardiogenic shock in patients with acute myocardial infarction. *Interv Cardiol Clin.* (2021) 10:345–57. doi: 10.1016/j.iccl.2021.03.006
4. Lemor A. Ya'qoub L, Basir MB. Mechanical Circulatory Support in Acute Myocardial Infarction and Cardiogenic Shock. *Interv Cardiol Clin.* (2021) 10:169–84. doi: 10.1016/j.iccl.2020.12.005
5. Rob D, Bělohlávek J. The mechanical support of cardiogenic shock. *Curr Opin Crit Care.* (2021) 27:440–6. doi: 10.1097/MCC.0000000000000837
6. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK investigators should we emergently revascularize occluded coronaries for cardiogenic shock. *N Engl J Med.* (1999) 341:625–34. doi: 10.1056/NEJM199908263410901
7. Harjola VP, Lassus J, Sionis A, Køber L, Tarvasmäki T, Spinar J, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Heart Fail.* (2015) 17:501–9. doi: 10.1002/ejhf.260
8. Pöss J, Köster J, Fuernau G, Eitel I, de Waha S, Ouarrak T, et al. Risk stratification for patients in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol.* (2017) 69:1913–20. doi: 10.1016/j.jacc.2017.02.027
9. Rivas-Lasarte M, Sans-Roselló J, Collado-Lledó E, González-Fernández V, Noriega FJ, et al. External validation and comparison of the CardShock and IABP-SHOCK II risk scores in real-world cardiogenic shock patients. *Eur Heart J Acute Cardiovasc Care.* (2020). doi: 10.1177/2048872619895230
10. Miller RJH, Southern D, Wilton SB, James MT, Har B, Schnell G, et al. Comparative Prognostic Accuracy of Risk Prediction Models for Cardiogenic Shock. *J Intensive Care Med.* (2020) 35:1513–9. doi: 10.1177/0885066619878125
11. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med.* (2012) 367:1287–96. doi: 10.1056/NEJMoa1208410
12. Thiele H, Zeymer U, Thelemann N, Neumann FJ, Hausleiter J, Abdel-Wahab M, et al. Intraaortic balloon pump in cardiogenic shock complicating acute myocardial infarction: long-term 6-year outcome of the randomized IABP-SHOCK II trial. *Circulation.* (2018). doi: 10.1161/CIRCULATIONAHA.118.038201
13. Ouweneel DM, Eriksen E, Sjauw KD, van Dongen IM, Hirsch A, Packer EJ, et al. Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol.* (2017) 69:278–87. doi: 10.1016/j.jacc.2016.10.022
14. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. *Catheter Cardiovasc Interv.* (2019) 94:29–37. doi: 10.1002/ccd.28329
15. Thayer KL, Zweck E, Ayouty M, Garan AR, Hernandez-Montfort J, Mahr C, et al. Invasive hemodynamic assessment and classification of in-hospital mortality risk among patients with cardiogenic shock. *Circ Heart Fail.* (2020) 13:e007099. doi: 10.1161/CIRCHEARTFAILURE.120.007099
16. Schrage B, Dabboura S, Yan I, Hilal R, Neumann JT, Sörensen NA, et al. Application of the SCAI classification in a cohort of patients with cardiogenic shock. *Catheter Cardiovasc Interv.* (2020) 96:E213–e219. doi: 10.1002/ccd.28707
17. Pareek N, Dworakowski R, Webb I, Barash J, Emezu G, Melikian N, et al. SCAI cardiogenic shock classification after out of hospital cardiac arrest and association with outcome. *Catheter Cardiovasc Interv.* (2021) 97:E288–e297. doi: 10.1002/ccd.28984
18. Padkins M, Breen T, Anavekar N, van Diepen S, Henry TD, Baran DA, et al. Age and shock severity predict mortality in cardiac intensive care unit patients with and without heart failure. *ESC Heart Fail.* (2020) 7:3971–82. doi: 10.1002/ehf2.12995
19. Jentzer JC, van Diepen S, Barsness GW, Henry TD, Menon V, Rihal CS, et al. Cardiogenic shock classification to predict mortality in the cardiac intensive care unit. *J Am Coll Cardiol.* (2019) 74:2117–28. doi: 10.1016/j.jacc.2019.07.077
20. Jentzer JC, Schrage B, Holmes DR, Dabboura S, Anavekar NS, Kirchhof P, et al. Influence of age and shock severity on short-term survival in patients with cardiogenic shock. *Eur Heart J Acute Cardiovasc Care.* (2021). doi: 10.1093/ehjacc/zuaa035
21. Jentzer JC, Henry TD, Barsness GW, Menon V, Baran DA, Van Diepen S. Influence of cardiac arrest and SCAI shock stage on cardiac intensive care unit mortality. *Catheter Cardiovasc Interv.* (2020) 96:1350–9. doi: 10.1002/ccd.28854
22. Hanson ID, Tagami T, Mando R, Kara Balla A, Dixon SR, Timmis S, et al. SCAI shock classification in acute myocardial

infarction: Insights from the National Cardiogenic Shock Initiative. *Catheter Cardiovasc Interv*. (2020) 96:1137–42. doi: 10.1002/ccd.29139

23. Garan AR, Kanwar M, Thayer KL, Whitehead E, Zweck E, Hernandez-Montfort J, et al. Complete hemodynamic profiling with pulmonary artery catheters in cardiogenic shock is associated with lower in-hospital mortality. *JACC Heart Fail*. (2020) 8:903–13. doi: 10.1016/j.jchf.2020.08.012
24. Baran DA, Long A, Badiye AP, Stelling K. Prospective validation of the SCAI shock classification: Single center analysis. *Catheter Cardiovasc Interv*. (2020) 96:1339–47. doi: 10.1002/ccd.29319

**Conflict of Interest:** DB has consulted with Abiomed, Abbott, Getinge, Livanova and is on steering committee of Procyrion and CareDx. He has spoken for Pfizer. None of these are related to the current work.

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# Monitoring Mitochondrial Partial Oxygen Pressure During Cardiac Arrest and Extracorporeal Cardiopulmonary Resuscitation. An Experimental Pilot Study in a Pig Model

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**Introduction:** Ischemia and reperfusion are crucial in determining the outcome after cardiac arrest and can be influenced by extracorporeal cardiopulmonary resuscitation (ECPR). The effect of ECPR on the availability and level of oxygen in mitochondria remains unknown. The aim of this study was to find out if skin mitochondrial partial oxygen pressure ($mitoPO_2$) measurements in cardiac arrest and ECPR are feasible and to investigate its course.

**Materials and Methods:** We performed a feasibility test to determine if skin $mitoPO_2$ measurements in a pig are possible. Next, we aimed to measure skin $mitoPO_2$ in 10 experimental pigs. Measurements were performed using a cellular oxygen metabolism measurement monitor (COMET), at baseline, during cardiac arrest, and during ECPR using the controlled integrated resuscitation device (CIRD).

**Results:** The feasibility test showed continuous $mitoPO_2$ values. Nine experimental pigs could be measured. Measurements in six experimental pigs succeeded. Our results showed a delay until the initial spike of $mitoPO_2$ after ECPR initiation in all six experimental tests. In two experiments (33%) $mitoPO_2$ remained present after the initial spike. A correlation of $mitoPO_2$ with mean arterial pressure (MAP) and arterial partial oxygen pressure measured by CIRD (CIRD-$PaO_2$) seemed not present. One of the experimental pigs survived.

**Conclusions:** This experimental pilot study shows that continuous measurements of skin $mitoPO_2$ in pigs treated with ECPR are feasible. The delay in initial $mitoPO_2$ and discrepancy of $mitoPO_2$ and MAP in our small sample study could point to the possible value of additional measurements besides MAP to monitor the quality of tissue perfusion during cardiac arrest and ECPR.

**Keywords: heart arrest, cardiac arrest, extracorporeal cardiopulmonary resuscitation, mitochondrial oxygen pressure, circulation monitoring**

## INTRODUCTION

In cardiac arrest, the duration of ischemia is an important determinant for survival and neurological outcome (1, 2). In order to shorten this ischemic period during cardiac arrest, extracorporeal cardiopulmonary resuscitation (ECPR) can be used to recover circulation and effective oxygen transport. The possible beneficial effect of ECPR on neurologically favorable survival has already been studied previously (3). However, the best treatment protocol of ECPR regarding ECPR settings is still unknown.

To determine if the recovery of circulation and oxygen delivery using ECPR are sufficient, we measured oxygen in the mitochondria, as final destination of oxygen. After all, mitochondria are important for generating energy, using oxygen, for cellular processes and maintaining life (4, 5). Protoporphyrine IX (PpIX) is an endogenously present porphyrin in the mitochondria, which can be enhanced by administrating 5-aminolevulinic acid hydrochloride (ALA) crème (6). The subcellular distribution of PpIX in ALA stimulated cells has been studied using wide-field fluorescence microscopy (7). Previous research has shown the possibilities of measuring partial oxygen pressure ($PO_2$) in the mitochondria by PpIX using its oxygen-dependent delayed fluorescence (7–10). To confirm that this delayed fluorescence truly measures inside the mitochondria, a previous study compared photobleaching (a contrast enhancement technique for PpIX) to MitoTracker Green (a method to identify mitochondria). This comparison showed a high degree of co-localization (7). This confirmed that, for a time window of several hours after ALA administration, PpIX measurements with delayed fluorescence corresponds to a mitochondrial localization (7). This method of measuring mitochondrial $PO_2$ ($mitoPO_2$) has also been validated to perform well in the skin (11). In addition, the possibility to perform continuous $mitoPO_2$ measurements is shown in adults by Ubbink et al. (10) and in newborns by Costerus et al. (12).

The primary aim of this study is to find out if continuous measurements of skin $mitoPO_2$ in a pig are feasible and what the course of this $mitoPO_2$ is during cardiac arrest and ECPR. The secondary aims are to investigate if there is a correlation between the course of $mitoPO_2$ and mean arterial pressure (MAP) and to identify the correlation between the course of $mitoPO_2$ and favorable neurological survival.

**Abbreviations:** ALA, 5-Aminolevulinic Acid Hydrochloride; ALS, Advanced Life Support; BLS, Basic Life Support; CARL, Controlled Automated Reperfusion of the Whole Body; CIRD, Controlled Integrated Resuscitation Device; CIRD-$PaO_2$, Partial oxygen pressure measured by Controlled Integrated Resuscitation Device; CPR, Cardiopulmonary Resuscitation; COMET, Cellular Oxygen Metabolism Monitor; ECPR, Extracorporeal Cardiopulmonary Resuscitation; MAP, Mean Arterial Pressure; $MitoPO_2$, Mitochondrial partial oxygen pressure; NaCl, Sodium Chloride; NDS, Neurologic Deficit Score; $PO_2$, Partial Oxygen Pressure; PpIX, Protoporphyrine IX; ROSC, Return Of Spontaneous Circulation; VA-ECMO, Venoarterial-Extracorporeal Membrane Oxygenation; VF, Ventricular Fibrillation.

## METHODS

Between November 2017 and September 2020, 11 male and female German landraces pigs (weight: 50.0–82.0 kg) were eligible for skin $mitoPO_2$ measurements. Continuous skin $mitoPO_2$ measurements in pigs with experimental settings of cardiac arrest treated with ECPR have not been performed before. In order to determine if these measurements are possible to perform and feasible in our test set up we first performed a feasibility test in one pig. This test showed that continuous measurements in this set up was possible. Therefore, we selected 10 pigs to perform continuous skin $mitoPO_2$ measurements as experimental test group. Of these 10 experimental tests, one could not be performed due to technical failure before the start of the test.

All animals received humane care and were treated in compliance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (13). The experiments were performed in accordance with the rules and regulations of the German animal protection law and the animal care guidelines of the European Community. The experiments were performed in the University of Freiburg, a highly experienced animal lab performing many ECPR procedures in pigs, and approved by the committee for ethics of the University Hospital Freiburg, Freiburg, Germany (no.G-15/148).

### Preparation of Tests

After premedication (20 mg/kg ketamine and 0.5 mg/kg midazolam) an intravenous (IV) access was placed, the pigs were sedated and paralyzed (3–4 mg/kg propofol and 0.2 mg/kg vecuronium), intubated, and mechanically ventilated. Continuous intravenous anesthesia consisted of the administration of 10–15 mg/kg/h propofol, 1–5 μg/kg/h fentanyl and 0.2–0.4 mg/kg/h vecuronium. In the pre-arrest period the core temperature we aimed for was 36–38°C. This temperature was measured by a nasal temperature sensor and in case of a low body temperature the pig was heated using a warming blanket.

In order to perform $mitoPO_2$ measurements, a part of the skin (∼1 $cm^2$) was prepared. First, hair was removed by shaving, the skin was roughened, and then the skin was cleaned using sodium chloride (NaCl 0.9%) and ethanol (70%). The 20% ALA crème was prepared by mixing 400 mg ALA (Fagron, Barsbüttel, Gemany) with 2 g Lanettecrème I FNA (Teva Nederland BV, Haarlem NL) (6). To avoid photobleaching of PpIX by light, the applied ALA crème was directly covered by a plaster and by aluminum foil. The crème was placed 3 h before the first measurement and during this waiting time it was continuously protected to light (7, 11). Because of the use of a mechanical cardiopulmonary resuscitation (CPR) device and cannulation in the right groin and neck, we measured the $mitoPO_2$ in the left axilla/neck region. Five minutes before induction of arrest, the effect of the ALA crème was tested by compression of the sensor on the skin (8, 10). When the measurements were finished, the skin was again covered to protect from light in order to protect it from burn lesions.

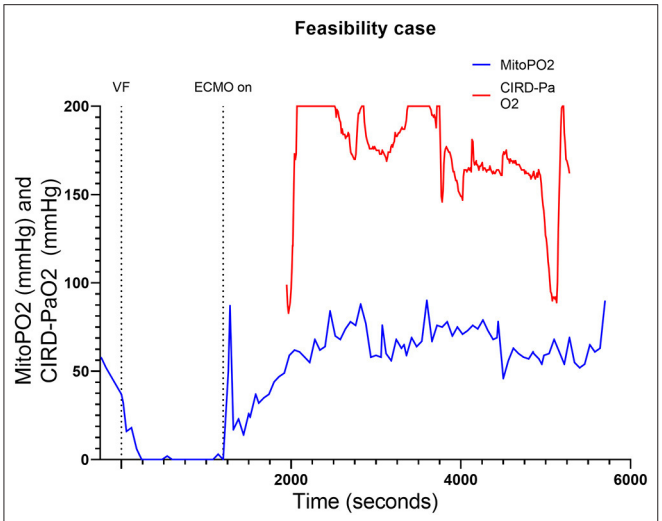


**FIGURE 1 |** Course of mitoPO$_2$ and CIRD-PaO$_2$ for the feasibility test. Course of mitoPO$_2$ and CIRD-PaO$_2$ in mmHg levels over time in seconds. VF, ventricular fibrillation; ECPR, extracorporeal cardiopulmonary resuscitation; CIRD-PaO$_2$, arterial partial oxygen pressure measured by controlled integrated resuscitation device; mitoPO$_2$, mitochondrial partial oxygen pressure.

## Test Procedure

The protocols and set up of the feasibility test and the experimental tests were slightly different, we will describe the test procedures separately.

### Feasibility Test

Ventricular fibrillation (VF) was induced by electrical stimulation *via* a Swan-Ganz catheter (Edwards Lifesciences Corp., Irvine, CA, USA). During 20 min of cardiac arrest, venous and arterial access was surgically generated via the right external jugular vein (23 Fr cannula) and the right common femoral artery (17 Fr cannula), respectively. In the period of cardiac arrest, mechanical ventilation was stopped and no life support was applied. After 20 min of cardiac arrest, ECPR was initiated with blood flow varying from 5.9 to 7.6 L/min. External defibrillation was performed in case of persisting VF. ECPR was weaned and stopped 60 min after initiation. If the animal could be weaned from ECPR, it was subsequently weaned from the ventilator and transferred to the animal facility after extubation. The pig was examined daily and neurological outcome was tested using a modified species-specific neurological deficit score (NDS) (14). This NDS ranges from 0 (normal) to 500 (brain death) and a favorable outcome was defined as NDS below 50 (14, 15). Euthanasia was performed in tabula in case the pig could not be weaned off extracorporeal circulation or invasive ventilation, in case the pig was expected to have inhumane suffering or prolonged death (an NDS of >200 at 24 h or an NDS of >120 at 48 h), and otherwise after 7 days (15).

### Experimental Tests

In the nine experimental tests, the ECPR implantation and induction of VF was the same as described at the feasibility test, except the timing of ECPR cannulation. In the experimental tests, this was already performed in the pre-arrest period. Next, after 5 min of VF, basic life support (BLS) was started with cardiopulmonary resuscitation (CPR) using a mechanical compression device (Corpuls CPR, GS Elektromedizinische Geräte G. Stemple GmbH, Kaufering, Germany) for 8 min. The next 22 min consisted of advanced life support (ALS), with additional administration of epinephrine every 4 min. After 35 min of cardiac arrest and CPR, ECPR was initiated with blood flow varying from 5.5 to 7.9 L/min and a 20 ml bolus of 7.45% potassium was applied for rhythm conversion. During ECPR in case of persisting VF, the heart was electrically defibrillated. If the VF sustained after three defibrillations, amiodarone and lidocaine were administered. If needed, continuous norepinephrine was administered with an aimed MAP of 60–80 mmHg. For these 10 experiments the controlled automated reperfusion of the whole body (CARL) protocol with the controlled integrated resuscitation device (CIRD, 1.0 Resuscitec GmbH, Freiburg/Germany) was used (15). ECPR was weaned around 120 min after initiation. This weaning consisted of slowly reducing the flow within 15–20 min until 1.5 L/min. If the pig displayed signs of sufficient circulation (i.e., arterial amplitude above 20 mmHg, MAP above 60 mmHg, and stable lactate measurements) ECPR was discontinued and surgically removed. All post ECPR care and neurologic outcome scoring was comparable to the feasibility test as described above.

## MitoPO$_2$ Measurements

The background of PpIX delayed fluorescence measurements is described in detail elsewhere (7). In short, PpIX is the final precursor of heme and is synthesized inside the mitochondria (7). When ALA crème is applied to the skin it enhances the endogenously present PpIX. The PpIX accumulates inside the mitochondria and possesses a triplet state, which reacts strongly with oxygen and therefore it can be used as an intramitochondrial oxygen sensor (7). For this experiment we used the previously described cellular oxygen metabolism monitor (COMET, Photonics Healthcare B.V., Utrecht, The Netherlands) to measure mitoPO$_2$ (10). The effect of the ALA crème was tested with an oxygen-consumption measurement performed by applying pressure on the skin sensor. This pressure causes an occlusion of microcirculatory blood flow and therefore oxygen delivery to the mitochondria is stopped, resulting in a decrease of mitoPO$_2$ (8, 10). A decrease of mitoPO$_2$ to ≤5 mmHg and a return to baseline values after release of the pressure on the skin sensor was defined as successful oxygen-consumption measurement. This measurement was performed at least two times before induction of cardiac arrest. During cardiac arrest and during ECPR mitoPO$_2$ was measured every minute and, on indication, more often with a maximum frequency of every second for 60 s.

## Other Measurements

Arterial PO$_2$ was measured via online blood gas sampling by the CIRD (CIRD-PaO$_2$). Systolic, diastolic, and mean arterial pressure were measured invasively via a carotid arterial cannula.

**TABLE 1 |** Individual characteristics of measurements in six experimental pigs.

| Case | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Sex | Male | Male | Male | Male | Male | Male |
| Weight (kg) | 50 | 54 | 59 | 62 | 70.5 | 70.5 |
| Time: initiation of VF until first low mito$PO_2$ (≤5 mmHg) in seconds | 26 | 23 | 13 | 31 | 60 | 64 |
| Time: initiation ECPR until mito$PO_2$ > 5 mmHg in seconds | 1,122 | 1,829 | 1,139 | 481 | 900 | 1,008 |
| Correlation of mito$PO_2$ and CIRD-$PaO_2$ | No | No | Yes | Yes | No | No |
| ECPR Survival | No | No | No | Yes, 2 days | No | No |

*Time initiation of VF until first low mito$PO_2$ is set as the time of initiation of VF until the first mito$PO_2$ measurement of ≤5mmHg. VF, ventricular fibrillation; mito$PO_2$, mitochondrial partial oxygen pressure; BLS, basic life support; ALS, advanced life support; ECPR, extracorporeal cardiopulmonary resuscitation; CIRD-$PaO_2$, partial oxygen pressure measured by controlled integrated resuscitation device.*

For the feasibility test we will plot the mito$PO_2$ and CIRD-$PaO_2$ in a graph. All outliers of >200 mmHg will be set at 200 mmHg. The mito$PO_2$ (in mmHg), CIRD-$PaO_2$ (in mmHg), and MAP (in mmHg) of the experimental tests will be plotted in graphs from baseline until discontinuation of ECPR flow, which will approximately be at 2.5–3.0 h after initiation of ECPR. Due to the small number of cases, the courses of these measured values cannot be compared using statistical testing. Therefore, the comparing of the graphs will be done by careful visual inspection.

# RESULTS

## Feasibility Test

The feasibility test we performed, was to find out if skin mito$PO_2$ measurements in a pig during cardiac arrest and ECPR were possible. As shown in **Figure 1**, mito$PO_2$ of this case dropped after initiation of VF. When ECPR was initiated (after 20 min of VF), an initial spike in mito$PO_2$ followed by a slow upslope was seen. After the initial spike, the level of mito$PO_2$ remained high. This pig survived after ECPR weaning with a NDS at day 1 of 100, at day 2 a NDS of 60, and the following days a NDS of 0. Seven days after the experiment, it was euthanized according to the protocol.

## Experimental Tests

Of the nine experimental tests we performed, four had to be excluded. A detailed description of reasons for exclusion is found in **Supplementary Appendix A** (10.6084/m9.figshare.13591211). In short, in one experimental test the skin with ALA was exposed to too much light. In two other experimental cases we failed to perform the measurements continuously during the tests. The last experimental case could not be performed due to complication during preparation. Two of these experimental pigs were male and two female.

We included six (50.0–70.5 kg) pigs in this experimental test group. The characteristics of the measurements of these pigs are reported in **Table 1**. **Figures 2–4** show the course of mito$PO_2$, CIRD-$PaO_2$, and MAP of the six experimental tests in separate graphs, from baseline (just before start of the cardiac arrest) until discontinuation of ECPR flow. In all pigs, directly after initiation of VF, the mito$PO_2$ decreased rapidly. As shown in **Table 2**, the median time from initiation of VF until a mito$PO_2$ of ≤5 mmHg was 29 s (interquartile range, IQR 23–60). The median time from initiation of ECPR until first rise in mito$PO_2$ above 5 mmHg was 1,066 s (i.e., 17 min and 46 s, IQR 900–1,139 s).

In four of the six experimental tests (case 1, 2, 5, and 6), after initiation of ECPR the initial spike of mito$PO_2$ did not result in persisting high mito$PO_2$ values. In the other two experimental tests (case 3 and 4), after initiation of ECPR the initial spike of mito$PO_2$ was followed by a continuous level of mito$PO_2$ which approached baseline levels. There was no correlation between mito$PO_2$, CIRD-$PaO_2$, and MAP in the tests without persisting mito$PO_2$ values. In the two patients with continuous higher levels of mito$PO_2$, comparing the correlation of mito$PO_2$, CIRD-$PaO_2$, and MAP is complex. With careful visual inspection, the difference between the three values is smaller and seems somewhat related, especially in case 4. Case 3 could not be successfully weaned from ECPR due to technical problems. Case 4 survived after ECPR weaning. The NDS of this pig was 130 at day 1 and 2 and it was euthanized at day 2 due to humane reasons. All other cases could not be successfully weaned from the ECPR and died at termination of the experiment.

# DISCUSSION

In this study we showed that skin mito$PO_2$ measurements in a pig during cardiac arrest and ECPR are feasible. In all six experimental tests we found a rapid decrease of mito$PO_2$ after initiation of VF and a remarkably delayed increase in the initial measured mito$PO_2$ after reperfusion via ECPR. In four of the six cases no continuously high mito$PO_2$ values were present. However, in two of the cases mito$PO_2$ remained near baseline levels after the initial spike. The course of mito$PO_2$ in these two cases seemed correlated with CIRD-$PaO_2$ and MAP. One of these pigs survived, but with an unfavorable neurological outcome until 2 days after the experiment.

The rapid decrease of mito$PO_2$ after initiation of VF was expected to be found, because of the immediate stop of oxygen delivery and uptake due to whole body ischemia. Harms et al. (8) showed a rapid decrease of mito$PO_2$ as soon as oxygen delivery to the skin is stopped by performing local pressure to the skin sensor, which occludes the microvessels, in a rat experiment. Ubbink et al. (10) repeated this test in humans and they also found a rapid decrease in mito$PO_2$ when applying local pressure. After initiation of VF in our tests, systemic blood flow stops and

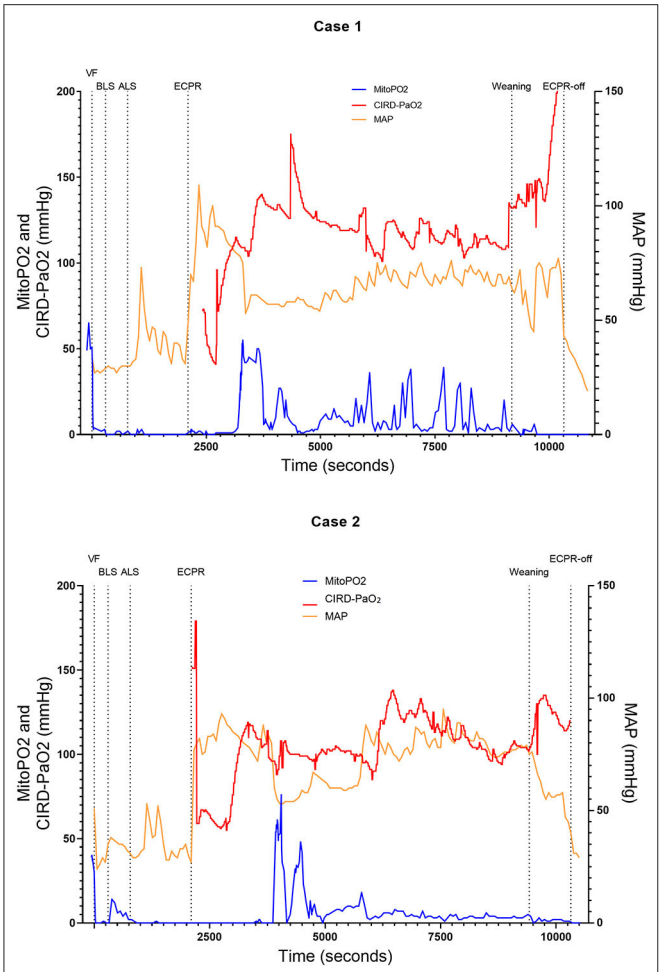


**FIGURE 2 |** Course of mitoPO$_2$, CIRD-PaO$_2$, and MAP for experimental tests case 1 and 2. Course of mitoPO$_2$ and CIRD-PaO$_2$ in mmHg levels at the left *Y*-axis and course of MAP in mmHg levels at the right *Y*-axis all over time in seconds. Case 1 at the above panel and case 2 at the below panel. VF, ventricular fibrillation; ECPR, extracorporeal cardiopulmonary resuscitation; CIRD-PaO$_2$, arterial partial oxygen pressure measured by controlled integrated resuscitation device; mitoPO$_2$, mitochondrial partial oxygen pressure.

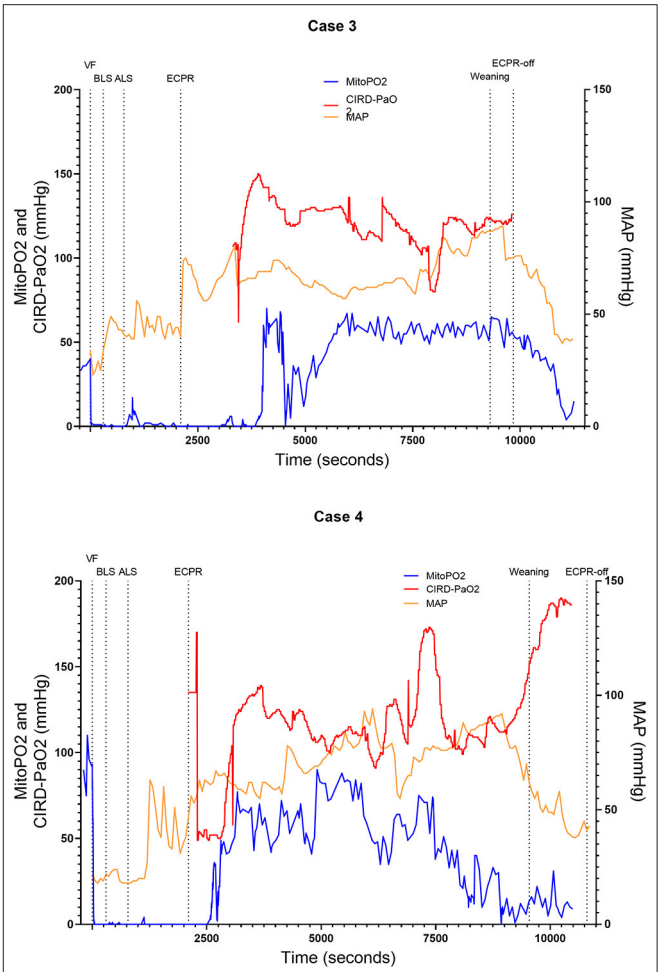


**FIGURE 3 |** Course of mitoPO$_2$, CIRD-PaO$_2$, and MAP for experimental tests case 3 and 4. Course of mitoPO$_2$ and CIRD-PaO$_2$ in mmHg levels at the left *Y*-axis and course of MAP in mmHg levels at the right *Y*-axis all over time in seconds. Case 3 at the above panel and case 4 at the below panel. VF, ventricular fibrillation; ECPR, extracorporeal cardiopulmonary resuscitation; CIRD-PaO$_2$, arterial partial oxygen pressure measured by controlled integrated resuscitation device; mitoPO$_2$, mitochondrial partial oxygen pressure.

therefore there will be a rapid decrease in oxygen delivery. This disappearance of blood flow and oxygen delivery acts the same as the oxygen consumption tests performing pressure to occlude the microvessels. This demonstrates the close relationship of tissue perfusion and tissue oxygenation.

The delay of increase in mitoPO$_2$ after initiation of ECPR we found is most probably due to adrenaline administered during ALS according to the resuscitation guidelines. The possible effects of medication on mitoPO$_2$ has been shown before. Ubbink et al. (10) showed, as an incidental finding, that the initial vasoconstriction caused by clonidine decreased the skin mitoPO$_2$ values. There was no effect on capillary venous oxygen saturation, however the effect on mitoPO$_2$ and flow remained present for around 15 min (10). Adrenaline stimulates the α1-receptors, among others, which causes vasoconstriction and centralization of blood flow (16). The effect of adrenaline on mitoPO$_2$ values has not been shown before. However, Fries et al. (17) showed that administration of adrenaline caused a decrease in capillary blood flow which persisted after the achievement of return of spontaneous circulation (ROSC). Therefore, administration of adrenaline might explain the delay of increase in skin mitoPO$_2$ values.

Another explanation for the delay of increase in mitoPO$_2$ after initiation of ECPR could be centralization, where the skin as an end organ will be the last organ to regain flow. After initiation of ECPR, the macrocirculation (MAP and blood flow) is restored immediately. However, the exact timing of restoration of the microcirculation in different tissues is unknown. In cardiac arrest, arterial blood flow decreases to zero and during CPR it will remain lower than normal (18). Therefore the

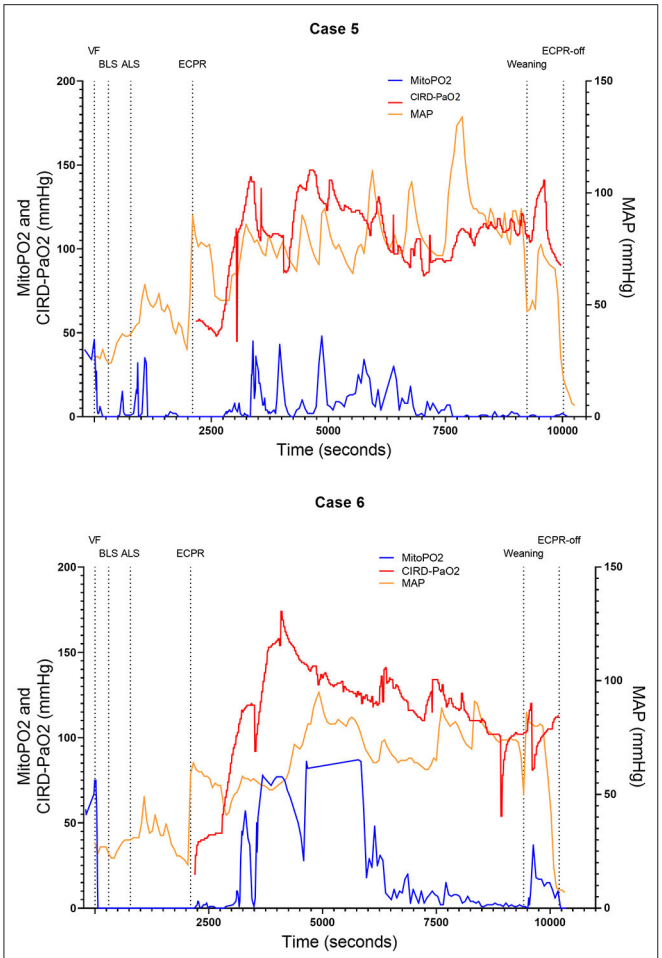


**FIGURE 4 |** Course of mitoPO$_2$, CIRD-PaO$_2$, and MAP for experimental tests case 5 and 6. Course of mitoPO$_2$ and CIRD-PaO$_2$ in mmHg levels at the left *Y*-axis and course of MAP in mmHg levels at the right *Y*-axis all over time in seconds. Case 5 at the above panel and case 6 at the below panel. VF, ventricular fibrillation; ECPR, extracorporeal cardiopulmonary resuscitation; CIRD-PaO$_2$, arterial partial oxygen pressure measured by controlled integrated resuscitation device; mitoPO$_2$, mitochondrial partial oxygen pressure.

**TABLE 2 |** Summary of characteristics.

| | |
|---|---|
| Time: initiation of VF until first low mitoPO$_2$ (≤5 mmHg) in seconds | 29 (23–60) |
| Time: initiation ECPR until mitoPO$_2$ > 5 mmHg in seconds | 1,066 (900–1,139) |
| Correlation of mitoPO$_2$ and CIRD-PaO$_2$ | 2/6 cases (66.7%) |
| ECPR survival | 1/6 cases (16.7%) |

*The continues variables are presented as medians and interquartile ranges, the categorical variables are presented as number and percentage.*
*VF, ventricular fibrillation; mitoPO$_2$, mitochondrial partial oxygen pressure; BLS, basic life support; ALS, advanced life support; ECPR, extracorporeal cardiopulmonary resuscitation; CIRD-PaO$_2$, partial oxygen pressure measured by controlled integrated resuscitation device.*

reduced stimulation of the arterial baroreceptors will activate the sympathetic system (19). This sympathetic system will centralize the blood flow and causes vasoconstriction to preserve heart and brain function (19). A hypothesis could be that when ECPR is initiated this vasoconstriction is present and only when the other vital organs are perfused, the perfusion of the skin will recover.

In four of the six experimental tests, the delay of increase in mitoPO$_2$ despite systemic reperfusion suggests irreversible damage to tissue perfusion, tissue oxygenation, or oxygen transport to the mitochondria. In these four tests, after the initial spike of high mitoPO$_2$ following ECPR initiation, no continuously high mitoPO$_2$ values were measured until the end of the experiment. In the two tests with recovery of the skin mitoPO$_2$ values, recovery of the tissue perfusion, tissue oxygenation, and oxygen transport to the mitochondria takes place. When high mitoPO$_2$ values were measured after the initial spike, the values remained high. The inadequacy of tissue oxygenation and long ischemic period could eventually lead to a microcirculatory shut down. A global shut down in cases of ischemia was already reported before (20). After an ischemic episode, the microcirculation respiration can recover to a certain extent, depending on the duration of ischemia and level of reperfusion (20). Ruggieri et al. (21) stated that, after severe ischemia some muscle cells in the heart can be irreversibly damaged and demarcation will occur, while the incompletely effected tissue can recover partly. The difference in mitoPO$_2$ course in the six experimental tests we performed could be explained by irreversible vs. incomplete effected tissue. We hypothesize that the quicker mitoPO$_2$ rises could be explained by less ischaemic cellular damage which could cause sooner re-activation of the mitochondrial function and therefore less overall ischaemic/reperfusion damage.

MitoPO$_2$ can be interpreted as determinant of the microcirculatory function. In order to regain oxygen levels into the mitochondria after cardiac arrest, tissue perfusion and tissue oxygenation have to be present. This tissue perfusion and oxygenation are largely influenced by an intact microcirculation. In case mitoPO$_2$ is detected, it can be expected that microcirculation has at least partly been recovered. Bodmer et al. (22) performed a study measuring the microcirculation and mitoPO$_2$ in the liver simultaneously. They found only a small difference of PO$_2$ in the microcirculation and mitoPO$_2$. Mik et al. (9) recently stated that average mitoPO$_2$ appears to be close to microvascular PO$_2$. MitoPO$_2$ measured by PpIX delayed fluorescence provides an estimation of microvascular PO$_2$ and therefore an it can be interpreted as determinant of the microcirculatory function.

The added value of monitoring microcirculatory function could be relevant in ECPR procedures, as the correlation between the mitoPO$_2$ and MAP is not consistently present in this study. In contrast to the abovementioned delay in recovery of tissue oxygenation due to an impaired microcirculatory function, the macrocirculation (MAP and blood flow) was restored immediately upon initiation of ECPR. This discrepancy between mitoPO$_2$, as a determinant of microcirculatory function, and MAP, as a determinant of macrocirculation, shows the importance of monitoring this microcirculatory function. Yu et al. (23) compared the microcirculation and macrocirculation and showed an inconsistent relation of microcirculation

(i.e., brain and brachioradial muscle) and macrocirculation (i.e., MAP) in pigs with cardiac arrest (23). Fritz et al. (24) performed ECPR in pigs, they found no differences in microcirculatory flow index at initiation and after 6 h of ECPR comparing the group treated with standard MAP to the group treated with high MAP. However, they did not directly investigate the relation between continuous microcirculatory function and MAP. In addition, two other studies compared microcirculation and macrocirculation in patients with cardiogenic shock treated with veno-arterial ECMO (VA-ECMO) (25, 26). Yeh et al. (26) showed no differences in early MAP for survivors and non-survivors, while early microcirculation was higher in survivors than in non-survivors. Chommeloux et al. (25) showed in successfully weaned patients despite normal MAP, normalization of microcirculatory values took 48 h after initiation of VA-ECMO. In order to apply personalized medicine and therefore a possible increase in the accuracy of treatment, monitoring of microcirculatory function should be the added to monitoring of macrocirculation.

In addition, the survival chance in pigs with continuously high mitoPO$_2$ is probably higher than in pigs without continuously high mitoPO$_2$. One of the two cases with continuously high mitoPO$_2$ survived this experiment. The other one died because of technical failure. In the experiments with pigs without continuously high mitoPO$_2$, none of them survived. No previous studies aimed on the course of mitoPO$_2$ measurements in ECPR in relation to survival outcome. However, Fries et al. (17) found less increase in microcirculation (i.e., capillary flow) in animals that failed resuscitation in a model with chest compressions. Furthermore, within 5 min of ROSC, microcirculation returned only within 20% of baseline values (17). This could point to the possible additional value of monitoring microcirculatory function during CPR, during ECPR, and after ROSC.

This study has several limitations. First, our sample size is small and of the experimental measurements only one pig survived. Therefore, we could not perform statistical tests to identify the correlation of the course of mitoPO$_2$ and survival or favorable neurological survival. Possible hypotheses for the low successful weaning numbers in this studies are described in the **Supplementary Appendix B**. Second, because of the preparation time of the ALA crème, mitoPO$_2$ measurements cannot be used during cardiac arrest and within the first hours after ECPR initiation in humans. In order to test our hypotheses and get more understanding of the pathophysiology, future experimental research should aim at the correlation of the course of mitoPO$_2$ and survival. Also, the course of mitoPO$_2$ comparing conventional CPR with ROSC and ECPR cases could extend the existing knowledge. Another topic which needs to be investigated in future research is if, in humans treated with ECPR, monitoring the microcirculatory function is a more accurate target than monitoring the macrocirculation in order to apply a more individually based treatment. If a method is found to shorten the time needed for ALA-induced PpIX enhancement within cells (e.g., with intravenous administration), mitoPO$_2$ measurements during ECPR could be also performed in humans.

## CONCLUSION

This experimental pilot study shows that continuous measurements of skin mitoPO$_2$ in pigs treated with ECPR are feasible. The delay in initial mitoPO$_2$ and discrepancy of mitoPO$_2$ and MAP in our small sample study could point to the possible value of additional measurements besides MAP to monitor the quality of tissue perfusion during cardiac arrest and ECPR.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

The animal study was reviewed and approved by Committee for Ethics of the University Hospital Freiburg, Freiburg, Germany (No. G-15/148).

## AUTHOR CONTRIBUTIONS

LM participated in the study design, acquired, analyzed, interpreted the data, and drafted and revised the manuscript. J-SP helped acquiring, analyzing, and interpreting the data and was a contributor in revising the manuscript. MW and DD helped interpreting the data and were major contributors in revising the manuscript. CU participated in the study design, helped interpreting the data, and was a major contributor in revising the manuscript. EM and GT participated in the study design, helped interpreting the data, and were contributors in revising the manuscript. SB helped acquiring the data and was a contributor in revising the manuscript. DG participated in the study design and was a contributor in revising the manuscript. DR majorly contributed to the conception of the study, participated in the study design, helped interpreting the data, and was a major contributor in revising the manuscript. All authors read and approved the final manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.754852/full#supplementary-material

## REFERENCES


1. Martinell L, Nielsen N, Herlitz J, Karlsson T, Horn J, Wise MP, et al. Early predictors of poor outcome after out-of-hospital cardiac arrest. *Crit Care.* (2017) 21:96. doi: 10.1186/s13054-017-1677-2
2. Adnet F, Triba MN, Borron SW, Lapostolle F, Hubert H, Gueugniaud PY, et al. Cardiopulmonary resuscitation duration and survival in out-of-hospital cardiac arrest patients. *Resuscitation.* (2017) 111:74–81. doi: 10.1016/j.resuscitation.2016.11.024
3. Holmberg MJ, Geri G, Wiberg S, Guerguerian AM, Donnino MW, Nolan JP, et al. Extracorporeal cardiopulmonary resuscitation for cardiac arrest: a systematic review. *Resuscitation.* (2018) 131:91–100. doi: 10.1016/j.resuscitation.2018.07.029
4. Gvozdjáková A. *Mitochondrial Medicine. Mitochondrial Medicine; Mitochondrial Metabolism, Diseases, Diagnosis and Therapy*. Dordrecht: Springer Science + Bussiness Media B.V (2008) p. 1–17.
5. Skulachev VP. Mitochondrial physiology and pathology; concepts of programmed death of organelles, cells and organisms. *Mol Aspects Med.* (1999) 20:139–84. doi: 10.1016/S0098-2997(99)00008-4
6. Harms FA, de Boon WM, Balestra GM, Bodmer SI, Johannes T, Stolker RJ, et al. Oxygen-dependent delayed fluorescence measured in skin after topical application of 5-aminolevulinic acid. *J Biophotonics.* (2011) 4:731–9. doi: 10.1002/jbio.201100040
7. Mik EG, Stap J, Sinaasappel M, Beek JF, Aten JA, van Leeuwen TG, et al. Mitochondrial $PO_2$ measured by delayed fluorescence of endogenous protoporphyrin IX. *Nat Methods.* (2006) 3:939–45. doi: 10.1038/nmeth940
8. Harms FA, Voorbeijtel WJ, Bodmer SI, Raat NJ, Mik EG. Cutaneous respirometry by dynamic measurement of mitochondrial oxygen tension for monitoring mitochondrial function *in vivo*. *Mitochondrion.* (2013) 13:507–14. doi: 10.1016/j.mito.2012.10.005
9. Mik EG, Balestra GM, Harms FA. Monitoring mitochondrial $PO_2$: the next step. *Curr Opin Crit Care.* (2020) 26:289–95. doi: 10.1097/MCC.0000000000000719
10. Ubbink R, Bettink MAW, Janse R, Harms FA, Johannes T, Munker FM, et al. A monitor for Cellular Oxygen METabolism (COMET): monitoring tissue oxygenation at the mitochondrial level. *J Clin Monit Comput.* (2017) 31:1143–50. doi: 10.1007/s10877-016-9966-x
11. Harms FA, Bodmer SI, Raat NJ, Stolker RJ, Mik EG. Validation of the protoporphyrin IX-triplet state lifetime technique for mitochondrial oxygen measurements in the skin. *Opt Lett.* (2012) 37:2625–7. doi: 10.1364/OL.37.002625
12. Costerus SA, Bettink MW, Tibboel D, de Graaff JC, Mik EG. Mitochondrial oxygen monitoring during surgical repair of congenital diaphragmatic hernia or esophageal atresia: a feasibility study. *Front Pediatr.* (2020) 8:532. doi: 10.3389/fped.2020.00532
13. National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals. *Guide for the Care and Use of Laboratory Animals*. 8th ed. Washington, DC: National Academies Press. (2011)
14. Forbess JM, Ibla JC, Lidov HG, Cioffi MA, Hiramatsu T, Laussen P, et al. University of Wisconsin cerebroplegia in a piglet survival model of circulatory arrest. *Ann Thorac Surg.* (1995) 60:S494–500. doi: 10.1016/0003-4975(95)00876-4
15. Taunyane IC, Benk C, Beyersdorf F, Foerster K, Cristina Schmitz H, Wittmann K, et al. Preserved brain morphology after controlled automated reperfusion of the whole body following normothermic circulatory arrest time of up to 20 minutes. *Eur J Cardiothorac Surg.* (2016) 50:1025–34. doi: 10.1093/ejcts/ezw186
16. Gough CJR, Nolan JP. The role of adrenaline in cardiopulmonary resuscitation. *Crit Care.* (2018) 22:139. doi: 10.1186/s13054-018-2058-1
17. Fries M, Weil MH, Chang YT, Castillo C, Tang W. Microcirculation during cardiac arrest and resuscitation. *Crit Care Med.* (2006) 34:S454–7. doi: 10.1097/01.CCM.0000247717.81480.B2
18. McDonald JL. Systolic and mean arterial pressures during manual and mechanical CPR in humans. *Ann Emerg Med.* (1982) 11:292–5. doi: 10.1016/S0196-0644(82)80125-X
19. Dunser MW, Takala J, Brunauer A, Bakker J. Re-thinking resuscitation: leaving blood pressure cosmetics behind and moving forward to permissive hypotension and a tissue perfusion-based approach. *Crit Care.* (2013) 17:326. doi: 10.1186/cc12727
20. Chun K, Zhang J, Biewer J, Ferguson D, Clemens MG. Microcirculatory failure determines lethal hepatocyte injury in ischemic/reperfused rat livers. *Shock.* (1994) 1:3–9. doi: 10.1097/00024382-199401000-00002
21. Ruggieri AJ, Levy RJ, Deutschman CS. Mitochondrial dysfunction and resuscitation in sepsis. *Crit Care Clin.* (2010) 26:567–75, x–xi. doi: 10.1016/j.ccc.2010.04.007
22. Bodmer SI, Balestra GM, Harms FA, Johannes T, Raat NJ, Stolker RJ, et al. Microvascular and mitochondrial PO(2) simultaneously measured by oxygen-dependent delayed luminescence. *J Biophotonics.* (2012) 5:140–51. doi: 10.1002/jbio.201100082
23. Yu J, Ramadeen A, Tsui AK, Hu X, Zou L, Wilson DF, et al. Quantitative assessment of brain microvascular and tissue oxygenation during cardiac arrest and resuscitation in pigs. *Anaesthesia.* (2013) 68:723–35. doi: 10.1111/anae.12227
24. Fritz C, Kimmoun A, Vanhuyse F, Trifan BF, Orlowski S, Falanga A, et al. High versus low blood-pressure target in experimental ischemic prolonged cardiac arrest treated with extra corporeal life support. *Shock.* (2017) 47:759–64. doi: 10.1097/SHK.0000000000000793
25. Chommeloux J, Montero S, Franchineau G, Brechot N, Hekimian G, Lebreton G, et al. Microcirculation evolution in patients on venoarterial extracorporeal membrane oxygenation for refractory cardiogenic shock. *Crit Care Med.* (2020) 48:e9–e17. doi: 10.1097/CCM.0000000000004072
26. Yeh YC, Lee CT, Wang CH, Tu YK, Lai CH, Wang YC, et al. Investigation of microcirculation in patients with venoarterial extracorporeal membrane oxygenation life support. *Crit Care.* (2018) 22:200. doi: 10.1186/s13054-018-2081-2


**Conflict of Interest:** DR declares having received speaking fees from Xenios GmbH and HillRom GmbH. EM is listed as inventor on patents related to mitochondrial oxygen measurements held by the Academic Medical Center Amsterdam and the Erasmus Medical Center Rotterdam, the Netherlands. EM is founder and shareholder of Photonics Healthcare, a company that holds exclusive licenses to these patents and that markets the COMET system. DG is a member of the medical advisory board of Xenios GmbH and received travel expenses and speaker fees from Xenios and Maquet GmbH. GT is shareholder of Resuscitec GmbH.

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