Veno-Arterial Extracorporeal Membrane Oxygenation

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Mortality in infarct-related cardiogenic shock (CS) remains high, reaching 40–50%. In refractory CS, active mechanical circulatory support devices including veno-arterial extracorporeal membrane oxygenation (VA-ECMO) are rapidly evolving. However, supporting evidence of VAECMO therapy in infarct-related CS is low. The basics of VA-ECMO therapy, current evidence, ongoing trials, patient selection and potential complications warrant focus.

Keywords: veno-arterial extracorporeal membrane oxygenation

1. Introduction

Cardiogenic shock (CS) is the leading cause of death in hospitalized patients with acute myocardial infarction (AMI) [1]. Up to 10% of AMI patients develop CS, with left ventricular (LV) failure being the leading cause (up to 80% of patients), followed by right ventricular failure and mechanical complications of AMI [2]. Despite major advances in acute cardiac care, mortality remains high, reaching 30–50% during the first 30 days [3][4] To date, revascularization of the culprit lesion is the only causal and effective evidence-based treatment [5][6]. The quest for further improvement of the treatment situation therefore continues and, in particular, the use of active mechanical circulatory support devices is rapidly evolving.

Next to percutaneous LV assist devices, veno-arterial extracorporeal membrane oxygenation (ECMO), also called extracorporeal life support (ECLS), is the major representative of mechanical circulatory support in CS. Compared to other mechanical circulatory support devices, VA-ECMO is able to give full hemodynamic and respiratory support. With 80% of all cases, CS is the leading entity for VA-ECMO use. Particularly between 2010 and 2015, its use increased exponentially [7]. In addition to facilitated availability, new percutaneous techniques for insertion, and the development of smaller and easier to use systems, this period coincides with the time when randomized controlled trials (RCT) showed that the intra-aortic balloon pump (IABP), as a former standard treatment option in AMI-CS, did not provide a survival benefit.

2. Basic Operating Principle of VA-ECMO

The detailed structure of ECMO devices vary between manufacturers. Basically, the VA-ECMO system contains of (1) an inflow cannula transporting blood from a central vein to the pump, (2) a pump with, today almost always, centrifugal flow to keep hemolysis to a minimum, (3) a membrane oxygenator able to fully undertake oxygenation and decarboxylation of the blood, (4) a blood warmer, and (5) an outflow cannula leading to a central artery. The device is, thus, able to give biventricular hemodynamic support. Cannulation can be performed either centrally (via right atrium and aorta or subclavian artery) or peripherally (predominantly via femoral vessels), which is nowadays more frequently chosen in non-post-cardiotomy CS. A major advantage of peripheral access is the less invasive approach and the absent need for a thoracic surgical intervention. This way, experienced centers without on-site cardiac surgery might also perform VA-ECMO therapy. However, in awake patients, central cannulation should be considered to allow for early mobilization. Additionally, severe peripheral vascular disease can be an indication for central cannulation. During VA-ECMO therapy, continuous parenteral anticoagulation is generally considered mandatory to avoid thrombotic complications.

3. Evidence of VA-ECMO Therapy in AMI-CS

Despite the steadily increasing use, available evidence of VA-ECMO in AMI-CS is low and guideline recommendations are relatively weak. European heart failure guidelines recommend a short-term percutaneous mechanical circulatory support in selected patients with refractory CS (class of recommendation IIa, level of evidence C) [8]. American guidelines only recommend considering VA-ECMO use in the setting of refractory cardiac arrest [9].

Outcome data on VA-ECMO in AMI-CS are mostly reduced to non-randomized trials. Sattler et al. showed in a very small retrospective single-center study in AMI-CS patients a higher number of survivors with VA-ECMO at short-term follow-up compared to patients without VA-ECMO [10]. In another small retrospective analysis, Sheu et al. demonstrated a survival

benefit for patients with AMI and profound CS (defined as systolic blood pressure < 75 mmHg despite medical and IABP treatment) [11]. In a meta-analysis including these two small studies covering only a total of 95 patients, VA-ECMO therapy was associated with improved survival at 30 days (absolute risk difference 0.33, 95% CI 0.14 to 0.52; $p = 0.0008$) [4]. However, these results need to be interpreted with caution because of the high risk of selection bias and an inclusion period during the early phase of VA-ECMO therapy. In the same meta-analysis, two observational studies were analyzed comparing VA-ECMO with TandemHeart or a percutaneous LV assist device (Impella®, Abiomed, Danvers, MA, USA). These showed no mortality benefit for VA-ECMO (absolute risk difference −0.03; 95% CI −0.21 to 0.14; $p = 0.70$).

The only available randomized trial on VA-ECMO in AMI-CS available to date included just 42 patients randomized in a 1:1 fashion to VA-ECMO or medical therapy only, in addition to revascularization [12]. The majority of patients experienced cardiopulmonary resuscitation (CPR) before study inclusion. With respect to the primary endpoint of LV ejection fraction, no difference was shown between the two groups at 30 days (50.0% in the VA-ECMO group (IQR: 44.0% to 59.0%) versus 50.8% in the control group (IQR: 47.2% to 60.6%), $p = 0.86$). Furthermore, there was no difference with respect to secondary endpoints such as all-cause mortality (19% in the VA-ECMO group vs. 33% in the control group, $p = 0.37$), stroke or bleeding. When comparing only in-hospital survivors, VA-ECMO therapy was associated with a longer intensive care unit stay and duration of mechanical ventilation. However, considering the comparatively low overall mortality and a median LV ejection fraction of 50% after 30 days, the severity of CS in the included patients may have been only modest. Further limitations include a higher number of diseased coronary vessels in the control group, which is known to be an independent predictor of worse outcome in CS [13][14].

Currently, three large randomized trials (RCT) are evaluating the use of VA-ECMO in AMI-CS (ECLS-SHOCK, EURO-SHOCK and ANCHOR). Detailed characterizations of the three trials are displayed in **Table 1**. All three trials are powered to assess potential differences in mortality or the combined endpoint of mortality and the requirement for active mechanical circulatory support.

Table 1. Ongoing Randomized Trials of VA-ECMO in AMI-CS.

	ECLS-SHOCK	EURO-SHOCK	ANCHOR
Identifier	**NCT03637205**	**NCT03813134**	**NCT04184635**
Sample Size	**420 patients**	**428 patients**	**400 patients**
First Patient in	**June 2019**	**January 2020**	**October 2021**
Patient enrolment as of January 2022	**300**	**33**	**<10**
Main Inclusion Criteria	• Infarct-related CS (STEMI or NSTEMI) < 12 h • Arterial lactate > 3 mmol/L • Planned revascularization • Age: 18–80 years • In case of prior CPR: duration < 45 min	• Infarct-related CS (STEMI or NSTEMI) • Presentation ≤ 24 h after ACS symptom onset • Persistence of CGS 30 min after revascularization attempt of culprit coronary artery • Arterial lactate > 2 mmol/L • Age: 18–90 years	• Infarct-related CS (STEMI or NSTEMI) < 24 h) • PCI performed or planned in the following 60 min • Age >18 years • In case of prior CPR: duration < 30 min
Treatment Arms	**Optimal medical therapy vs. VA-ECMO plus optimal medical therapy**	**Optimal medical therapy vs. Early VA-ECMO plus optimal medical therapy**	**Optimal medical therapy vs. Early VA-ECMO and IABP plus optimal medical therapy**
Primary Outcome	**All-cause 30-day mortality**	**All-cause 30-day mortality**	**Treatment failure at day 30 (death in the ECMO group and death or rescue ECMO in the control group)**

	ECLS-SHOCK	EURO-SHOCK	ANCHOR
Special Characteristics	**VA-ECMO arm: VA-ECMO insertion preferably prior PCI Non-VA-ECMO arm: Use of other mechanical circulatory support than VA-ECMO possible in case of defined escalation criteria**	**VA-ECMO arm: VA-ECMO insertion 30 min until 6 h after PCI Non-VA-ECMO arm: IABP insertion not permitted**	**VA-ECMO arm: VA-ECMO insertion as soon as possible Non-VA-ECMO arm: Use of IABP not recommended, other mechanical circulatory support devices not permitted**

IABP = intra-aortic balloon counterpulsation; (N)STEMI = (non-)ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.

Patients with CS due to mechanical complications of AMI play a special role in VA-ECMO therapy. In these, VA-ECMO might be used as an option for bridging to surgical or interventional therapy, which is often performed after an interval of one week or longer. Again, there is little evidence. In contrast to the European heart failure guidelines, guidelines in acute coronary syndromes recommend short-term mechanical circulatory support with a class of recommendation IIb, level of evidence C for ventricular septal rupture and refractory CS [15]. A recent review addressed the use of active mechanical circulatory support in the setting of ventricular septal defects [16].

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