Levosimendan in venoarterial ECMO weaning. Rational and design of a randomized double blind multicentre trial

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Abstract

Aims Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly being used in circulatory failure. The main indications are cardiogenic shock, post-cardiotomy cardiac failure, and refractory cardiac arrest. However, VA-ECMO weaning is particularly challenging, and weaning failure is reported to be as high as 50%, with increased related mortality. Levosimendan is a novel long acting effect inodilator used in cardiogenic shock and terminal heart failure decompensation. Levosimendan use in VA-ECMO patients seems to reduce weaning failure regardless of the initial aetiology and to reduce mortality when administrated early after VA-ECMO initiation. However, studies are limited to retrospective analyses and reported case series. The aim of the WEANILEVO trial is to evaluate whether administration of levosimendan before VA-ECMO weaning is associated with a reduced rates of weaning failure and recourse to other temporary circulatory support.

Methods and results WEANILEVO is a randomized, prospective, multicentre, double-blind, parallel-group, controlled trial. One hundred eighty patients will be enrolled if they had acute circulatory heart failure treated with VA-ECMO and for whom weaning is expected within 48 h. The study drugs are either levosimendan (0.2 μg/kg/min for 24 h) or a placebo. The primary endpoint of the trial is the absence of VA-ECMO weaning, recourse to another VA-ECMO, or other temporary circulatory assistance or death within 7 days of VA-ECMO weaning.

Conclusions Levosimendan use in VA-ECMO appears to be beneficial for reducing weaning failure and mortality. The results of WEANILEVO should significantly influence decisions regarding the use of levosimendan for VA-ECMO weaning.

Keywords Levosimendan; Heart failure; ECMO; Weaning; Mortality

Received: 17 December 2020; Revised: 25 April 2021; Accepted: 2 May 2021
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Introduction

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly being used in circulatory failure. The main indications are cardiogenic shock, post-cardiotomy cardiac failure, and refractory cardiac arrest. VA-ECMO provides early adequate organ perfusion in order to avoid multi-organ failure, allowing patients to benefit from cardiac transplantation or long-term mechanical circulatory support. Despite the increasing use of VA-ECMO and the growing number of dedicated centres with highly trained teams, morbidity and mortality remain high, ranging between 60% and 70%. VA-ECMO is still associated with multiple severe complications, particularly haemorrhagic, ischaemic, and
infectious ones. Moreover, VA-ECMO weaning is particularly challenging due to multifactorial conditions. The coexisting retrograde flow with the enhanced afterload of the left ventricle and unloaded right ventricle renders the evaluation of myocardial recovery difficult. Moreover, there is a lack of robust clinical and echocardiographic criteria to predict weaning success in VA-ECMO patients, and weaning failure is reported to be as high as 50%. Reducing the rate of weaning failure would likely result in reduced VA-ECMO-related mortality and morbidity.

Levosimendan is a novel inodilator that was introduced in 2000. It is used for multiple conditions including cardiogenic shock due to left or right ventricular failure and terminal heart failure decompensation. Levosimendan acts indirectly by enhancing actin-myosin sensitivity to calcium and contractility, without increasing myocardial oxygen consumption, with probable anti-inflammatory and cardio-protective effects as well. Moreover, the effect of levosimendan is sustained due to its long-acting active metabolite. Nevertheless, recent trials in cardiac surgery for the prevention or treatment of low output syndrome failed to demonstrate a benefit on mortality.

Treatment with levosimendan appears to be beneficial for VA-ECMO patients: levosimendan seems to reduce weaning failure regardless of the initial aetiology and to reduce mortality when administered early after VA-ECMO initiation. However, available studies are limited to retrospective analyses and reported case series. Moreover, early administration of levosimendan before VA-ECMO weaning in VA-ECMO patients with massive myocardial infarction and extended myocardial necrosis who have a reduced potential of cardiac recovery or for patients receiving extracorporeal cardiopulmonary resuscitation, for whom neurological recovery considerably affects weaning from VA-ECMO and mortality. In this context, levosimendan could be beneficial for reducing weaning failure in patients who meet specific weaning criteria. Treatment with levosimendan may enhance cardiac output and reduce the risk of organ failure, limiting recourse to another VA-ECMO or other form of mechanical circulatory support.

The aim of the WEANILEVO trial is to evaluate whether administration of levosimendan before VA-ECMO weaning in patients with predefined weaning criteria is associated with a reduced rate of weaning failure and of recourse to other temporary circulatory support.

Study design

The WEANILEVO study is a randomized, prospective, multicentre, double-blind, parallel-group, controlled trial aiming to evaluate the efficacy of levosimendan in reducing VA-ECMO weaning failure in adult patients. Patients receiving a continuous perfusion of levosimendan will be compared with a group of patients receiving a continuous perfusion of placebo before VA-ECMO weaning. The study is conducted in adherence to the principles of the World Medical Association’s Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act. This trial received approval for all participating centres from the local Ethics Committee (Comité de Protection des Personnes Ile de France) under the number ph-60-2019 CPP IDF X and from the Agence National de Sécurité des Médicaments et des Produits de Santé (ANSM, French national agency for the safety of drugs and medical products, approval number MEDAECPP-2019-06-00). The trial was also registered on ClinicalTrials.gov (No. NCT04158674). Specific insurance for the study has been contracted by the sponsor from the Hospital Mutual Insurance Company. Informed consent to participate in the clinical trial will be obtained, and information on the clinical trial will be given to each patient. If the patient is not capable of giving informed consent at the time of enrolment, informed consent will be sought by the investigator from his or her legally designated representative or responsible surrogate. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is provided in Supporting Information, and the SPIRIT figure for chronology of the protocol is included in the main body of the manuscript (Table 1). The first subject was randomized on 24 February 2020, and the last patient follow-up is planned for 2024. Twenty patients were included in two centres as per February 2021. Follow-up will include daily visits from the day of randomization to 7 days after VA-ECMO weaning, a visit 30 days after VA-ECMO weaning, a visit on the day of hospital discharge (maximum 6 months after weaning), and an evaluation of one-year mortality (Table 1). All participating centres are French tertiary cardiovascular intensive care units experienced in the management of VA-ECMO patients: Department of Anaesthesia and Critical Care of the University Hospital of Dijon, Amiens, Caen, Rouen, Strasbourg, Lille and the Institut Mutualiste Montsouris, Paris.

Study population

Patients are eligible for enrolment if they had acute circulatory heart failure due to medical causes or post-cardiotomy, treated with VA-ECMO in one of the participating centres, and for whom weaning is expected within 48 h. The detailed list of inclusion and exclusion criteria is provided in Tables 2 and 3.

Study treatment

The study treatments are either levosimendan or a placebo consisting of riboflavin contained in a multivitamin preparation (CERNEVIT®). CERNEVIT® is used to keep the blind, due
| TIMEPOINT               | Study period                                                                 |
|------------------------|------------------------------------------------------------------------------|
|                        | Enrolment | Allocation                              | Post-allocation              | Close-out                      |
|                        |           | Day 0 Drug infusion does not exceed 8 h after randomization                   | Daily until Day 7 after VA ECMO removal | Day 30 after VA ECMO removal | Discharge from hospital Does not exceed 6 months | One-year mortality |
|                        | Planned VA ECMO removal                                                     | VA ECMO removal does not exceed 48 h after the end of drug perfusion |                             |                                |                                                 |                   |
| ENROLMENT:             | Eligibility screen                                                          | X                             |                                 |                                 |                                                 |                   |
|                        | Informed consent                                                            | X                             |                                 |                                 |                                                 |                   |
|                        | Allocation                                                                  | X                             |                                 |                                 |                                                 |                   |
| INTERVENTIONS:         | Levosimendan Group                                                           | X                             |                                 |                                 |                                                 |                   |
|                        | Control Group                                                               | X                             |                                 |                                 |                                                 |                   |
| ASSESSMENTS:           | VIS score, temporary circulatory support, death                             | X                             |                                 |                                 |                                                 |                   |
|                        | Long term mechanical circulatory support, heart transplantation, renal- replacement therapy, ICU discharge, unwanted events | X                             |                                 |                                 |                                                 |                   |
|                        | Hospital discharge                                                          | X                             | X                               | X                               |                                                 |                   |
|                        | Mortality                                                                   | X                             | X                               | X                               |                                                 |                   |

ICU, intensive care unit; VA ECMO, veno arterial extracorporeal membrane oxygenation; VIS, vasoactive inotropic score.
to the yellow colour of the solution of diluted levosimendan. The study drugs are stored by the pharmacy of each centre according to the recommendations of the manufacturer. The reconstitution and dilution of the study drugs will be carried out as close as possible to the start of infusion for stability reasons. Twenty-four hour stability of the reconstituted and diluted solutions will be carried out as close as possible to the start of infusion for stability reasons.

### Table 2 Inclusion criteria of the WEANILEVO trial

- Patient aged ≥ 18 years
- Acute circulatory heart failure treated with VA-ECMO
- VA-ECMO weaning criteria defined as:
  - VA-ECMO flow at 1.0–1.5 L/min and/or VA-ECMO pump speed at 1500 rpm and
  - Left ventricular ejection fraction > 20% and subaortic velocity time integral > 10 cm
  - VIS ≤ 10
  - Arterial lactate ≤ 2 mmol/L
  - Right ventricular fractional area change > 30%
  - Right ventricular end-diastolic diameter < 35 mm
  - Combined fraction of inspired oxygen for VA ECMO and ventilator < 80%
- VA ECMO weaning expected within 48 h
- No documented or suspected bacterial infection within 48 h before inclusion (no antibiotic introduced during the previous 48 h)
- VA ECMO: venoarterial extracorporeal membrane oxygenation; RPM: revolutions per minute; VIS: vasoactive inotropic score.

### Randomization

Randomization will be performed online using the secure Cleanweb™ system after a final check of the eligibility criteria, 24 h (maximum 48 h) before the scheduled date of VA-ECMO weaning. Participants will be randomized in a 1:1 ratio to one of two arms: levosimendan or placebo. This allocation is stratified on centre, age (≥ 60 vs. < 60 years old) and VA-ECMO initial indication: cardiac arrest, cardiogenic shock or post-cardiotomy. Investigators and patients are blinded to the treatment assignment.

### Endpoints or outcome measures

The primary endpoint of the trial is VA-ECMO weaning failure, defined as the absence of VA-ECMO weaning, recourse to another VA-ECMO or other temporary circulatory assistance [Impella® pump device (Abiomed, Danvers, MA) or intra-aortic balloon pump], or death within 7 days of VA-ECMO weaning. The secondary endpoints are need for long-term circulatory assistance (i.e. left ventricular assist device or total artificial heart), heart transplant within 30 days of VA-ECMO weaning, renal insufficiency and/or renal replacement therapy, 30-day mortality regardless of cause, evolution of daily vasoactive-inotropic score (VIS)²⁰ beyond 24 h after the end of perfusion, length of intensive care unit stay, and length of hospital stay.

### Data collection

Data will be collected by investigators with the help of clinical research assistants and recorded on electronic case report forms (eCRF) available online at a dedicated website. With protected individual access for each participating centre. Patient data will be anonymous and coded according to a number. The eCRF includes tools to promote data quality, such as range checks for data values. Data monitoring will be performed by means of queries on the database done by statisticians and analysed to identify abnormalities and inconsistencies. At enrolment, we will collect patients demographic information (e.g. age, sex, height, and weight), past medical history with chronic medications, Sequential Organ Failure Assessment (SOFA) score and Simplified Acute Physiology score (SAPS II), haemodynamic parameters (e.g. arterial
pressure and heart rate), VIS, recourse to left ventricular unloading, biological data including lactate level, and renal replacement therapy use before enrolment. All initial indications and associated complications and time of VA-ECMO support before enrolment will be recorded. Inotropic treatment, VIS, recourse to mechanical circulatory assistance, heart transplantation, vital status, use of a respirator, haemodynamic parameters and biological data, ICU, and hospitalization release date will be recorded daily during 7 days after VA-ECMO weaning. At 30 days after weaning, recourse to mechanical circulatory assistance, heart transplantation, vital status, ICU, and hospitalization release date will be collected. If the patient is released before 30 days after weaning, he or she will be contacted by phone by a clinical research assistant to collect vital status and the cause of death if indicated. One year vital status will also be collected by phone by the clinical research assistant.

**Statistics**

Sample size was determined to detect a clinically significant 20% reduction in the primary endpoint. Considering a VA-ECMO weaning failure rate of 50% in the placebo group and a failure rate of 30% in the levosimendan group, 206 patients (103 per group) are required with 80% power at a bilateral alpha risk of 0.05 assuming that 10% of cases would be non-evaluable. The sample size was calculated using PASS software (version 11, Kayesville, Utah, United States). All randomized participants will be analysed regardless of the treatment allocated (intention to treat analyses) and after excluding patients with deviation from the protocol (per-protocol analyses). The main analysis will be carried out with the intention to treat population, by comparing the proportions of weaning failure (as defined in the outcomes section) in the two treatment groups using a Pearson χ² test or an exact Fisher’s test depending on the conditions of application. This analysis will be completed by a logistic regression, if imbalances between the groups on prognostic variables are found. A subgroup analysis will allow to evaluate if the effect of levosimendan varies according to the indication of the VA-ECMO (medical or surgical). The same analysis will be conducted in the per-protocol population. For second analyses, the frequencies of recourse to long-term assistance such as left ventricular assist device or total heart, recourse to heart transplantation, occurrence of renal failure and recourse to renal replacement therapy, all-cause mortality at 30 days, and 1 year after VA-ECMO withdrawal will be described in both groups and compared using a χ² test or an exact Fisher’s test. The mean VIS will be described in both groups and compared using Student’s t-test or a Mann–Whitney U-test. These comparisons will be made on intention-to-treat and per-protocol population. The mean lengths of resuscitation and hospital stays will be described and compared among survivors. The significance threshold of the analyses is set at 5% for all final analyses. The analyses will be performed under SAS version 9.4 by the team of statisticians, Direction of Clinical Research, University Hospital of Dijon, France. An interim analysis was planned after the inclusion of 80 patients to re-evaluate the number of subjects required given the assumptions. Based on the Peto-Haybittle method, the bilateral alpha risk was set to 0.001 for the interim analysis in order to not modify the level of significance in the final analysis.

**Data and safety monitoring board**

An independent Data and Safety Monitoring Board (DSMB) will monitor the safety and efficacy of the trial and periodically assess whether the trial should continue to the planned termination. Based on the safety data, the DSMB may recommend modifications to the protocol (e.g. amendments or termination of the study), and when needed, the DSMB will decide on stopping rules. They will declare any conflicts of interest if such should arise. The DSMB will report to the chairman of the steering committee, who in turn is responsible for implementing a decision to terminate the trial prematurely if deemed necessary.

**Discussion**

Venoarterial extracorporeal membrane oxygenation is extensively used for temporary mechanical circulatory support in order to restore adequate end-organ perfusion in refractory cardiogenic shock or cardiac arrest. However, despite increased use worldwide and dedicated highly trained teams, VA-ECMO mortality remains high, ranging between 60% and 70%. Mortality rates have been linked to patients’ initial condition and associated VA-ECMO complications. These complications are significant and can include life-threatening strokes, bleeding, and infections. Likewise, VA-ECMO weaning is critical and challenging. Optimal timing is unknown, and standardized criteria for successful weaning of patients under VA-ECMO are lacking. Weaning failure can be as high as 50% and is associated with secondary shock, recourse to another form of temporary mechanical circulatory support, high levels of inotrope or vasopressor use, and increased mortality. Moreover, weaning success is not associated with survival and complications occur following VA-ECMO weaning due to incomplete cardiac recovery, organ hypo-perfusion, and associated organ failure, particularly renal and liver. Weaning criteria are generally based on local protocols and vary considerably between centres, taking into consideration clinical, biological, and ultrasound evaluations. Clinical criteria usually include haemodynamic stability with mean arterial pressure >60 mmHg, with minimum or no...
infusion of vasopressors and/or inotropes, and VA-ECMO flow between 0.5–1.5 L/min or pump speed below 1500 revolutions per minute (rpm). Nevertheless, this low level of support can hide incomplete left and right ventricular recovery, given the associated partial unloading. Echocardiography parameters mainly evaluate left ventricular systolic function, right ventricular systolic function and dimensions, valvular function, and pericardial effusion before starting weaning. A left ventricle ejection fraction >20–25%, subaortic velocity time integral >10 cm, and mitral annular plane systolic excursion >10 cm/s have been associated with VA-ECMO weaning success. However, these criteria were retrospectively analysed in a small VA-ECMO cohort. Huang et al. evaluated right ventricular ultrasound parameters associated with VA-ECMO weaning: three dimensional right ventricular ejection fraction >24% and right ventricular fraction area change >25% were associated with weaning success. Low lactate level is the main biological criteria used for VA-ECMO weaning. Cut-offs range between 2 and 4 mmol/L. In a recent large multi-centric study of post-cardiomyopathy cardiac failure treated with VA-ECMO, lactate level >1.6 mmol/L at weaning was predictive of in-hospital mortality. However, weaning failure remains higher than 50% even when these criteria are fulfilled and is associated with an increase in overall mortality. Indeed, weaning failure is associated with the use of another form of temporary mechanical circulatory support, weaning failure related shock requiring the use of high dose vasopressors and inotropes, increased arrhythmia, a greater myocardial energy imbalance, excessive peripheral vasoconstriction and subsequent organ hypo-perfusion, and mortality. As such, reducing weaning failure is necessary to optimize patient management and reduce associated mortality. Levosimendan is a novel inodilator that enhances myocardial contractility by binding to troponin C and increasing calcium sensitivity, with prolonged actin-myosin contraction, without increasing oxygen myocardial consumption. Moreover, levosimendan has vasodilatory properties through adenosine triphosphate-sensitive potassium (KATP) channels present in the smooth muscle cells in coronary, pulmonary, and peripheral arteries as well as systemic veins. These vasodilatory properties could reduce afterload of both right and left ventricles with potential improvement of ventricular-arterial coupling. Moreover, levosimendan seems to have a cardio-protective effect by opening KATP channels in mitochondria. Nevertheless, there are conflicting results with levosimendan. Indeed, the first large randomized controlled trial in patients with decompensated heart failure failed to show improved survival at 180 days compared with dobutamine. Moreover, there is little data about levosimendan in cardiogenic shock with conflicting results on survival. Levosimendan in cardiac surgery seems to be ineffective in reducing low cardiac output syndrome in patients with reduced left ventricular ejection fraction with a composite end point including 30 day mortality and recourse to mechanical circulatory support or renal replacement therapy. Moreover, levosimendan compared with placebo in patients with post-operative low cardiac output syndrome after cardiac surgery did not reduce 30 day mortality. Nevertheless, in this randomized, double blind controlled trial, levosimendan doses varied considerably between centres, ranging from 0.025 to 0.2 μg/kg/min. However, according to a recent meta-analysis of randomized controlled trials, levosimendan appears to reduce mortality after cardiac surgery in patients with preoperative reduced systolic ventricular function.

Levosimendan use in VA-ECMO is an emerging practice aiming to reduce weaning failure and mortality. In a recent meta-analysis, levosimendan use in VA-ECMO adult patients was associated with a reduced rate of weaning failure and mortality from all causes. However, all data were extracted from retrospective analyses. Distelmaier et al. found that early perfusion of levosimendan in the first 24 h following VA-ECMO for cardiac failure after cardiomyopathy reduced the rate of weaning failure, as well as both 30 day and long-term mortality. Vally et al. evaluated the effect of levosimendan in VA-ECMO patients following medical cardiogenic shock and after cardiomyopathy. Levosimendan was administered 3.2 ± 2.8 days following VA-ECMO initiation. Weaning failure was reduced in the levosimendan group, but without reduced 30 day mortality, after propensity score matching analysis. In our study, we chose to administer levosimendan when all existing weaning criteria were present. Indeed, initial administration in patients suffering from major myocardial infarction with poor recovery possibilities will not reduce weaning failure and mortality. In these patients, early evaluation and orientation for long-term mechanical circulatory support, or heart transplantation is mandatory. Moreover, after initial cardiac injury and VA-ECMO initiation, inflammation and ischaemia–reperfusion injury are major with secondary myocardial injury, stunning, and necrosis. Minimal myocardial recovery is essential before inotrope administration in order to reduce weaning failure. Jacky et al. compared levosimendan infusion versus milrinone 24 h before VA-ECMO removal in a before and after retrospective study. Weaning success was higher in the levosimendan group, but the difference was not significant. In a retrospective analysis of 200 adult patients under VA-ECMO for cardiogenic shock, Guilherme et al. found no difference in weaning success or mortality in the levosimendan group compared with the control group even after matching groups with a propensity score analysis. Nevertheless, these studies used different levosimendan infusion doses and protocols. They are also retrospective analyses and underpowered to draw any strong conclusion.

Our objective was to use widely recognized clinical, biological, and ultrasound weaning criteria in a large multicentre randomized double blind study in order to unify criteria in each centre, and to evaluate the effect of levosimendan as
accurately as possible. Indeed, echocardiography criteria as described by Aissaoui et al. were used before VA-ECMO weaning in most studies. However, data on right ventricular evaluation are missing, except right ventricular 3D ejection fraction, which is not calculated in routine practice. Thereby, we decided to evaluate only the right ventricular fractional area change which is correlated with right ventricular ejection fraction in MRI and is routinely used. Moreover, radial contraction of the right ventricle is not altered after cardiac surgery, unlike longitudinal contraction, and both TAPSE and S′ value are poor values in this context.

Lactate levels are a marker of organ hypo-perfusion due to incomplete myocardial recovery, and a normal lactate level is mandatory before VA-ECMO weaning. High lactate levels at weaning were predictive of in-hospital mortality in post-cardiotomy patients treated with VA-ECMO. VIS was used in order to homogenize data concerning vasopressor or inotrope use after VA-ECMO removal, and value \( \leq 10 \) was used according to previous studies. We decided to administer levosimendan before VA-ECMO weaning. Indeed, early administration of levosimendan after VA-ECMO implantation could be ineffective to reduce weaning failure rate and VA-ECMO duration. In the case of extensive myocardial necrosis, recovery is uncertain, and levosimendan is ineffective. Switching to another form of long-term mechanical circulatory support or heart transplantation is the best alternative. The timing used to define weaning failure varies considerably—between 6 h and 30 days after VA-ECMO removal depending on the study. Tohme et al. showed that the median time between VA-ECMO weaning and related shock was 4 days. We chose 7 days after VA-ECMO weaning to define weaning related failure, which cover the levosimendan acting period.

**Conclusion**

Venoarterial extracorporeal membrane oxygenation is increasingly used for circulatory support, but weaning continues to be a critical period with a high risk of failure. Levosimendan is a novel inodilator that improves myocardial contractility without increasing oxygen consumption. Levosimendan use in VA-ECMO appears to be beneficial for reducing weaning failure and mortality. The results of our study should significantly influence decisions regarding the use of levosimendan for VA-ECMO weaning.

**Conflict of interest**

The authors report no conflict of interest.

**Funding**

The WEANILEVO trial is supported by Orion Pharmaceutical. Orion Pharmaceutical had no role in the trial design or in the data collection and analysis. All the centres will purchase the drug at full cost.

**Authors’ contributions**

O.E., P.G.G., and A.S.F. designed the trial. O.E. obtained funding for the trial. O.E., P.G.G., and A.S.F. drafted the manuscript. E.K. and B.B. helped to draft the manuscript. M.R., O.A., E.B., M.M., A.C., M.O.F., and P.M.M. provided critical revision of the manuscript. A.S.F. and E.K. are responsible for the statistical analyses. O.A.A., E.B., M.M., M.O.F., and P.M.M. are the coordinators of the clinical centres that will enrol the trial participants. The corresponding author had final responsibility for the decision to submit for publication. All authors have read and approved the final version of the manuscript.

**Supporting information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Data S1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents**

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