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Effects of Induced Moderate HYPOthermia on mortality in Cardiogenic Shock Patients Rescued by veno-arterial ExtraCorporeal Membrane Oxygenation (ECMO)

HYPO ECMO STUDY

Version ~~n°7 du 06/11/2017~~ n°7.1 du 25/04/2018

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LIST OF ABBREVIATIONS

AEs	Adverse events
AMI	Acute Myocardial Infarction
ANSM	Agence Nationale de Sécurité des Médicaments et des Produits de Santé
BP	Blood Pressure
CES	Centre d'Epidémiologie Clinique
CHRU	Centre Hospitalier Régional Universitaire
CIC	Centre d'Investigation Clinique
CPP	Comité de Protection des Personnes
CS	Cardiogenic Shock
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DRI	Department of Research and Innovation
ECMO	ExtraCorporeal Membrane Oxygenation
ICU	Intensive Care Unit
IABP	Intra-Aortic Balloon Pump
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LVAD	Left Ventricular Assist Device
MI	Myocardial Infarction
SAE	Serious Adverse Event
SAE/R	Serious Adverse Event/Reaction
SBP	Systolic Blood Pressure
VA-ECMO	Veno Arterial ExtraCorporeal Membrane Oxygenation

SYNOPSIS

TITLE	Effects of Induced Moderate HYPOthermia on mortality in Cardiogenic Shock Patients Rescued by veno-arterial ExtraCorporeal Membrane Oxygenation (ECMO) (HYPO ECMO study)
SPONSOR	Centre Hospitalier Universitaire Régional de Nancy
PROTOCOL VERSION	~~n°6 du 01/09/2017~~ n°7.1 du 25/04/2018
TYPE OF STUDY	Biomedical research
NUMBER OF RECRUITING CENTER	20
RATIONALE /BACKGROUND	Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is widely and increasingly used to support the most severe forms of cardiogenic shock (CS).Nevertheless, despite ECMO use, mortality remains high (50%). Moderate hypothermia (33-34°C) is widely used to improve the cerebral consequences of cardiac arrest. The use of moderate hypothermia during CS is strongly supported by experimental and preliminary clinical data. Hypothermia improves both myocardial performance and systemic hemodynamics, reduces infarct size and decrease mortality through a reduction in ischemia/reperfusion injury. In addition to its direct cardiovascular effects, hypothermia decreases the production of numerous pro-inflammatory cytokines. Furthermore, hypothermia attenuates ischemia/reperfusion injury in other organ systems and reduces endothelial cell apoptosis as well as systemic oxidative stress. The feasibility and good tolerance of moderate hypothermia is widely supported by its common use in patients with cardiac arrest, including CS patients. Therapeutic hypothermia has been reported in a few short studies in adult patients with CS. In CS, hypothermia improved cardiac index, mixed venous saturation and urine output without changes in mean arterial pressure, heart rate, systemic vascular resistance or pH. Finally, hypothermia resulted in less vasopressor use. To the best of our knowledge, there have been no published randomized human studies of therapeutic hypothermia in post-MI cardiogenic shock treated with VA-ECMO. We found only one ongoing clinical trial (NCT01890317) to test the effects of moderate hypothermia in CS following myocardial infarction. Importantly, in this study, patients will not be treated with VA- ECMO. CS patients treated with VA-ECMO have severe cardiac failure, associated with severe ischemia-reperfusion injury and pro-inflammatory profile leading to increased NO production and subsequent severe vasoplegia and multiple organs failure. We have demonstrated in a porcine model of cardiogenic shock treated with VA–ECMO that hypothermia leads to a marked decrease in vasopressor and fluid use (submitted). Therefore, we hypothesized that an early use of hypothermia aimed at protecting the body from ischemia-reperfusion injury and protecting the heart may decrease mortality in VA-ECMO-treated CS patients. The HYPO-ECMO trial will test the hypothesis that moderate hypothermia (temperature between 33°C≤ T°C ≤34°C) associated with VA-ECMO support results in a reduction in 30-day mortality in comparison with the normothermia 36°C≤ T°C ≤37°C.
MAIN OBJECTIVE	The study objective is to determine whether early moderate hypothermia (33°C≤ T°C ≤34°C) is superior to normothermia (36°C≤ T°C ≤37°C) in patients with cardiogenic shock treated with VA-ECMO with respect to 30-day mortality.
SECONDARY OBJECTIVES	<u>Evaluation of the impact of moderate hypothermia on</u>: - Mortality during hospitalization and up to 180 days. - VA-ECMO weaning time - Adverse cardiovascular events - Necessity of fluid and vasopressor (norepinephrine, epinephrine) - Lactate clearance - Duration of organ failure - Mechanical ventilation support use - Renal replacement therapy use - Duration of ICU stay and total duration of hospitalization;

	- The risk of bleeding - The risk of Sepsis (pulmonary, blood, venous lines, VA-ECMO cannulaes)
PRIMARY ENDPOINT	All-cause mortality at day 30 following randomization (i.e. 30 day mortality)
SECONDARY ENDPOINTS	- All-cause mortality at 48 hours and day 7, 60, 180 - VA-ECMO duration - Composite endpoint of death, cardiac transplant, escalation to LVAD, stroke at days 30, 60, 180 - Cumulated amount of administered fluids and duration of vasopressors use in ICU - Duration to normalization of lactate - Number of days alive without organ failure(s), defined with the SOFA score and its components (respiratory, liver, coagulation and renal), between inclusion, D7 and D30. - Duration of mechanical ventilation and the number of days between inclusion and day 30, day 60 and D180, alive without mechanical ventilation - Number of days alive without renal replacement therapy, and the number of days, between inclusion and day 30, day 60 and D180, without renal replacement therapy - Duration of ICU stay, of hospitalization - Number of severe and moderate bleeding complications (GUSTO-definition, N Engl J Med. 1993;329:673–682) and the number of packed red blood cells transfused under VA-ECMO - Infection probability: pulmonary, blood and VA-ECMO cannulaes
STUDY DESIGN	A multicenter, prospective, controlled, randomized (moderate hypothermia 33°C≤ T°C ≤34°C) during 24 hours ± 1h versus normothermia 36°C≤ T°C ≤37°C, comparative open trial will be conducted on two parallel groups of patients with cardiogenic shock treated with VA-ECMO.
STUDY TREATMENTS/STRATEGIES PROCEDURES	Venoarterial ECMO (VA-ECMO) will be implanted in accordance to the local practice with flow settings to ensure sufficient tissue perfusion. With the exception of temperature control, all other diagnostic and therapeutic procedures will be done according to the current standard of care at the tertiary cardiovascular center. After inclusion and randomization (by CleanWeb® software), the patients according to the group allocated will be placed on moderate hypothermia (33°C≤ T°C ≤34°C) during 24 hours ± 1h or maintained on normothermia (36°C≤ T°C ≤37°C). **Hypothermia group**: Hypothermia will be induced as soon as possible during the first 6 hours (preferably 4 hours) after VA-ECMO implementation. Moderate hypothermia will be induced using the heat controller of the VA-ECMO circuit and other classical temperature management if necessary (external or internal technique) Temperature will be maintained between 33°C≤ T°C ≤34°C during 24 hours ± 1h followed by a progressive reheating (0.2±0.1°C/h) to reach 37 °C. Temperature at 37°C ± 0.3°C will be maintained during 48 hours ± 4h after having reached 37 °C. In cases of uncontrolled bleeding, hypothermia will be stopped and resumed as soon as the bleeding is controlled for a total duration of 24 hours of moderate hypothermia. The tolerance to hypothermia will be ensured with the cautious use of sedation and eventually with the use of a paralyzing agent in cases of shivering. **Normothermia group**: the extracorporeal life support organization (ELSO) recommends "Temperature can be maintained at any level by adjusting the temperature of the water bath. Temperature is usually maintained close to 37° C." A large amount of patients that need VA-ECMO experiment a cardiac arrest before ECMO implantation. Concerning the patients with cardiac arrest it is now recommended to maintain the patients between 33 and 36 degrees. Therefore,,the temperature will be maintained at 36°C≤ T°C ≤37°C.

	In both group, temperature will be measured every two hours during intervention (time during the first 92 hours at the allocated group). Follow up (vital status and cause of death) at D30 ± 5 days, D60 ± 5 days and D180 ± 15 days for all the patients.
MAIN INCLUSION CRITERIA	- Age ≥ 18 years - Intubated patients with cardiogenic shock treated with VA-ECMO - Patient affiliated to social security plan
NON-INCLUSION CRITERIA	- VA-ECMO after cardiac surgery for heart transplantation or heart - lung transplantation or left or biventricular assist device implantation - VA-ECMO for acute poisoning with cardio-toxic drugs - Pregnancy - Uncontrolled bleeding (bleeding despite medical intervention (surgery or drugs)) - Implantation of VA-ECMO under cardiac massage with a duration of cardiac massage ≥ 45 minutes - Out of hospital refractory cardiac arrest - Cerebral deficit with fixed dilated pupils - Participation in another interventional research involving therapeutic modifications - Patient moribund on the day of randomization - Irreversible neurological pathology - Minor patients - Patients under tutelage
RECRUITMENT PROCEDURES	All intubated patients with cardiogenic shock supported with VA-ECMO will be screened. Patients with cardiogenic shock treated with VA-ECMO in the intensive care unit meeting all of the inclusion and non-inclusion criteria will be enrolled and randomized in the study (emergency consent process cf chapter 13. 2).
EXCLUSION PERIOD	Individuals cannot participate simultaneously in other biomedical Research for the duration of the study. There is no exclusion period.
ACT REQUIRED LOGISTIC	Randomization
STUDY SIZE	**N= 334 patients** We considered that mortality in cardiogenic patients supported with VA-ECMO will be 50% (based both on ELSO data, Combes data (*Crit Care Med.* 2008 May;36(5):1404-11) and study principal investigator's personal data (database of 150 patients) The objective of the study is to demonstrate the superiority of the treatment with VA-ECMO plus moderate hypothermia as compared to VA-ECMO alone on mortality. Therefore, considering a total event risk (for the primary endpoint) of 50 % in the control group, a sample size of **N = 167 patients/group** will detecting a 15% absolute difference in favor the VA-ECMO group using a chi-square test with a 80 % power and considering a two-sided global alpha level of 5% using the LanDe Mets method with O'BrienFleming boundary for one interim analysis (efficacy and futility) after inclusion of 2/3 of the patients. De-identified hospitalization reports will be collected from the associated centers. These reports will be centralized at the CIC-P of the CHRU of Nancy and will be submitted to a reading committee.
STUDY PERIOD	Duration of participation of each patient: **6 months (D180)** Anticipated duration of recruitment: **36 months** Anticipated total duration of the study (statistical analysis included): **49 months**
STATISTICAL ANALYSIS OF THE DATA	**Statistical analysis for the primary endpoint:** The differences between the 2 study groups (i.e. intervention and controls) in the risk of all-cause mortality at day 30 following randomization will be studied using the Chi-2 test. To illustrate the association, both an odd-ratio and a hazard ratio will be provided. In addition, survival curves using the Kaplan-Meier method will be constructed.

	<u>Statistical analysis for the secondary endpoints</u>: For the secondary analysis of a) all-cause mortality at 48 hours and day 7, 60, 180, b) the composite endpoint of death, cardiac transplant, escalation to LVAD, stroke at days 30, 60, 180 the same analysis strategy will be performed as for the primary endpoint. Unpaired t-test will be performed, after checking for normality of the variables'distribution, for continuous outcomes. Importantly, In case of non-normal distributions, non-parametric tests will be performed. Chi-square tests (or Fisher exact test in case of insufficient number of expected patients in on of the 2x2 cell) will be performed for categorical outcomes other than those mentioned above and odd-ratios will be provided for illustration purposes.
FEASIBILITY OF THE PROJECT	Hypothermia induction during VA-ECMO does not require any additional device or supplementary catheter insertion. During therapeutic hypothermia, all centers monitore central temperature. Central temperature will be measured in each group in accordance with local practice (e.g bladder catheter, oesophageal probe…). All centers have Heater-Cooler Unit such as HCU 35 (Maquet company). This device allows a perfect control and hold of the target temperature .The water tank for the patient circuits is divided into two parts to ensure quick temperature adjustments at the outlets. In addition, it has exceptional cooling capacity through its fast ice-building technique using highly effective cooling plates and a powerful compressor. Moreover, considering the main objective, the HYPO-ECMO trial will be a pragmatic study in order to facilitate patient inclusion and monitoring. For each center we have obtained the agreement of both the intensivist and the cardiac surgeon. Finally, the trial will be integrated into the F-CRIN (French Clinical Research Infrastructure Network) INI-CRCT network (Cardiovascular and Renal Clinical Trialists). This network is very experimented regarding to patient recruitment. INI CRCT Network will accompany centers in collaboration with the sponsor and CIC-P in order to boost recruitment; implementation of BPC training (certificate transcelerate) using e-learning software; elaboration of communication tools (flyers, newsletter.....); organisation of investigator meetings. In case of lower than expected recruitment, initiation of satellite sites could be considered. Potential sites could be proposed by INI CRCT to the study's steering committee to improve the recruitment.
POTENTIAL IMPACT	The annual incidence of CS is estimated at 20 per 100,000 inhabitants (including myocardial infarction, myocarditis, cardiomyopathy and shock post cardiac surgery) in France with a mortality rate of 50 %. Reducing the death rate by 15% would save up to 1860 lives in France. This decrease in death rate might be accompanied by a reduction in the duration of ICU and hospital stays, therefore reducing the costs associated with the care of these critically ill patients. Better long-term outcomes might also be expected. This issue is important because ECMO use during cardiogenic shock management is still increasing worldwide and it is now urgent to determine the best approach to optimize such promising therapy. Recent papers demonstrated that the use of ECMO has increased rapidly, whereas rates of in-hospital mortality have decreased. These changes have taken place in the context of declining hospital costs associated with ECMO. Finally, comparatively to drug/new device research, hypothermia is inexpensive and very simple to implement in real life. Therefore, the only cost for society will be the grant for the study. This study is also the first step in the constitution of an "ECMO trial group". The originality is that this group will associate intensivist (medical or surgical), cardiologist and cardiac surgeons. The study coordinator (Prof Levy) has recently coordinated an expert group that published international recommendations for cardiogenic shock management. One very important

	recommendation was “The experts highlighted the fact that CS is a rare disease management of which requires a multidisciplinary technical platform and specialized and experienced medical teams. In particular, each expert center must be able to provide, at the same site, skills in a variety of disciplines (medical and interventional cardiology, anesthesia, thoracic and vascular surgery, intensive care, cardiac assistance, radiology including for interventional vascular procedures, circulatory support mobile unit). We firmly think that the network “ECMO trial group” is an important point to ameliorate cardiogenic shock management by grouping cardiologist, cardiac surgeons, anesthesiologist and intensivist.
FUNDING	***PHRC National 2015***

1 SCIENTIFIC *JUSTIFICATION AND GENERAL DESCRIPTION OF THE RESEARCH*

1.1 BACKGROUND

Cardiogenic shock (CS) is generally defined by cardiac index <2.2 l/min/m^2, hypotension, elevated pulmonary capillary wedge pressure, and end-organ hypoperfusion. The leading cause of CS is myocardial infarction (MI)[1] . CS affects approximately 5% to 7% of patients with MI. Mortality in CS remains high. For example, for CS complicating MI, mortality is still 50 % [1, 2]. Importantly, long-term outcome for 1-year survivors of CS is similar to that of non-shock acute MI survivors. That points the importance of improving short-term survival, which remains unacceptably low. This should place the focus on very early reperfusion in MI to prevent shock and novel therapies targeting patients with CS. Efforts to improve early survival are only made more important by the observation that survivors will likely enjoy good quality of life; most will be in New York Heart Association functional class I or II at 1 year of follow-up [3]. Further improving short-term outcomes has proven challenging. Recent attempts to inhibit inflammatory cytokine and nitric oxide-mediated systemic inflammatory response syndrome pathways in CS have yielded disappointing results Unfortunately, there have been few recent advances in the treatment of cardiogenic shock on the exception of ExtraCorporeal Membrane Oxygenation (ECMO). As recently suggested , therapeutic hypothermia is a possibility to treat cardiogenic shock [4]. Therapeutic hypothermia is widely available and has become a standard component of treatment for out-of-hospital ventricular tachycardia/ventricular fibrillation arrest. It also has wide-ranging systemic effects that might be particularly advantageous when considering the systemic manifestations of cardiogenic shock [5].

We hypothesized the following: first, the properties of therapeutic hypothermia that protect the brain and the heart and promote recovery after cardiac arrest will have similar effects on other vital organs and may improve short-term mortality; and second, therapeutic hypothermia merits further study as a potential novel treatment for cardiogenic shock patients treated with ECMO.

1.2 RATIONAL: CELLULAR AND ANIMAL MODELS

Hypoperfusion in the setting of CS leads to multiple end-organ damage and dysfunction that contributes to morbidity and mortality. Hypothermia decreases metabolic rate 5% to 7% per degree reduction of body temperature, and it decreases oxygen consumption, carbon dioxide production, and glucose consumption [5]. In addition, hypothermia affects the cardiovascular (CV) system in multiple ways, many of which could be potentially beneficial in CS, especially in a post-MI setting. In dogs, reduction of body temperature to 34°C in conjunction with vasodilator therapy results in increased contractility and external work of the left ventricle without increasing myocardial oxygen consumption [6]. In a dog model of post-MI CS, treatment with hypothermia to 32°C reduced heart rate, left ventricular (LV) end-diastolic pressure, systemic oxygen consumption, and estimated myocardial oxygen consumption while maintaining cardiac output and improving survival [7]. This study was validated recently in a porcine model of post-MI CS showing that animals treated with hypothermia had increased mean arterial pressure, stroke volume, pH, and mixed venous oxygen saturation with

decreased heart rate. Mortality was also improved in the hypothermia group (0% mortality in the hypothermia group vs. 63% in the control group) [8]. The inotropic effects of hypothermia seem to be at least partially related to an increase in action potential duration, calcium transients, sarcoplasmic reticulum calcium stores, and the fractional release of calcium in individual cardiac myocytes.

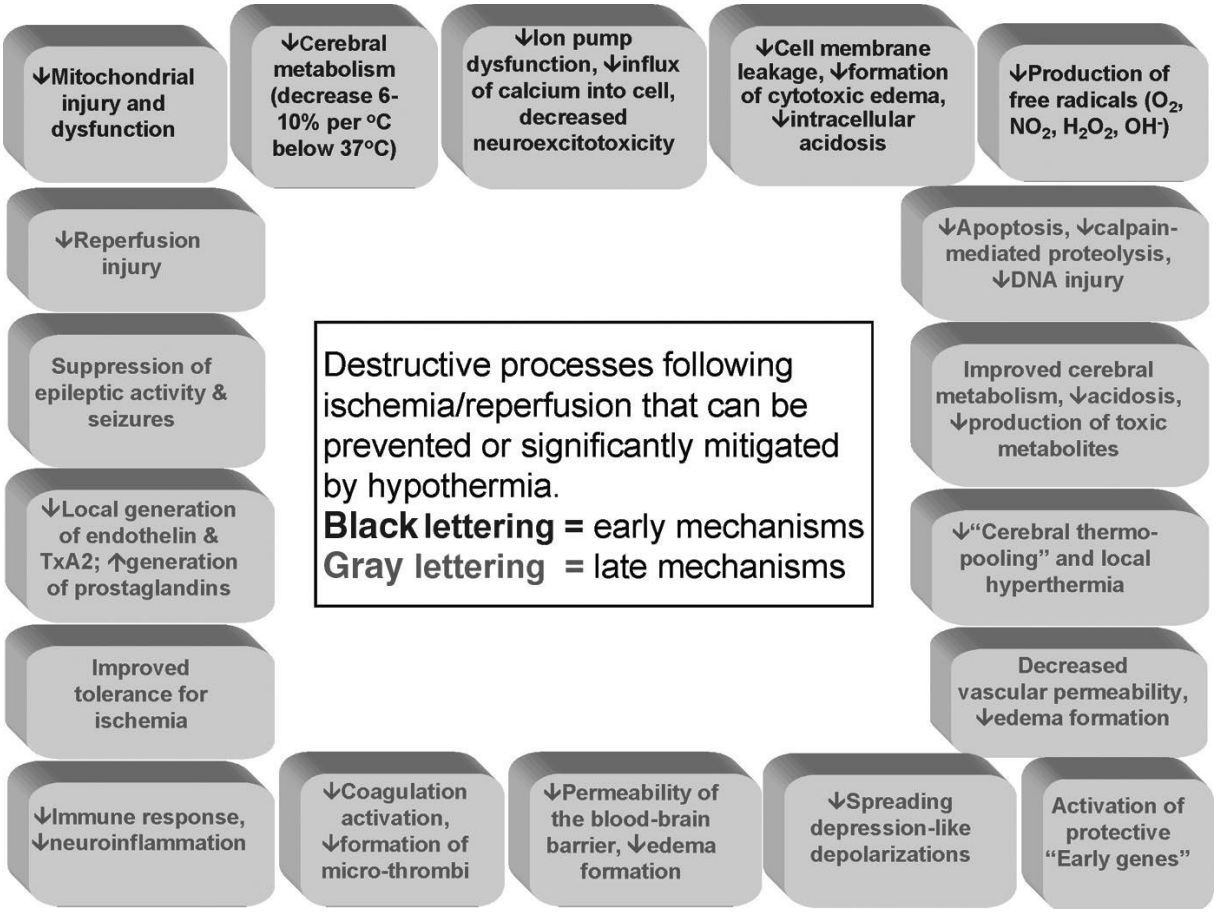

Figure1. Potential cerebral and systemic effects of moderate hypothermia (from Polderman KH, Critical Care Medicine 2009)

Results of animal models further suggest that therapeutic hypothermia may reduce ischemia/reperfusion injury after urgent revascularization for acute MI. In dogs, hypothermia beginning 30 min after left anterior descending coronary artery occlusion and continued through reperfusion 3 hours later improved cardiac function during occlusion, blunted hemodynamic derangements during reperfusion, and reduced infarct size at 7 days [9]. In sheep, in addition to greater immediate myocardial salvage, LV systolic function was improved at 8 weeks in animals treated with therapeutic hypothermia [10].

Hypothermia has additional outcomes outside its direct CV effects that may benefit patients with post-MI cardiogenic shock [11] (for review see reference 4). Accumulation of oxygen free radicals and an intense inflammatory response are hallmarks of myocardial ischemia and systemic hypoperfusion in post-MI cardiogenic shock. Hypothermia impairs neutrophil and macrophage phagocytic function and production of many proinflammatory cytokines. Therefore, therapeutic hypothermia could decrease the

severity of myocardial injury and dysfunction associated with MI. Furthermore, hypothermia attenuates ischemia/reperfusion injury in other organ systems and reduces endothelial cell apoptosis and systemic oxidative stress. Hypothermia also increases urine output, likely via reduction in fluid resorption beyond the mid-distal tubule in the kidney, an effect that could prove beneficial in post-MI cardiogenic shock patients with difficult-to-manage volume status.
The Figure 1 identifies potential pathways leading to or mediating the systemic effects of CS and where preclinical data suggest therapeutic hypothermia may modulate these effects.

Concerning VA-ECMO, Han et al [12] investigated in a rodent model the role of core body temperature in hypothermic protection after cardiac arrest. In these experiments, hypothermic ECMO was found to be significantly better than normothermic ECMO since hypothermia trended toward better 72-h survival. Finally, we have demonstrated (Critical Care Medicine, submitted) in a porcine model of CS treated with VA–ECMO) that hypothermia when compared to normothermia leads to a marked decrease in vasopressor and fluid use and to a better myocardial function. The potential beneficial effects of moderate hypothermia are summarized in figure 2

From bench to bedside : Important points and consequences for the HYPO-ECMO study. Studies on mechanisms underlying hypothermia's protective effects point to four key factors determining success or failure of cooling treatment. These are:

- **a)** Speed of induction of hypothermia; outcomes in animal experiments are far better when cooling is initiated rapidly after injury [13]. ***In HYPO-ECMO study we will use an early and fast cooling*.**
- b) Duration of cooling (depending on the severity of the initial injury and the time interval until target temperature is reached). ***In HYPO-ECMO study we will use 24 hours which is the most common duration used for cardiac arrest patients.***
- **c)** Speed of rewarming (this should be slow lest the destructive processes be reinitiated; this happens frequently if rewarming speeds are high). ***In HYPO-ECMO study the patient will be rewarmed in 24 hours (0.2±0.1°C/h) follow by 48 hours of maintained normothermia.***
- **d)** Proper management of side effects. Side effects include immunosuppression with increased infection risk, cold diuresis and hypovolemia, electrolyte disorders, insulin resistance, and mild coagulopathy. Targeted interventions are required to effectively manage these side effects. ***Specific management based on the literature for these potential side effects will be propose in HYPO-ECMO study (cf chapter 1.4.2)***

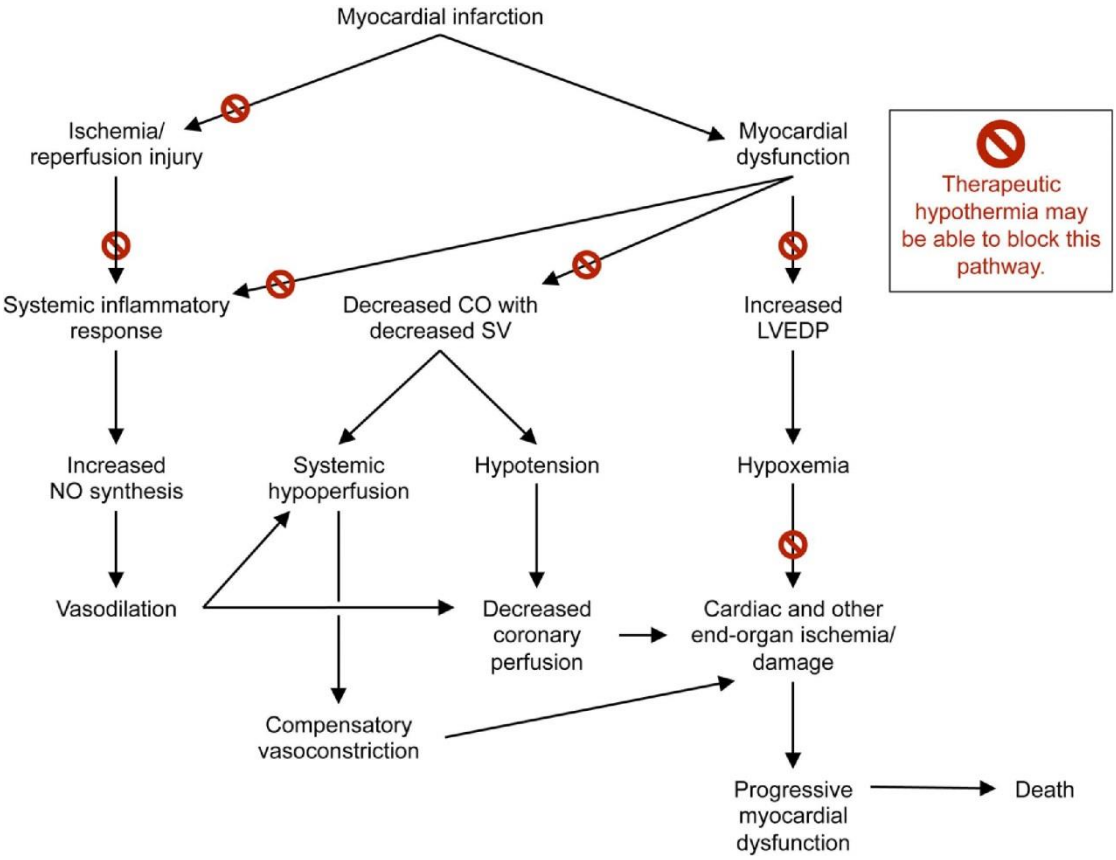

Figure 2: Potential effects of hypothermia in cardiogenic shock (from Stegman BM, J Am Coll Cardiol 2012)

1.3 HUMAN STUDIES OF HYPOTHERMIA

1.3.1 **In non-complicated myocardial infarction.**

One study in humans showed decreased infarct size among patients with anterior infarcts treated with therapeutic hypothermia who reached a temperature of <35°C at time of reperfusion [14]. In this study, cooling was well tolerated, with no hemodynamic instability or increase in arrhythmia. Nine patients experienced mild episodic shivering. Major adverse cardiac events occurred in 0% vs. 10% (p = NS) of treated versus control patients. The median infarct size was slightly smaller in patients who received cooling compared with the control group (2% vs. 8% of the left ventricle, p = 0.80).

More recently, a pilot study [15] of 20 patients with acute MI undergoing endovascular cooling and cold saline infusion to ensure body temperature of <35°C at time of reperfusion. Twenty patients with acute MI scheduled to undergo primary percutaneous coronary intervention were enrolled in this prospective, randomized study. After 4 ± 2 days, myocardium at risk and infarct size were assessed by cardiac magnetic resonance using T2-weighted imaging and late gadolinium enhancement imaging, respectively. A core body temperature of <35°C (34.7 ± 0.3°C) was achieved before reperfusion without significant delay in door-to-balloon time (43 ± 7 minutes versus 40 ± 6 minutes, hypothermia versus control, P=0.12). Despite similar duration of ischemia (174 ± 51 minutes versus 174 ± 62

minutes, hypothermia versus control, P=1.00), infarct size normalized to myocardium at risk was reduced by 38% in the hypothermia group compared with the control group (29.8 ± 12.6% versus 48.0 ± 21.6%, P=0.041). This was supported by a significant decrease in both peak and cumulative release of Troponin T in the hypothermia group (P=0.01 and P=0.03, respectively).The authors concluded that the protocol demonstrates the ability to reach a core body temperature of <35°C before reperfusion in all patients without delaying primary percutaneous coronary intervention and that combination hypothermia as an adjunct therapy in acute MI may reduce infarct size at 3 days as measured by MR

1.3.2 In myocardial infarction complicated by Cardiogenic Shock non treated with VA-ECMO

There are only a few case reports and case series of hypothermia in patients with CS, mostly limited to pediatric and adult cardiac surgery patients whose postoperative courses were complicated by CS [16, 17] and none were from patients with CS in the acute MI setting. It is also important to recognize that these are reports of highly selected cases in which treatment was nonrandomized and concurrent therapy was uncontrolled. Only a well-designed randomized clinical trial can provide evidence sufficient to support clinical practice in post-MI patients.

In general, whether in infants or children, when hypothermia is added to conventional therapy in patients with refractory shock after cardiothoracic surgery, it resulted in decreases in heart rate and increases in mean arterial pressure and urine output with improved clinical stability. Therapeutic hypothermia has been reported in only three case series in adult patients with refractory heart failure.

Yahagi et al [16] reported 10 adult patients experienced post–cardiac surgery cardiogenic shock that was refractory to medical therapy, including multiple vasopressors and intra-aortic balloon pumping; the use of external cooling along with cold gastric lavage to a temperature of 34.5°C was associated with an increase in cardiac index (1.9 ± 0.3 to 2.2 ± 0.3), mixed venous saturation (55 ± 7% to 64 ± 6%), and urine output (2.1 ± 1.1 ml/kg/h to 3.4 ± 2.2 ml/kg/h) compare to baseline without changes in mean arterial pressure, heart rate, systemic vascular resistance, or pH. Eight of 10 patients survived to discharge. This study did not provided controls, but the expected mortality of patients in such condition is >50%.

Zobel et al [18] reported the effects of moderate hypothermia in 20 patients admitted in CS after resuscitation from cardiac arrest. Patients were matched with a historical normothermic group by means of propensity score. Moderate therapeutic hypothermia was associated with a significant decrease in heart rate from 74 to 64 beats per minute. Despite the reduction in heart rate, cardiac index remained unchanged under moderate therapeutic hypothermia likely due to an increase in ejection fraction from 43 ± 4% to 55 ± 4%. Mean arterial pressure increased rapidly from 75 ± 2 mmHg to 84 ± 3 mmHg (p = .001) upon induction of hypothermia paralleled by an initial increase in systemic vascular resistance. Accordingly, patients with moderate therapeutic hypothermia required lower cumulative doses of vasopressors and inotropes. They concluded that in CS moderate therapeutic

hypothermia provides circulatory support and an increase in systemic vascular resistance that leads to reduced vasopressor use and may result in lower oxygen consumption.

Finally, Schmidt-Schweda [19] in 12 patients in CS found that hypothermia consistently decreased heart rate, and increased stroke volume, cardiac index and cardiac power output. Metabolic and electrocardiographic parameters remained constant during cooling.

Patients with signs of CS after cardiac arrest who underwent cooling provide another possible source of information, although little is currently available. In one study [20], 28 of 56 patients who were cooled after cardiac arrest also had CS, although it was not reported how many of these patients had acute MI concurrent with the cardiac arrest. Among the CS patients, after 24 to 48 h of therapeutic hypothermia, cardiac index increased from 1.5 ± 0.26 to 2.3 ± 0.371. In addition, heart rate decreased among CS patients but to a lesser extent than among patients without shock; mean arterial pressure increased in patients with CS whereas it decreased in patients without initial signs of shock.

To summarize, preliminary data demonstrated that moderate hypothermia during cardiogenic shock is well tolerated and improves hemodynamic parameters.

Finally, to the best of our knowledge, there have been no published randomized human studies of therapeutic hypothermia in post-MI cardiogenic shock treated with VA-ECMO. We found only one ongoing clinical trial (NCT01890317) to test the effects of moderate hypothermia in CS following MI. Importantly, in this study, patients will not be treated with VA-ECMO.

1.4 POTENTIAL RISKS AND BENEFITS

1.4.1 Expected patient or public health benefit

Potential advantages of adding moderate hypothermia to VA-ECMO: Moderate hypothermia improves cardiac function and attenuates ischemia/reperfusion injury in other organ systems and reduces endothelial cell apoptosis and systemic oxidative stress. CS patients treated with ECMO have severe cardiac failure, associated with severe ischemia-reperfusion injury and pro-inflammatory profile leading to increased NO production and subsequent severe vasoplegia and multiple organs failure. Therefore, adding hypothermia in the very early phase of ECMO may alleviate the deleterious effects of ischemia-reperfusion. Moreover, moderate hypothermia is well tolerated. Finally, we intend to identify an absolute difference in the risk of death of 15%. In the field of cardiovascular medicine, the trials are usually intending to identify a 15% reduction of relative risk, usually translating in 5% reduction of absolute risk. The risk difference we intend to identify is consequently highly clinically relevant. Yet, even if this effect size is large, it appears congruous with the strong preclinical and clinical evidence we provide.

The annual incidence of AMI (Acute Myocardial Infarction) is estimated at 100–150 per 100,000 inhabitants in France and 5-8% of AMI patients will develop cardiogenic shock. Therefore, the annual

incidence for cardiogenic shock following MI is 12 per 100,000 inhabitants. It was recently found that cardiogenic shock was secondary to AMI in 68 % [21]. Interestingly, in this study, post cardiac surgery cardiogenic shock patients were not included. Therefore, the annual incidence of all causes of CS might be estimated at 18-20 per 100,000 inhabitants (including MI, myocarditis, cardiomyopathy and shock post cardiac surgery) in France with a mortality rate of 50 %.

Reducing the death rate by 15% would save up to 1860 lives in France. This decrease in death rate might be accompanied by a reduction in the duration of ICU and hospital stays, therefore reducing the costs associated with the care of these critically ill patients. Better long-term outcomes might also be expected.

This issue is important because ECMO use during CS management is still increasing worldwide and it is now urgent to determine the best approach to optimize such promising therapy. Recent papers demonstrated that the use of ECMO has increased rapidly, whereas rates of in-hospital mortality have decreased. These changes have taken place in the context of declining hospital costs associated with ECMO.

Finally, lessons from the SHOCK study [22] demonstrate that an efficient treatment of cardiogenic shock may be associated with a delay improvement in mortality. In the SHOCK study, emergency revascularization did not significantly reduce overall mortality at 30 days. However, after six months there was a significant survival benefit. Therefore, we will also study the effects of moderate hypothermia on mortality at 180 days.

1.4.2 **Risks**

The induction of moderate hypothermia induces numerous changes throughout the body. The most important physiological changes and side effects, and their consequences for patient management, are discussed below.

Moderate hypothermia is/might be associated with shivering, modifications in blood gas management, hyperglycemia, electrocardiographic changes, mild coagulopathy and increased sensitivity to infection [5].

Since moderate hypothermia is widely used for resuscitated patients after cardiac arrest, strategies have been developed to minimize these potential side effects. Finally, moderate hypothermia was used for patients with resuscitated cardiac arrest treated with ECMO and none particular side effects have been described [23].

Management of physiological effects of hypothermia ***based on the literature [5]***:

a) The tolerance to hypothermia will be ensured with the cautious use of **sedation and eventually with the use of a paralyzing agent in cases of shivering**. Use of a developed shivering assessment scale will be proposed for this purpose [23] .

b) **<u>Management of blood gas</u>**: Blood gas values are temperature dependent, and if blood gas are warmed to 37°C before analysis (as is common in most laboratories), Po_2 and Pco_2 will be overestimated and pH underestimated in hypothermic patients. **For accurate temperature correction, blood gas will be analyzed at the patient's real temperature**.

c) **<u>Glycemia management</u>**: Hypothermia can also decrease insulin sensitivity and the amounts of insulin secreted by the pancreas. This can lead to hyperglycemia and/or an increase in the doses of insulin required to maintain glucose levels within target range. **Prevention and/or prompt correction of severe hyperglycemia will be part of the therapeutic strategy during hypothermia treatment**. Furthermore, it should be realized that doses of insulin required to maintain normoglycemia are likely to decrease when the patient is rewarmed; this means that hypoglycemia can easily develop in the rewarming phase as insulin sensitivity is restored, particularly if the patient is rewarmed (too) quickly.

d) **<u>Coagulation</u>**: Very mild hypothermia (35°C) does not affect coagulation, and can be safely used even if bleeding risks are high. **Temperatures of 33°C to 35°C affect platelet function only; if surgical procedures are performed under hypothermic conditions, platelet transfusion may be considered.** Coagulation factors other than platelet function are affected only when temperatures decrease below 33°C.

In normothermia group, no additional risk linked to research is expected.

1.4.3 Benefits/risks balance

The hypothermia side effects are well known. Strategies described above allow to minimizing these potential side effects. No severe side effects associated have been described in previous studies especially when compared to the high severity of CS patients treated with ECMO. Therefore potential benefits/risks balance is clearly positive in this study.

1.5 ORIGINALITY AND INNOVATIVE ASPECTS

The study is original since despite very suggestive pre-clinical and clinical proof of concepts, there is only one ongoing study in CS patients non-treated with VA-ECMO (NCT01890317) and **no reported study regarding the use of hypothermia during CS treated with VA-ECMO**.
Moreover, hypothermia induction during VA-ECMO does not require any additional device or supplementary catheter insertion since body temperature is easily controlled with the circuit heat controller which is available in all potential centers

This issue is important because VA-ECMO use during CS management is still increasing worldwide and it is now urgent to determine the best approach to optimize such promising therapy. Recent papers demonstrated that the use of VA-ECMO has increased rapidly, whereas rates of in-hospital mortality have decreased. These changes have taken place in the context of declining hospital costs associated with VA-ECMO.

Finally, comparatively to drug/new device research, hypothermia is inexpensive and very simple to implement in real life. Therefore, the only cost for society will be the grant for the study.

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3 STUDY OBJECTIVES

In this chapter, and accordingly to the literature, moderate hypothermia is definite as a temperature between 33°C≤ T°C ≤34°C. Normothermia is definite as a temperature at 36°C≤ T°C ≤37°C.

3.1 PRIMARY OBJECTIVE

The study objective is to determine whether early moderate hypothermia (33°C≤ T°C ≤34°C) is superior to normothermia 36°C≤ T°C ≤37°C in patients with cardiogenic shock treated with VA-ECMO with respect to 30-day mortality.

3.2 SECONDARY OBJECTIVES

Evaluation of the impact of moderate hypothermia on:

- Mortality during hospitalization and up to 180 days
- VA-ECMO weaning time
- Adverse cardiovascular events
- Necessity of fluid and vasopressor (norepinephrine, epinephrine)
- Lactate clearance
- Duration of organ failure
- Mechanical ventilation support use
- Renal replacement therapy use
- Duration of ICU stay and total duration of hospitalization
- The risk of bleeding
- The risk of Sepsis (pulmonary, blood, venous lines, VA-ECMO cannulaes)

3.3 STUDY OUCOME MEASURES

3.3.1 **Primary endpoints**

All-cause mortality at day 30 following randomization (i.e. 30 day mortality)

3.3.2 **Secondary endpoints:**

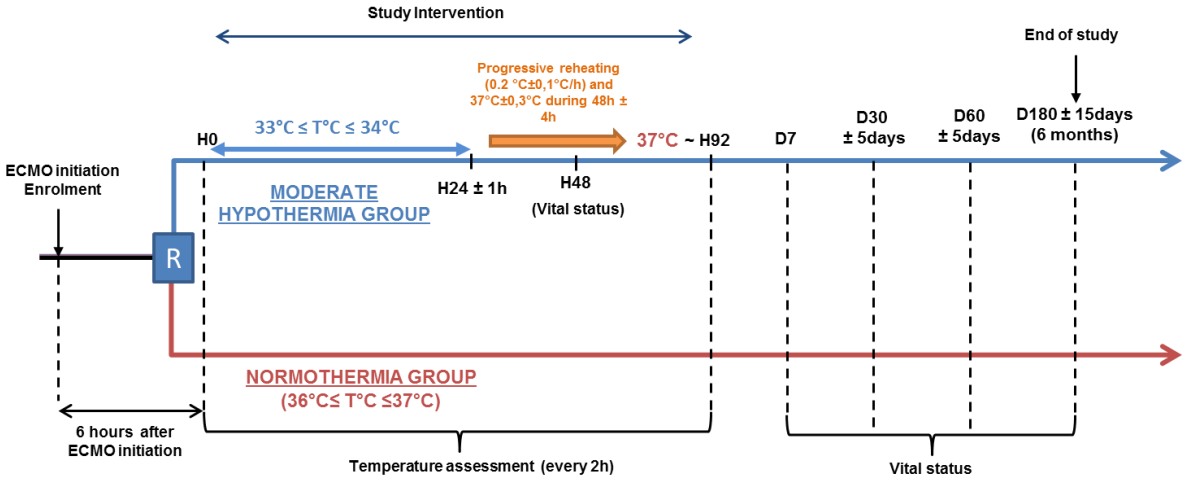
- All-cause mortality at 48 hours and day 7, 60, 180
- VA-ECMO duration
- Composite endpoint of death, cardiac transplant, escalation to LVAD, stroke at days 30, 60, 180
- Cumulated amount of administered fluids and duration of vasopressors use in ICU
- Duration to normalization of lactate
- Number of days alive without organ failure(s), defined with the SOFA score and its components (respiratory, liver, coagulation and renal), between inclusion, D7 and D30
- Duration of mechanical ventilation and the number of days between inclusion and day 30/ day 60/ day 180, alive without mechanical ventilation
- Number of days alive without renal replacement therapy, and the number of days, between inclusion and day 30, day 60 and day 180, without renal replacement therapy

- Duration of ICU stay, of hospitalization
- Number of severe and moderate bleeding complications (GUSTO-definition, N Engl J Med. 1993;329:673–682) and the number of packed red blood cells transfused under VA-ECMO
- Infection probability: pulmonary, blood and VA-ECMO cannulaes

4 STUDY DESIGN AND PROCEDURES

4.1 EXPERIMENTAL STUDY DESIGN

A multicenter, prospective, controlled, randomized (moderate hypothermia during 24 hours ± 1h versus normothermia), comparative open trial will be conducted on two parallel groups of patients with CS treated with VA-ECMO.



4.1.1 Common management for all patients before and during intervention

For all patient enrolled in the study, VA-ECMO will be initiated in accordance to the local practice with flow settings to ensure sufficient tissue perfusion.

With the exception of temperature control, all other diagnostic, therapeutic and weaning procedures will be done according to the current standard of care at the tertiary CV center and at the discretion of the investigator.

For reference, the current standard of care is described in appendix A

4.1.2 Heater-Cooler Unit and temperature control for all patients

Each circuit will be associated with a device able to control temperature used in this study in conformity of the device CE Label such as “Heater-Cooler Unit HCU 35 from Maquet compagny”.
These devices are available in each center. This device allows a perfect control and hold of the target temperature. The water tank for the patient circuits is divided into two parts to ensure quick temperature adjustments at the outlets. In addition, it has exceptional cooling capacity through its fast

ice-building technique using highly effective cooling plates and a powerful compressor. In our study each center will use his local heater-cooler unit to control temperature (described in Appendix B).

Temperature management (hypothermia, normothermia or reheating) will be performed using the heat controller of the VA-ECMO circuit and other classical temperature management if necessary (external or internal technique).

4.1.3 Temperature assessment method

During therapeutic hypothermia, all centers monitore central temperature. Central temperature will be measured in each group in accordance with local practice (e.g bladder catheter, oesophageal probe…)
In both group, temperature will be measured every two hours during intervention (time during the first 92 hours at the allocated group (cf figure in chapter 4.1).

4.1.4 Inclusion and randomization of patient

The inclusion and randomization of the patient will be performed after VA-ECMO indication and implementation. Inclusion and study intervention will be performed as soon as possible **during the first 6 hours (preferably 4 hours) after VA-ECMO initiation.**

After eligibility verification, complete clinical examination and inform consent process (cf chapter 13.2), patient will be randomized. The patients will be placed on moderate hypothermia (33°C≤ T°C ≤34°C) or maintained on normothermia 36°C≤ T°C ≤37°C during 24 hours ± 1h according to the group.

Data collected *(*nonspecific to the study) at inclusion and during ICU stay after randomization : demographic data, medical history, SOFA score, biological data (Arterial Lactate, ASAT, ALAT, urea, creatinine, coagulation parameters..), amount of paralyzing agent and sedative, amount of insulin…), concomitant drugs, treatments (fluid amount, vasopressors, inotropes, echocardiography at inclusion performed before study intervention (echocardiography data result from usual care…))…

4.1.5 Moderate hypothermia group

Moderate hypothermia will be induced as soon as possible **during the first 6 hours (preferably 4 hours) after VA-ECMO initiation (H0) and randomization.** Moderate hypothermia will be induced using the heat controller of the VA-ECMO circuit and other classical temperature management if necessary (external or internal technique). Temperature will be maintained between 33°C≤ T°C ≤34°C during 24 hours ± 1h followed by a progressive reheating (0.2±0.1°C/hour) to reach 37°C. Température at 37°C ± 0.3°C will be maintained during 48 hours ± 4h after having reached 37 °C.

The potential physiological effects of hypothermia and their managements based on literature are described in chapter 1.4.2. Their managements will be done according to the local practice and to the discretion of investigator.

4.1.6 Normothermia group

The extracorporeal life support organization (ELSO) recommends "Temperature can be maintained at any level by adjusting the temperature of the water bath. Temperature is usually maintained close to 37° C." A large amount of patients that need VA-ECMO experiment a cardiac arrest before ECMO implantation. Concerning the patients with cardiac arrest it is now recommended to maintain the patients between 33 and 36 degrees. Therefore,the temperature will be maintained at
Therefore the temperature will be maintained at 36°C≤ T°C ≤37°C under VA-ECMO.

4.1.7 Discontinuation of experimental study intervention (moderate hypothermia group)

In the moderate hyperthermia group, in cases of uncontrolled bleeding (bleeding despite medical intervention (surgery or drugs)), moderate hypothermia will be stopped and resumed as soon as the bleeding is controlled for a total duration of 24 hours ± 1h of moderate hypothermia. Under VA-ECMO, rhythms disturbances are not an indication to stop moderate hypothermia.

4.1.8 Prohibited treatment for the subject participation

None, all medications or treatments are authorized.

4.1.9 Follow up after intervention (H48, day 7, day 30 (± 5 days), day 60 (± 5 days), Day 180 (± 15 days) (end of the study) after randomization for all patient)

Vital status (and date/cause of death) will be collected for all patients and if necessary obtained by the investigator or his staff by contacting the patient, the family or his/her primary care physician.

4.2 FLOWCHART

			After randomization					
	Inclusion	**Randomization (*a*)**	**H0**	**H48**	**Day 7**	**Day 30 ± 5 days**	**Day 60 ± 5 days**	**Day 180 (6 months) (± 15 days)**
Informed and signature of consent (cf chap 13.2)	x							
Inclusion and non-inclusion criteria verification	x							
Study Intervention Moderate hypothermia/normothermia *(b)*			x					
Vital Status (date and cause of death)				x	x	x	x	x
Medical events reporting (AE/SAE)	x		x	x	x	X (LT or fatal)	X (LT or fatal)	X (LT or fatal)

a) During the first 6 hours (preferably 4 hours) after VA-ECMO implementation
b) Induced as soon as possible during the first 6 hours (preferably 4 hours) after VA-ECMO implementation and randomization
LT : life threatening

4.3 BIAS CONSIDERATION

4.3.1 Randomization procedure

Randomization will be performed after enrolment using a centralized on-line randomization system (Cleanweb™) available 24h/24h.

Treatments arms :

- **Experimental group:** Patients with CS allocated to a strategy of moderate hypothermia (33°C≤ T°C ≤34°C) associated with usual care.
- **Control group**: Patients with CS allocated to a strategy of normothermia 36°C≤ T°C ≤37°C associated with usual care.

Randomization will be stratified on the center. The randomization plan will be devised by Centre investigation Clinique 1433 module Plurithématique de Nancy, France.

4.3.2 Replacement procedures for patients

All patients non randomized will be replaced to reach 334 patients (167 patients in each group) (cf chapter 11.8)

4.4 STUDY PERIOD

Duration of participation of each patient: **6 months (D180)**

Anticipated duration of recruitment: **36 months**

Anticipated total duration of the study (statistical analysis included): **49 months**

4.5 TERMINATION RULES

4.5.1 Patient Premature termination

Any subject can stop his participation to the research at any time and for any reason.

The investigator can permanently end a subject's participation in the research for any reason that affects the subject's safety or which would be in the subject's best interests.

If a subject leaves the research prematurely, data relating to the subject can be used unless an objection was recorded when the subject signed the consent form.

4.5.2 Exclusion period

Patient cannot participate simultaneously in other biomedical research during the research. There is no exclusion period.

4.5.3 Follow-up after end of study

Patient will be follow up in accordance with the current standard of care.

4.6 DATA LIST NOT AVAILABLE IN THE PATIENT FILE

All medical data will be available in the patient medical file.

5 STUDY POPULATION

5.1 PARTICIPATING CENTERS

Patients will be enrolled in 17 ECMO French centers. All centers are well trained for VA-ECMO.

5.2 PATIENT SCREENING AND ENROLMENT

All intubated patients with CS supported with VA-ECMO will be screened.
Patients with CS treated with VA-ECMO in the intensive care unit meeting all of the inclusion and non-inclusion criteria will be enrolled in the study (emergency consent process cf chapiter 13.2).
Reasons for non-eligibility will be listed in a dedicated screening log file.

5.3 INCLUSION CRITERIA

- Age ≥ 18 years
- Intubated patients with cardiogenic shock treated with VA-ECMO
- Patient affiliated to social security plan

5.4 NON-INCLUSION CRITERIA

- VA-ECMO after cardiac surgery for heart transplantation or heart - lung transplantation or left or biventricular assist device implantation
- VA-ECMO for acute poisoning with cardio-toxic drugs
- Pregnancy
- Uncontrolled bleeding (bleeding despite medical intervention (surgery or drugs))
- Implantation of VA-ECMO under cardiac massage with a duration of cardiac massage ≥ 45 minutes
- Out of hospital refractory cardiac arrest
- Cerebral deficit with fixed dilated pupils
- Participation in another interventional research involving therapeutic modifications
- Patient moribund on the day of randomization
- Irreversible neurological pathology
- Minor patients
- Patients under tutelage

6 METHODS USED FOR THE EVALUATION OF EFFICACY

Cf chapter 3

7 SAFETY ASSESSMENT

7.1 DESCRIPTION OF SAFETY ASSESSMENT PARAMETERS, METHOD AND CALENDAR USED FOR THE EVALUATION OF SAFETY

In both group, the VA-ECMO implementation and monitoring will be done in accordance with the current standard of care. All adverse events will be documented during this study from medical examinations, biological and imaging exams if necessary and will be complied in the electronic case report form (eCRF).

In particular, glycaemia, blood gas and coagulation will be followed up and the occurrence of shivering, modifications in blood gas management, hyperglycemia, electrocardiographic changes, mild coagulopathy and increased sensitivity to infection will all be recorded as adverse events.
Uncontrolled bleeding and coagulation disorders that require blood cells or platelet transfusion will be considered as serious events.
In normothermia group, no additional risk linked to research is expected.

All adverse events between inclusion and D7 will be recorded.
After D7, only serious life-threatening and fatal adverse events will be recorded until the end of the follow-up of the patient.

7.2 REPORTING AND TRANSMISSIONS OF SAE/R

7.2.1 **Definitions:**

Adverse event (AE) (article R.1123-39 of the French Public Health Code): Any harmful event occurring in a person participating in a biomedical study, whether or not this event is in relation or not with the study or the product studied.

Serious adverse event (SAE) (article R.1123-39 of the French Public Health Code and ICH E2B guide). Any adverse event that:

- ✓ results in death,
- ✓ is life-threatening,
- ✓ requires hospitalization or prolongation of existing hospitalization,
- ✓ results in persistent or significant incapacity/disability,
- ✓ or any other medically important condition,
- ✓ and when regarding a medicinal product, whatever the administered dose.

The expression “life-threatening” is reserved to immediate threat to life occurring at the time of adverse event occurrence, and this, independently of the consequences that corrective or palliative treatments may have.

Certain circumstances that require hospitalization do not correspond to the “hospitalization” seriousness criterion, such as:

- admission for administrative or social reason,
- hospitalization predefined by the protocol,
- hospitalization for medical treatment or surgery that was scheduled before the start of study,
- out-patient hospitalization.

Unexpected serious adverse effect (article R.1123-39 of the French Public Health Code):
Any adverse effect, of which the nature, the severity or the progression does not concord with the information in the submissions to the ethics committee (Comité de Protection des Personnes, CPP) and the competent authority.

New safety data, that may lead to the re-evaluation of the benefit-risk ratio and the risks associated with the study, or that may be sufficient to consider modifications to the study documents, study conduct, and, if applicable, the use of the product.

7.2.2 **List of expected adverse events suspected**

All potential adverse events associated with the use of hypothermia may be also encountered in the control group (normothermia group) and are well described during an ICU stay for cardiogenic shock (cf chapter 1.4.2).

- Shivering
- Modifications in blood gas management
- Hyperglycemia
- Electrocardiographic changes
- Mild coagulopathy
- Increased sensitivity to infection

Therefore, we will record in the patient’s e-CRF the occurrence of hyperglycemia (appreciated by the amount of insulin), nosocomial infection and hemorrhagic disorder (number of packed red cell transfused).
We will consider as **serious adverse events** in the hypothermia group the occurrence of uncontrolled bleeding. In this case, hypothermia will be stopped and resumed as soon as the bleeding is controlled for a total duration of 24 hours.

7.2.3 Serious adverse events/ reactions and new facts reporting

- As soon as an investigator becomes aware of a SAE/R or a new fact, he/she advises the sponsor without delay by faxing the SAE/R declaration form at **03 83 32 33 44.**
- If it is a an *unexpected serious adverse reactions* (USAR) or if it is a new fact, the sponsor will contact the investigator in order to prepare an initial report which will be forwarded to the ANSM, the CPP and to the coordinating investigator within 7 days in case of death or life threatening SAE, otherwise within 15 days. An additional information will be forwarded within 7 days of death or life-threatening SAE.
- When the event is not resolved at the time of fax transmission, the investigator must send a supplementary report to document the changes or to update the missing data.
- If it is an *expected serious adverse effect*, the sponsor will compile it for the drafting of annual safety reports.
- *Expected non-serious adverse reactions* will be briefly described by the investigator on the summary sheet dedicated to this effect in the data collection notebook.

7.2.4 Non-serious adverse events/ reactions reporting

Non serious adverse event/reaction will be compiled in the eCRF. These data will be available to sponsor for any safety evaluation for the study and for the final report. Date of event and his resolution will be described in the eCRF.

7.2.5 Adverse event/reaction monitoring

Any patient presenting an adverse event must be followed until resolution or stabilization thereof :

- If the event is not serious, evolution/changes will be noted on the relevant page of the case report form in the designated section reserved for this purpose.
- If the event is serious, a SAE/R follow-up will be sent to the sponsor.

7.2.6 Safety report

- Annual safety reports: the sponsor words the annual safety reports and submits them to the ANSM, the CPP and the coordinating investigator. The coordinating investigator will transmit all data necessary for the preparation of this report to the sponsor.

- Final report: the final report is prepared after data reconciliation with the safety data by the sponsor and the coordinating investigator within one year of the end of the study. All investigators are informed of the results of the study. A summary is forwarded to the French competent authorities (ANSM) by the sponsor.

8 ORGANIGRAM AND FEASIBILITY

8.1 PROJECT ORGANIZATION SCHEME

8.1.1 **Steering Committee**

Role

The Steering Committee initiates the project and is responsible for writing and validating the observation notebooks. Its members initially determine the methodology and decide during the trial the responses to unforeseen events, monitors the course of the project, especially concerning safety and side effects.

Committee members define the general organization and course of the project and coordinate the information. They oversee the analysis of data and the writing of scientific documents derived from the research project.

The Steering committee will be comprised of:

- Prof Bruno LEVY (Intensivist – CHRU Nancy, France)
- Prof Alain Combes (intensivist – APHP-la Pitié Salpêtrière, France)
- Dr Nicolas GIRERD (cardiologist – CHRU Nancy, France)
- Dr Fabrice VANHUYSE (Cardiovascular surgeon – CHRU Nancy, France)
- Prof Patrick ROSSIGNOL (Nephrologist, Professor in Therapeutic –CHRU Nancy, France)

8.1.2 **Data safety monitoring board (DSMB)**

The DSMB will be responsible for the review of the study data in order to identify any potential safety issues. Based on the safety data, the DSMB may recommend modifications to the protocol (e.g. amendments, termination of the study) and, when needed, the DSMB will decide on stoppage rules.

Members of this board are independent of the study. The DSMB will be composed of two intensivists and a biostatistician or methodologist.

The chairman of the DSMB will inform the Steering Committee members in writing whether or not any safety issues are identified during DSMB meetings or telephone conferences.

The DSMB will review aggregate SAEs at 6 months intervals. At this time, the DSMB will recommend to the HYPO-ECMO steering committee and sponsor to a) continue the study as scheduled, b) suspend enrolment, or c) obtain more information before a recommendation can be made.

9 FEASIBILITY

Considering the main objective, the HYPO-ECMO trial will be a pragmatic study in order to facilitate patient inclusion and monitoring.

HYPO ECMO project is included in the large clinical network F-CRIN (French Clinical Research Infrastructure Network) INI CRCT (Cardiovascular and Renal Clinical Trialists coordinated by Prof. Rossignol *www.inicrct.org<http://www.inicrct.org/>*).

10 DATA MANAGEMENT AND STATISTICS

10.1 DATA MANAGEMENT

10.1.1 Electronic Case report form

Data management will be carried out by the "Centre d'Investigation Clinique 1433, Plurithématique department, CHRU-Nancy". Data collection for this study will be made via an electronic Case Report Form (eCRF).

Each patient will be identified on the eCRF with his/her initials (first letter of the name and first letter of the surname), birth date (month and year) and an identification number indicating his/her rank of inclusion into the study. Investigators must not provide other personal information about the patients to the staff in charge of the data management and data analysis (i.e full names and last known addresses).

The investigator or a qualified designee from the site should complete the eCRF as soon as the data are available. The data manager in charge of the study will provide access codes as well as guidance for the completion of e-CRF.

As a matter of regulations, the investigator is responsible for the accuracy and authenticity of all clinical data entered onto eCRFs. Each page of the completed eCRFs must be reviewed for accuracy by the investigator, corrected as necessary, and e-signed.

The investigator's e-signature serves to attest that the investigator has reviewed the information contained on the eCRF and is true and accurate.

11 DATA ANALYSIS AND STATISTICAL DETERMINATION

11.1 DESCRIPTION OF ANTICIPATED STATISTICAL ANALYSIS METHODS

11.1.1 ***Statistical analysis for the primary endpoint***

The differences between the 2 study groups (i.e. intervention and controls) in the risk of all-cause mortality at day 30 following randomization will be studied using the Chi-2 test. To illustrate the association, both an odd-ratio and a hazard ratio will be provided. In addition, survival curves using the Kaplan-Meier method will be constructed.

11.1.2 Statistical analysis for the secondary endpoints

For the secondary analysis of a) all-cause mortality at 48 hours and day 7, 60, 180, b) the composite endpoint of death, cardiac transplant, escalation to LVAD, stroke at days 30, 60, 180 the same analysis strategy will be performed as for the primary endpoint.

Unpaired t-test will be performed, after checking for normality of the variable's distribution, for the outcomes mentioned below. Importantly, In case of non-normal distributions (which is highly likely for all duration data), non-parametric tests will be performed.

- VA-ECMO duration
- cumulated amount of administered fluids and duration of vasopressors use
- duration to normalization of lactate
- Number of days alive without organ failure(s), defined with the SOFA score and its components (respiratory, liver, coagulation and renal), between inclusion, D7 and D30
- duration of mechanical ventilation and the number of days, between inclusion and day 30/ day 60/ day 180 , alive without a mechanical ventilation
- number of days alive without renal replacement therapy, and the number of days, between inclusion and day 30/ day 60/ day 180, without renal replacement therapy
- duration of ICU stay, of hospitalization
- number of severe and moderate bleeding complications (gusto-definition) and number of packed red blood cells transfused under VA-ECMO

Chi-square tests (or Fisher exact test in case of insufficient number of expected patients in on of the 2x2 cell) will be performed for the outcomes mentioned below:

- Pulmonary, blood and VA-ECMO cannulaes infections

To illustrate the association, an odd-ratio will be provided.

11.2 SAMPLE SIZE CONSIDERATION

We considered that mortality in cardiogenic patients supported with VA-ECMO will be 50% (based both on ELSO data, Combes data (*Crit Care Med.* 2008 May;36(5):1404-11) and study principal investigator's personal data (database of 150 patients)

The objective of the study is to demonstrate the superiority of the treatment with VA-ECMO plus moderate hypothermia as compared to VA-ECMO alone on mortality.

Therefore, considering a total event risk (for the primary endpoint) of 50 % in the control group, a sample size of **N = 167 patients/group** will detecting a 15% absolute difference in favor the VA-ECMO group using a chi-square test with a 80 % power and considering a two-sided global alpha level of 5% using the LanDe Mets method with O'BrienFleming boundary for one interim analysis (efficacy and futility) after inclusion of 2/3 of the patients.

11.3 DEGREES OF STATISTICAL SIGNIFICANCE

A bilateral p value lower than 4.9% will be considered significant for the final analysis. A p value threshold lower than 5% is mandatory given the planned interim analyses to ensure a global alpha level at 5%.

11.4 PLANNED INTERIM ANALYSES (IF APPLICABLE)

One interim analysis for efficacy/futility will be performed after inclusion of 2/3 of the patients.

De-identified hospitalization reports will be collected from the associated centers. These reports will be centralized at the CIC-P of the CHRU of Nancy and will be submitted to a reading committee.

11.5 STATISTICAL CRITERIA FOR STUDY TERMINATION

A p-value threshold of 0.001 will be used for this interim analysis as calculated with the LanDe Mets method with O'BrienFleming boundary.

11.6 METHOD FOR ADDRESSING MISSING, INVALID OR UNUSED DATA

For the primary outcome, we do not expect missing variables. All-cause 30 days mortality is a straightforward outcome that does not require detailed information. Yet, in the unlikely case of missing vital status at 30 days, patients with missing data will be analyzed with the last observation being carried forward. In a sensitivity analysis, the worst case scenario method will be used (i.e. all patients with incomplete follow-up data died in the intervention group and died in the no intervention group).

11.7 MANAGEMENT OF AMENDMENTS TO THE ANALYSIS PLAN OF THE INITIAL STRATEGY

No amendments are expected. Amendments can be decided by the steering committee.

11.8 SELECTION OF SUBJECTS TO BE INCLUDED IN THE ANALYSIS

As per intention to treat analysis, every randomized patients will be included in the analysis.

12 CONTROL AND QUALITY ASSURANCE

12.1 ACCESS TO SOURCE DATA AND DOCUMENTS

The sponsor is responsible for obtaining the agreement of all parties involved in the study so as to guarantee direct access to all study sites, source data, source documents, and reports so that the sponsor may control data quality and perform an audit.

Investigators accept to give access to all relevant data and records to the sponsor (Sponsor's monitors, auditors, the Sponsor's Quality Assurance representatives) and all authorized Sponsor personnel, and regulatory authorities, under strict confidentiality condition and in compliance to the French regulatory.

12.2 STUDY MONITORING

Monitoring will be performed by the sponsor (Department of Research and Innovation CHRU de Nancy) during the study to ensure that compliance with the Protocol and applicable regulations is maintained, that data are collected in a timely, accurate and complete manner and that the investigator continues to have sufficient staff and facilities to conduct the study safely and effectively.
Details of the monitoring visits will be work out in the sponsor monitoring plan.

13 ETHICAL CONSIDERATIONS AND REGULATIONS

13.1 REGULATORY AND ETHICAL CONSIDERATIONS

Before initiating a trial, according to the French local regulation, the sponsor (CHRU Nancy) should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and authorization from the French Health Authorities for the reseach.

The sponsor and investigators commit that this research is conducted according to the protocol and his procedures, to the French local regulation (law n ° 2004-806 of August 9, 2004), as well as in agreement with Good Clinical Practices (I.C.H. version 4 of May 1, 1996 and Decision of November 24, 2006) and the Helsinki Declaration (Ethical Principles for Medical Research Involving Human Subjects, Tokyo 2004).

13.2 INFORMED CONSENT PROCESS

Before collecting the patient's consent, the investigator will give complete information about the proposed study.

In the particular context of this protocol, the persons include in this research may not be able to receive information about the study and give their consent before the implementation of the protocol due to their medical condition.
In this case, if a member of the patient's family (or support person defined in Article L.1111-6 - Appendix 5) is present, this person will be informed and consent will be gathered.
In the absence of a family member or support person, the investigator will include the patient in the study and will gather the consent of the family member or support person as soon as possible.
The patient will be asked to give his/her consent for the continuation of the trial when his/her condition will allow.

Patient, family member or support person, is free to refuse participation in the study and may at any time and for whatever reason withdraw its consent.

The consent form will be signed in two originals copy by the subject and the investigator and a member of the family / support person if applicable:
- An exemplary will be given to the subject or family member / support person if applicable
- An exemplary will be retained and archived by the investigator

Particular case:
Given the studied pathology (cardiogenic choc), the prognosis for survival of the patient included in emergency setting is threatened and the death probability stays high.

If the patient died after inclusion in emergency setting and no support person is written in the medical file or support person can’t be contacted by investigator, consent must be gathered from a family

member. If the patient does not have a family or if the investigator can't contact the family or if the investigator can't contact again family after obtaining an oral agreement from a family member, the investigator will have to write all the steps taken in the medical file and note his inability to contact the family.

The inclusion of the patient in the protocol and the use of the data are possible without signed consent if all these 3 conditions are met:
- The patient died after inclusion in emergency setting without family or support person, properly documented in the medical file by the investigator.

- no support person is noted in the medical file or the inability to contact support person or to contact again support person after obtaining an oral agreement in spite of the implemented efforts properly documented by investigator in the medical file.

- the inability to contact family member or to contact again family member after obtaining an oral agreement in spite of the implemented efforts properly documented by investigator in the medical file.
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13.3 PROTOCOL AMENDMENT

Any change or addition to the protocol can only be made in a written protocol amendment (modification of an inclusion criterion, extending the inclusion period, participation of new centers ...) that must be approved by the sponsor, French Health Authorities and the IRB/IEC prior to implementation.

13.4 PATIENT DATA CONFIDENTIALITY

Throughout the study, confidentiality shall be observed, at all times, by all parties involved, and all data shall be secured against unauthorized access.
Confidentiality of each subject shall be preserved in reports and any publication of the results.
Only authorized Sponsor staff and regulatory authorities may have access to these confidential files.
The data collected during the study will be performed according to the French local regulation (Commission Nationale de l'Informatique et des Libertés (CNIL), in compliance with the MR001 methodology)

13.5 ARCHIVING STUDY DOCUMENTS AND STUDY DATA

All study documents including patient's identification list and signed informed consent should be keep for at least 15 years**.** For each patient, documentation must clearly specify the following:

- Participation of the patient in the study (patient and study's identification),
- Concomitant treatments or medications,
- Any visit to the hospital, particularly those visits made for the sole purposes of the study,
- Serious adverse events (SAEs).

13.6 AUDIT AND INSPECTION

Audits or inspections may be performed at any time by persons mandated by the sponsor and independent of those in charge of the study or by French Health Authority respectively.
Investigators accept to give access to all relevant data and records to the auditors and inspector. If an inspection of the clinical site is requested by the French Health Authority, the investigator must inform the sponsor immediately that this request has been made.

14 INSURANCE

14.1 INSURANCE

The sponsor has subscribed an insurance for the duration of the study guaranteeing its own civil liability as well as that of any stakeholder involved in the conducting of the study, regardless of the nature of existing ties between the stakeholders and the sponsor.

15 PUBLICATION POLICY

15.1 FINAL RESEARCH REPORT

The final report of the research will be written collaboratively by the coordinator and the biostatistician mandated for this search. This report will be submitted to each of the investigators for review. Once a consensus has been reached, the final version must be endorsed with the signature of each of the investigators and sent to the sponsor as early as possible after the effective end of the research.

Data is the property of the sponsor. The conditions for data transfer of all or part of the study database are decided by the study sponsor.

“CHRU Nancy” should be mentioned as sponsor of this study.
The publications resulting from this work will be labeled by « The study was supported by a grant from the French Ministry of Health (Programme de Recherche Hospitalier National 2015) »

16 APPENDIX

Appendix A: Common management for all included patients treated with VA-ECMO before and during study intervention

1. <u>ECMO initiation;</u>

Veno-Arterial ECMO (VA-ECMO) support will be used. The extracorporeal system will consist of polyvinyl chloride tubing, a membrane oxygenator, a centrifugal pump, and percutaneous arterial and venous femoral cannulae. An oxygen/air blender will be used to ventilate the membrane oxygenator. An 7-10-Fr cannula will be inserted distally into the superficial femoral artery to prevent severe leg ischemia. Heparin boluses at the time of VA-ECMO implantation will be discouraged however a low dose bolus is permitted according to the experience of the ECMO team.

2. <u>Initial parameter settings for VA-ECMO</u>

The pump flow will be set to 3.5-5 l/min, to provide adequate systemic perfusion. Pump flow might be reduced in case of cessation of LV ejection or major pulmonary edema. Percentage of oxygen contained in the ventilating gaseous air–oxygen mixture will be adjusted to obtain PaO2 between 65 and 90 mmHg and/or arterial oxygen saturation >90%. The membrane ventilation will be adjusted to maintain PaCO2 between 40 and 45 mmHg.

3. <u>VA-ECMO monitoring (extracorporeal circuit, anticoagulation, possible complications)</u>

The VA-ECMO circuit will be monitored several times daily by the medical and nursing team caring for the patient and at least once every 48 hours by a perfusionist. Circuit and cannula surveillance is intended to verify the correct functioning of the device and early screening for complications (leg ischemia, fibrin deposits or clots on the VA-ECMO membrane, clots in the cannulae or in the pump, bleeding or signs of inflammation or cutaneous infection at the cannula insertion sites, unexpected drop of the VA-ECMO outflow, appearance of clinical or biological signs of intravascular hemolysis). Should any of these complications occur, a medical–surgical consultation will be held to discuss the best therapeutic approach to take.

Anticoagulation will be obtained with non-fractionated heparin to a target aPTT of 55-70 sec or heparinemia (antiXa activity) between 0.2 and 0.3 IU/ml. A bolus of heparin is not encouraged at the time of circuit implantation. Should severe bleeding occur that is not immediately controllable by specific treatment, heparin will be discontinued.

Intravascular hemolysis will be sought should unexpected dark urine be excreted or in the case of obvious circuit dysfunction. It is recommended that plasma free hemoglobin be measured every 48 hours and immediately if hemolysis linked to the circuit is suspected.

The membrane and VA-ECMO circuit will be changed in the following situations: massive intravascular hemolysis linked to the device, severe thrombopenia linked to the circuit, clots preventing the pump and/or lines from functioning properly or systemic defibrination.

The hemoglobin threshold for red cells transfusion will be 9-10 g/dl (may be decreased to 7-8 g/dl if the patient is stabilized and does not have residual myocardial ischemia). Platelet transfusion will be discouraged except when severe thrombopenia is associated by bleeding complications or when platelet count will be <20 G/L.

Connecting an extrarenal dialysis circuit to the VA-ECMO circuit will be permitted under strict supervision of perfusionnists.

4. Intra-aortic balloon pump (IABP) support in addition to VA-ECMO

An IABP will be inserted according to the physician choice in the contralateral femoral artery. A strategy of liberal use of IABP has been associated with less pulmonary edema and better LV unloading in patients with severe LV dysfunction under VA-ECMO.

5. Weaning criteria and ECMO weaning

Weaning from VA-ECMO should not be attempted in the first 48 hours. Before a first weaning trial, the patient should be hemodynamically stable, with baseline mean arterial pressure (MAP) > 60 mmHg in the absence or at low doses of vasoactive agents and pulsatile arterial waveform maintained for at least 24 hours. The weaning will be conducted under echocardiographic monitoring. The ECMO flow will be decreased progressively to a minimum of 1–1.5 L/min. If mean blood pressure is constantly > 60 mmHg during the trial, the VA-ECMO flow rate will be returned to its baseline value. VA-ECMO removal will be considered if the patient does not have end-stage cardiac disease, tolerates the full weaning, and has LVEF ≥ 20–25%, aortic velocity-time integral ≥ 12 cm and lateral mitral annulus peak systolic velocity of ≥ 6 cm/s under minimal VA-ECMO support.

Appendix B : ECMO device

Centres	Type	Nom du dispositif (dénomination commune et commerciale)	Marque	Fournisseur	N° Marquage CE
Nancy	Echangeur thermique	HU 35	Maquet	Maquet	CE 0124
	Pompe	Rotaflow Cardiohelp	Maquet Maquet	Maquet Maquet	CE 0124 CE 0124
	Oxygénateur	BE-PLS 2051 BE-PLS 2050	Maquet	Maquet	CE 0124
	Membrane (polymethylpentene)	Quadrox	Maquet	Maquet	
Nantes	Echangeur thermique	Biocal 370 Deltastream HC IPX1	Medtronic Medos Stockert	Medtronic Xenios Sorin	CE 0123 CE 0123 CE 0123
	Pompe	Deltastream DP3 Rotaflow Biomedicus	Medos Maquet IBC	Xenios Maquet Xenios	CE 0123 CE 0124 CE 0481
	Oxygénateur	Hilite	Medos	Xenios	CE 0481
	Membrane	Membrane Hilite	Medos	Xenios	
Bordeaux	Echangeur thermique	HU 35	Maquet	Maquet	CE 0124
	Pompe	Rotaflow	Maquet	Maquet	CE 0124
	Oxygénateur	Quadrox ID Adult	Maquet	Maquet	CE 0124
	Membrane	Quadrox	Maquet	Maquet	
Paris (Bichat)	Echangeur thermique	Réchauffeur	Maquet	Maquet	CE 0124
	Pompe	Rotaflow coude	Maquet	Maquet	CE 0413
	Oxygénateur	Sechrisy	Maquet	Maquet	CE 0124
	Membrane	Quadrox	Maquet	Maquet	
Toulouse	Echangeur thermique	Stockert (3T) HU35	Stockert Maquet	Sorin Maquet	CE 0123 CE 0124
	Pompe	Rotaflow Cardiohelp D 905	Maquet Maquet Sorin	Maquet Maquet Sorin	CE 0124 CE 0124 CE 0123
	Oxygénateur	Quadrox	Maquet	Maquet	CE 0124
	Membrane	Quadrox	Maquet	Maquet	
Genoble	Echangeur thermique	HU 35 70103.3557	Maquet	Maquet	CE 0124
	Pompe	ROTAFLOW CONSOLE 706045	Maquet	Maquet	CE 0124

	Oxygénateur	Quadrox BE-HQV 50600	Maquet	Maquet	CE 0124
	Membrane	Quadrox	Maquet	Maquet	
Clermont-Ferrand	Echangeur thermique	HU 35	Maquet	Maquet	CE 0124
	Pompe	Rotaflow	Maquet	Maquet	CE 0124
	Oxygénateur	Quadrox	Maquet	Maquet	CE 0124
	Membrane	Quadrox	Maquet	Maquet	
Marseille	Echangeur thermique	HU 35	Maquet	Maquet	CE 0124
	Pompe	Cardiohelp Biomedicus	Maquet Medtronic	Maquet Medtronic	CE 0124 CE 0123
	Oxygénateur	Quadrox PLS oxygenator HLS Module Advance 7.0	Maquet	Maquet	CE 0123
	Membrane	Quadrox	Maquet	Maquet	
Rouen	Echangeur thermique	Générateur thermique 3 T	Stockert	Sorin	CE 0123
	Pompe	ROTAFLOW	Maquet	Maquet	CE 0413
	Oxygénateur	Quadrox ID Adult	Maquet	Maquet	CE 0124
	Membrane	Quadrox	Maquet	Maquet	
Strasbourg	Echangeur thermique	Générateur thermique	Stochert	Sorin	CE 0123
	Pompe	Révolution Biomédicus Rotaflow	Sorin Medtronic Maquet	Sorin Medtronic Maquet	CE 0123 CE 0123 CE 0123
	Oxygénateur	Oxygénateur	Euroset	Euroset	CE 0123
	Membrane	Membrane	Euroset	Euroset	
Amiens	Echangeur thermique	Heater Unit 35	Maquet	Maquet	CE 0124
	Pompe	Rotaflow Cardiohelp Base Unit	Maquet Maquet	Maquet Maquet	CE 0124 CE 0124
	Oxygénateur	Quadrox PLS oxygenator HLS Module Advance 7.0	Maquet	Maquet	CE 0124
	Membrane	Quadrox	Maquet	Maquet	
Montptellier	Echangeur thermique	HU 35	Maquet	Maquet	CE 0123
	Pompe	Revolution	Sorin	Sorin	CE 0123
	Oxygénateur	Alone (adulte) EOS	Euroset Sorin	Euroset Sorin	CE 0123 CE 0123 CE 0123
	Membrane	Membrane	Euroset	Euroset	
Paris (La Pitié)	Echangeur thermique	HU 35	Maquet	Maquet	CE 0124

	Pompe	Cardiohelp Rotaflow Evolution	Maquet Maquet Sorin	Maquet Maquet Sorin	CE 0124 CE 0124 CE 0123
	Oxygénateur	HLS Module Advance 7.0 Quadrox EOS	Maquet Maquet Sorin	Maquet Maquet Sorin	CE 0124 CE 0124 CE 0124
	Membrane	Quadrox Membrane EOS	Maquet Sorin	Maquet Sorin	
Besançon	Echangeur thermique	HU 35	Maquet	Maquet	CE 0124
	Pompe	STOCKERT	Sorin	Levinova	CE 0123
	Oxygénateur	EOS	Sorin	Levinova	CE 0123
	Membrane	D905	D 905	Levinova	
Rennes	Echangeur thermique	Deltastream	Medos	Xenios	CE 0123
	Pompe	Deltastream MDC	Medos	Xénios	CE 0123
	Oxygénateur	300000072 MEH2C3943	Medos	Xenios	CE 0481
	Membrane	Medos	Medos	Xenios	
Lyon	Echangeur thermique	HU 35 Deltastream HC	Maquet Medos	Maquet Xenios	CE 0124 CE 0123
	Pompe	Rotaflow Deltastream MDC	Maquet Medos	Maquet Xenios	CE 0413 CE 0123
	Oxygénateur	Quadrox Hilite	Maquet Medos	Maquet Medos	CE 0124 CE 0481
	Membrane	Quadrox Membrane Hilite	Maquet Medos	Maquet Medos	
Annecy	Echangeur thermique	Heater-Cooler	Stockert S III	Sorin	CE 0123
	Pompe	Stockert scpc	Sorin	Sorin	CE 0120
	Oxygénateur	Sorin	Sorin	Sorin	CE 0123
	Membrane	Membrane Sorin	Sorin	Sorin	