

Protocol

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This trial protocol has been provided by the authors to give readers additional information about their work

- 29 This supplement contains the following items:
- 30 1. Protocol :
- 31 a. Original protocol (Version 1.0)
- 32 b. Final protocol (Version 7.1)
- 33 c. Summary of changes
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- 35 2. Statistical plan
- 36 a. Original and final statistical analysis plan
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- 38

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**Centre Hospitalier Régional
Universitaire de Nancy**
Direction de la Recherche et de l'Innovation

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Clinical Trial Protocol

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Effects of Induced Moderate HYPOthermia on mortality in

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Cardiogenic Shock Patients Rescued by veno-arterial

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ExtraCorporeal Membrane Oxygenation (ECMO)

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HYPO ECMO STUDY

50

51

Version n° 1.0 du 04/03/2016

52

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213 **LIST OF ABBREVIATIONS**

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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

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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° 1, 04/03/2016
TYPE OF STUDY	Biomedical research
NUMBER OF RECRUITING CENTER	17
RATIONALE /BACKGROUND	<p>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.</p> <p>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.</p> <p>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.</p> <p>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).</p> <p>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.</p> <p>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 group (37°C ± 0.3°C).</p>
MAIN OBJECTIVE	The study objective is to determine whether early moderate hypothermia (33°C ≤ T°C ≤ 34°C) is superior to normothermia (37°C ± 0.3°C) in patients with cardiogenic shock treated with VA-ECMO with respect to 30-day mortality.
SECONDARY OBJECTIVES	<p>Evaluation of the impact of moderate hypothermia on:</p> <ul style="list-style-type: none"> - 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;

	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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 and D30 - Duration of mechanical ventilation and the number of days between inclusion and day 30/ day 60, alive without mechanical ventilation - Number of days alive without renal replacement therapy, and the number of days, between inclusion and day 30 and day 60, 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 $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) during 24 hours \pm 1h versus normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$), comparative open trial will be conducted on two parallel groups of patients with cardiogenic shock treated with VA-ECMO.
STUDY TREATMENTS/STRATEGIES PROCEDURES	<p>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.</p> <p>After inclusion and randomization (by CleanWeb® software), the patients according to the group allocated will be placed on moderate hypothermia ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) during 24 hours \pm 1h or maintained on normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$).</p> <p>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. Temperature will be maintained between $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$ during 24 hours \pm 1h followed by a progressive reheating ($0.2 \pm 0.1^{\circ}\text{C}/\text{h}$) to reach 37°C. Temperature at $37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$ will be maintained during 48 hours \pm 4h after having reached 37°C.</p> <p>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.</p> <p>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." Therefore the temperature will be maintained at $37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$.</p> <p>In both group, temperature will be measured every two hours during intervention (time during the first 92 hours at the allocated group).</p> <p>Follow up (vital status and cause of death) at D30 \pm 5 days, D60 \pm 5 days and</p>

	D180 ± 15 days for all the patients.
MAIN INCLUSION CRITERIA	<ul style="list-style-type: none"> - Age ≥ 18 years - Intubated patients with cardiogenic shock treated with VA-ECMO - Patient affiliated to social security plan
NON-INCLUSION CRITERIA	<ul style="list-style-type: none"> - VA-ECMO after cardiac surgery for 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)) - Indication of therapeutic hypothermia for cardiac arrest - Resuscitation >30 minutes - Cerebral deficit with fixed dilated pupils - Participation in another biomedical research - Patient moribund on the day of randomization - Irreversible neurological pathology - Minor patients - Patients under tutelage
RECRUITMENT PROCEDURES	<p>All intubated patients with cardiogenic shock supported with VA-ECMO will be screened.</p> <p>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).</p>
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	<p>N= 334 patients</p> <p>We considered that mortality in cardiogenic patients supported with VA-ECMO will be 50% (based both on ELSO data, Combes data (<i>Crit Care Med.</i> 2008 May;36(5):1404-11) and study principal investigator's personal data (database of 150 patients)</p> <p>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.</p> <p>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.</p>
STUDY PERIOD	<p>Duration of participation of each patient: 6 months (D180)</p> <p>Anticipated duration of recruitment: 36 months</p> <p>Anticipated total duration of the study (statistical analysis included): 49 months</p>
STATISTICAL ANALYSIS OF THE DATA	<p>Statistical analysis for the primary endpoint:</p> <p>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.</p> <p>Statistical analysis for the secondary endpoints:</p> <p>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.</p> <p>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.</p> <p>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</p>

	<p>than those mentioned above and odd-ratios will be provided for illustration purposes.</p>
FEASIBILITY OF THE PROJECT	<p>Hypothermia induction during VA-ECMO does not require any additional device or supplementary catheter insertion. During therapeutic hypothermia, all centers monitor central temperature. Central temperature will be measured in each group in accordance with local practice (e.g bladder catheter, oesophageal probe...).</p> <p>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.</p> <p>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.</p> <p>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 experienced 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.</p>
POTENTIAL IMPACT	<p>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 %.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>

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219 **1 SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION OF THE**
220 **RESEARCH**

221 **1.1 BACKGROUND**

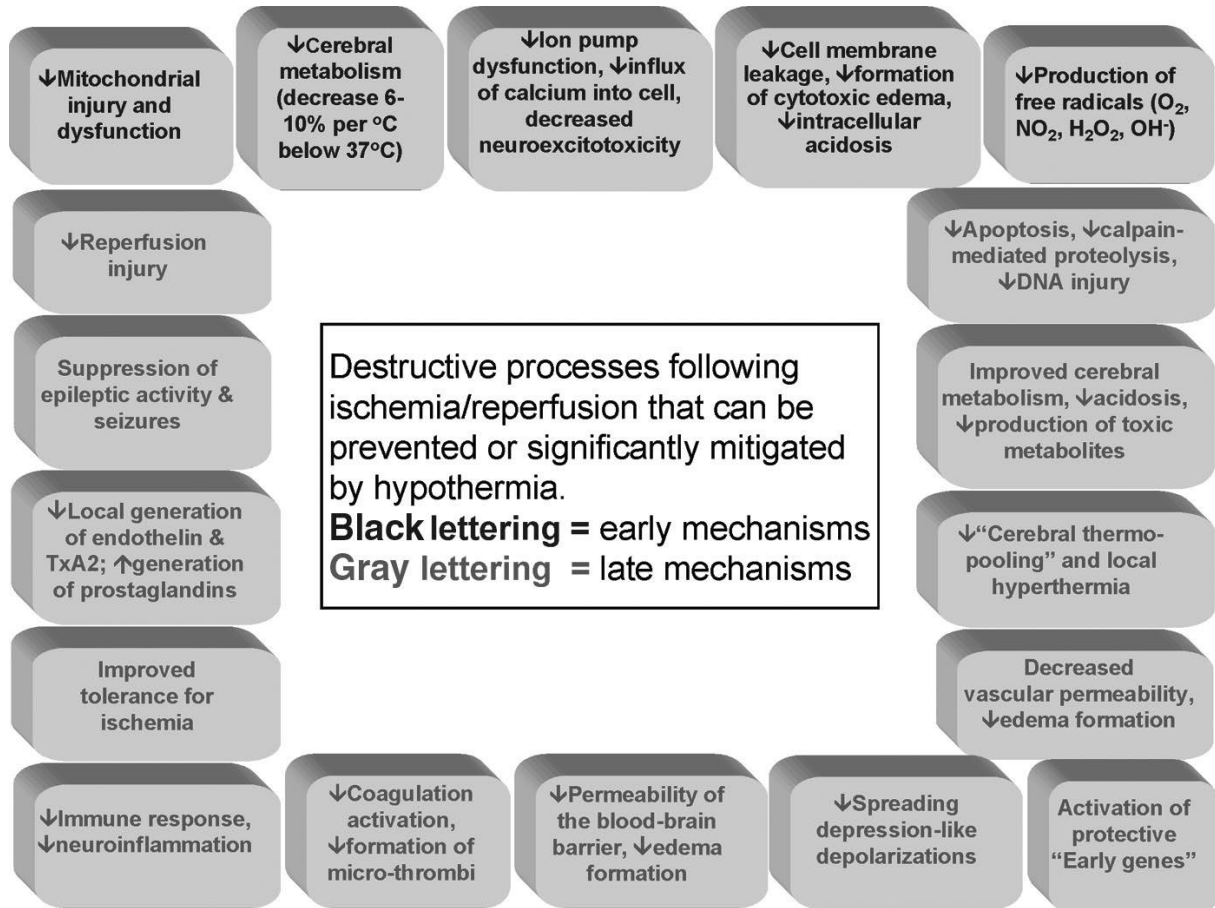
222 Cardiogenic shock (CS) is generally defined by cardiac index <2.2 l/min/m², hypotension,
223 elevated pulmonary capillary wedge pressure, and end-organ hypoperfusion. The leading cause of CS
224 is myocardial infarction (MI)[1]. CS affects approximately 5% to 7% of patients with MI. Mortality in CS
225 remains high. For example, for CS complicating MI, mortality is still 50 % [1, 2]. Importantly, long-term
226 outcome for 1-year survivors of CS is similar to that of non-shock acute MI survivors. That points the
227 importance of improving short-term survival, which remains unacceptably low. This should place the
228 focus on very early reperfusion in MI to prevent shock and novel therapies targeting patients with CS.
229 Efforts to improve early survival are only made more important by the observation that survivors will
230 likely enjoy good quality of life; most will be in New York Heart Association functional class I or II at 1
231 year of follow-up [3]. Further improving short-term outcomes has proven challenging. Recent attempts
232 to inhibit inflammatory cytokine and nitric oxide-mediated systemic inflammatory response syndrome
233 pathways in CS have yielded disappointing results. Unfortunately, there have been few recent
234 advances in the treatment of cardiogenic shock on the exception of ExtraCorporeal Membrane
235 Oxygenation (ECMO). As recently suggested, therapeutic hypothermia is a possibility to treat
236 cardiogenic shock [4]. Therapeutic hypothermia is widely available and has become a standard
237 component of treatment for out-of-hospital ventricular tachycardia/ventricular fibrillation arrest. It also
238 has wide-ranging systemic effects that might be particularly advantageous when considering the
239 systemic manifestations of cardiogenic shock [5].

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

244 **1.2 RATIONAL: CELLULAR AND ANIMAL MODELS**

245 Hypoperfusion in the setting of CS leads to multiple end-organ damage and dysfunction that
246 contributes to morbidity and mortality. Hypothermia decreases metabolic rate 5% to 7% per degree
247 reduction of body temperature, and it decreases oxygen consumption, carbon dioxide production, and
248 glucose consumption [5]. In addition, hypothermia affects the cardiovascular (CV) system in multiple
249 ways, many of which could be potentially beneficial in CS, especially in a post-MI setting. In dogs,
250 reduction of body temperature to 34°C in conjunction with vasodilator therapy results in increased
251 contractility and external work of the left ventricle without increasing myocardial oxygen consumption
252 [6]. In a dog model of post-MI CS, treatment with hypothermia to 32°C reduced heart rate, left
253 ventricular (LV) end-diastolic pressure, systemic oxygen consumption, and estimated myocardial
254 oxygen consumption while maintaining cardiac output and improving survival [7]. This study was
255 validated recently in a porcine model of post-MI CS showing that animals treated with hypothermia
256 had increased mean arterial pressure, stroke volume, pH, and mixed venous oxygen saturation with

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



261
 262 *Figure 1. Potential cerebral and systemic effects of moderate hypothermia (from Polderman KH, Critical Care*
 263 *Medicine 2009)*

264 Results of animal models further suggest that therapeutic hypothermia may reduce
 265 ischemia/reperfusion injury after urgent revascularization for acute MI. In dogs, hypothermia beginning
 266 30 min after left anterior descending coronary artery occlusion and continued through reperfusion 3
 267 hours later improved cardiac function during occlusion, blunted hemodynamic derangements during
 268 reperfusion, and reduced infarct size at 7 days [9]. In sheep, in addition to greater immediate
 269 myocardial salvage, LV systolic function was improved at 8 weeks in animals treated with therapeutic
 270 hypothermia [10].

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

276 severity of myocardial injury and dysfunction associated with MI. Furthermore, hypothermia attenuates
277 ischemia/reperfusion injury in other organ systems and reduces endothelial cell apoptosis and
278 systemic oxidative stress. Hypothermia also increases urine output, likely via reduction in fluid
279 resorption beyond the mid-distal tubule in the kidney, an effect that could prove beneficial in post-MI
280 cardiogenic shock patients with difficult-to-manage volume status.

281 The Figure 1 identifies potential pathways leading to or mediating the systemic effects of CS and
282 where preclinical data suggest therapeutic hypothermia may modulate these effects.

283

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

291

292 **From bench to bedside : Important points and consequences for the HYPO-ECMO study.**

293 Studies on mechanisms underlying hypothermia's protective effects point to four key factors
294 determining success or failure of cooling treatment. These are:

295 a) Speed of induction of hypothermia; outcomes in animal experiments are far better when
296 cooling is initiated rapidly after injury [13]. ***In HYPO-ECMO study we will use an early and
297 fast cooling.***

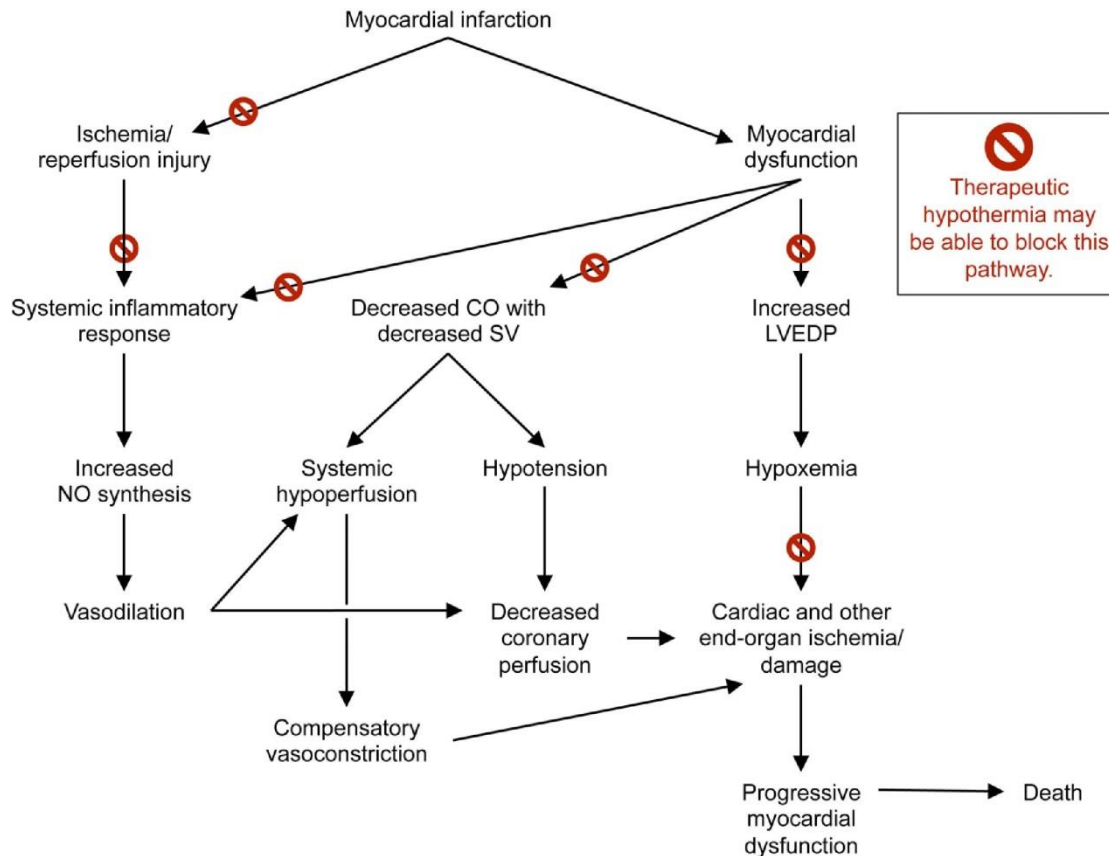
298 b) Duration of cooling (depending on the severity of the initial injury and the time interval until
299 target temperature is reached). ***In HYPO-ECMO study we will use 24 hours which is the
300 most common duration used for cardiac arrest patients.***

301 c) Speed of rewarming (this should be slow lest the destructive processes be reinitiated; this
302 happens frequently if rewarming speeds are high). ***In HYPO-ECMO study the patient will be
303 rewarmed in 24 hours (0.2±0.1°C/h) follow by 48 hours of maintained normothermia.***

304 d) Proper management of side effects. Side effects include immunosuppression with increased
305 infection risk, cold diuresis and hypovolemia, electrolyte disorders, insulin resistance, and mild
306 coagulopathy. Targeted interventions are required to effectively manage these side effects.
307 ***Specific management based on the literature for these potential side effects will be
308 propose in HYPO-ECMO study (cf chapter 1.4.2)***

309

310



311

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

313

314 1.3 HUMAN STUDIES OF HYPOTHERMIA

315 1.3.1 In non-complicated myocardial infarction.

316 One study in humans showed decreased infarct size among patients with anterior infarcts
 317 treated with therapeutic hypothermia who reached a temperature of <35°C at time of reperfusion [14].
 318 In this study, cooling was well tolerated, with no hemodynamic instability or increase in arrhythmia.
 319 Nine patients experienced mild episodic shivering. Major adverse cardiac events occurred in 0% vs.
 320 10% (p = NS) of treated versus control patients. The median infarct size was slightly smaller in
 321 patients who received cooling compared with the control group (2% vs. 8% of the left ventricle, p =
 322 0.80).

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

331 minutes, hypothermia versus control, $P=1.00$), infarct size normalized to myocardium at risk was
332 reduced by 38% in the hypothermia group compared with the control group ($29.8 \pm 12.6\%$ versus 48.0
333 $\pm 21.6\%$, $P=0.041$). This was supported by a significant decrease in both peak and cumulative release
334 of Troponin T in the hypothermia group ($P=0.01$ and $P=0.03$, respectively). The authors concluded that
335 the protocol demonstrates the ability to reach a core body temperature of $<35^{\circ}\text{C}$ before reperfusion in
336 all patients without delaying primary percutaneous coronary intervention and that combination
337 hypothermia as an adjunct therapy in acute MI may reduce infarct size at 3 days as measured by MR

338 1.3.2 In myocardial infarction complicated by Cardiogenic Shock non treated 339 with VA-ECMO

340
341 There are only a few case reports and case series of hypothermia in patients with CS, mostly
342 limited to pediatric and adult cardiac surgery patients whose postoperative courses were complicated
343 by CS [16, 17] and none were from patients with CS in the acute MI setting. It is also important to
344 recognize that these are reports of highly selected cases in which treatment was nonrandomized and
345 concurrent therapy was uncontrolled. Only a well-designed randomized clinical trial can provide
346 evidence sufficient to support clinical practice in post-MI patients.

347
348 In general, whether in infants or children, when hypothermia is added to conventional therapy in
349 patients with refractory shock after cardiothoracic surgery, it resulted in decreases in heart rate and
350 increases in mean arterial pressure and urine output with improved clinical stability. Therapeutic
351 hypothermia has been reported in only three case series in adult patients with refractory heart failure.

352
353 Yahagi et al [16] reported 10 adult patients experienced post-cardiac surgery cardiogenic shock that
354 was refractory to medical therapy, including multiple vasopressors and intra-aortic balloon pumping;
355 the use of external cooling along with cold gastric lavage to a temperature of 34.5°C was associated
356 with an increase in cardiac index (1.9 ± 0.3 to 2.2 ± 0.3), mixed venous saturation ($55 \pm 7\%$ to $64 \pm$
357 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
358 mean arterial pressure, heart rate, systemic vascular resistance, or pH. Eight of 10 patients survived to
359 discharge. This study did not provided controls, but the expected mortality of patients in such condition
360 is $>50\%$.

361
362 Zobel et al [18] reported the effects of moderate hypothermia in 20 patients admitted in CS after
363 resuscitation from cardiac arrest. Patients were matched with a historical normothermic group by
364 means of propensity score. Moderate therapeutic hypothermia was associated with a significant
365 decrease in heart rate from 74 to 64 beats per minute. Despite the reduction in heart rate, cardiac
366 index remained unchanged under moderate therapeutic hypothermia likely due to an increase in
367 ejection fraction from $43 \pm 4\%$ to $55 \pm 4\%$. Mean arterial pressure increased rapidly from 75 ± 2 mmHg
368 to 84 ± 3 mmHg ($p = .001$) upon induction of hypothermia paralleled by an initial increase in systemic
369 vascular resistance. Accordingly, patients with moderate therapeutic hypothermia required lower
370 cumulative doses of vasopressors and inotropes. They concluded that in CS moderate therapeutic

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

373
374 Finally, Schmidt-Schweda [19] in 12 patients in CS found that hypothermia consistently decreased
375 heart rate, and increased stroke volume, cardiac index and cardiac power output. Metabolic and
376 electrocardiographic parameters remained constant during cooling.

377
378 Patients with signs of CS after cardiac arrest who underwent cooling provide another possible source
379 of information, although little is currently available. In one study [20], 28 of 56 patients who were
380 cooled after cardiac arrest also had CS, although it was not reported how many of these patients had
381 acute MI concurrent with the cardiac arrest. Among the CS patients, after 24 to 48 h of therapeutic
382 hypothermia, cardiac index increased from 1.5 ± 0.26 to 2.3 ± 0.371 . In addition, heart rate decreased
383 among CS patients but to a lesser extent than among patients without shock; mean arterial pressure
384 increased in patients with CS whereas it decreased in patients without initial signs of shock.

385
386 **To summarize, preliminary data demonstrated that moderate hypothermia during cardiogenic**
387 **shock is well tolerated and improves hemodynamic parameters.**

388
389 **Finally, to the best of our knowledge, there have been no published randomized human studies**
390 **of therapeutic hypothermia in post-MI cardiogenic shock treated with VA-ECMO. We found only**
391 **one ongoing clinical trial (NCT01890317) to test the effects of moderate hypothermia in CS**
392 **following MI. Importantly, in this study, patients will not be treated with VA-ECMO.**

393 **1.4 POTENTIAL RISKS AND BENEFITS**

394 **1.4.1 Expected patient or public health benefit**

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

407
408
409 The annual incidence of AMI (Acute Myocardial Infarction) is estimated at 100–150 per 100,000
410 inhabitants in France and 5-8% of AMI patients will develop cardiogenic shock. Therefore, the annual

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

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

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

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

430 1.4.2 Risks

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

434 Moderate hypothermia is/might be associated with shivering, modifications in blood gas management,
435 hyperglycemia, electrocardiographic changes, mild coagulopathy and increased sensitivity to infection
436 [5].

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

441
442 Management of physiological effects of hypothermia ***based on the literature [5]:***

443 a) The tolerance to hypothermia will be ensured with the cautious use of **sedation and**
444 **eventually with the use of a paralyzing agent in cases of shivering**. Use of a developed
445 shivering assessment scale will be proposed for this purpose [23] .
446

447 b) **Management of blood gas:** Blood gas values are temperature dependent, and if blood gas
448 are warmed to 37°C before analysis (as is common in most laboratories), Po₂ and Pco₂ will be
449 overestimated and pH underestimated in hypothermic patients. **For accurate temperature**
450 **correction, blood gas will be analyzed at the patient's real temperature.**

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- c) **Glycemia management:** 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) **Coagulation:** 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.

489 Finally, comparatively to drug/new device research, hypothermia is inexpensive and very simple to
490 implement in real life. Therefore, the only cost for society will be the grant for the study.
491

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- 569

570

571 **3 STUDY OBJECTIVES**

572 **In this chapter, and accordingly to the literature, moderate hypothermia is definite as a**
573 **temperature between $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$. Normothermia is definite as a temperature at 37**
574 **degrees $\pm 0.3^{\circ}\text{C}$.**

575

576 **3.1 PRIMARY OBJECTIVE**

577 The study objective is to determine whether early moderate hypothermia ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) is
578 superior to normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) in patients with cardiogenic shock treated with VA-ECMO
579 with respect to 30-day mortality.

580 **3.2 SECONDARY OBJECTIVES**

581 Evaluation of the impact of moderate hypothermia on:

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

593 **3.3 STUDY OUTCOME MEASURES**

594 **3.3.1 Primary endpoints**

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

596 **3.3.2 Secondary endpoints:**

- 597 - All-cause mortality at 48 hours and day 7, 60, 180
- 598 - VA-ECMO duration
- 599 - Composite endpoint of death, cardiac transplant, escalation to LVAD, stroke at days 30, 60,
600 180
- 601 - Cumulated amount of administered fluids and duration of vasopressors use in ICU
- 602 - Duration to normalization of lactate
- 603 - Number of days alive without organ failure(s), defined with the SOFA score and its
604 components (respiratory, liver, coagulation and renal), between inclusion and D30
- 605 - Duration of mechanical ventilation and the number of days between inclusion and day 30/ day
606 60, alive without mechanical ventilation

- 607 - Number of days alive without renal replacement therapy, and the number of days, between
- 608 inclusion and day 30 and day 60, without renal replacement therapy
- 609 - Duration of ICU stay, of hospitalization
- 610 - Number of severe and moderate bleeding complications (GUSTO-definition, N Engl J Med.
- 611 1993;329:673–682) and the number of packed red blood cells transfused under VA-ECMO
- 612 - Infection probability: pulmonary, blood and VA-ECMO cannulaes

613 4 STUDY DESIGN AND PROCEDURES

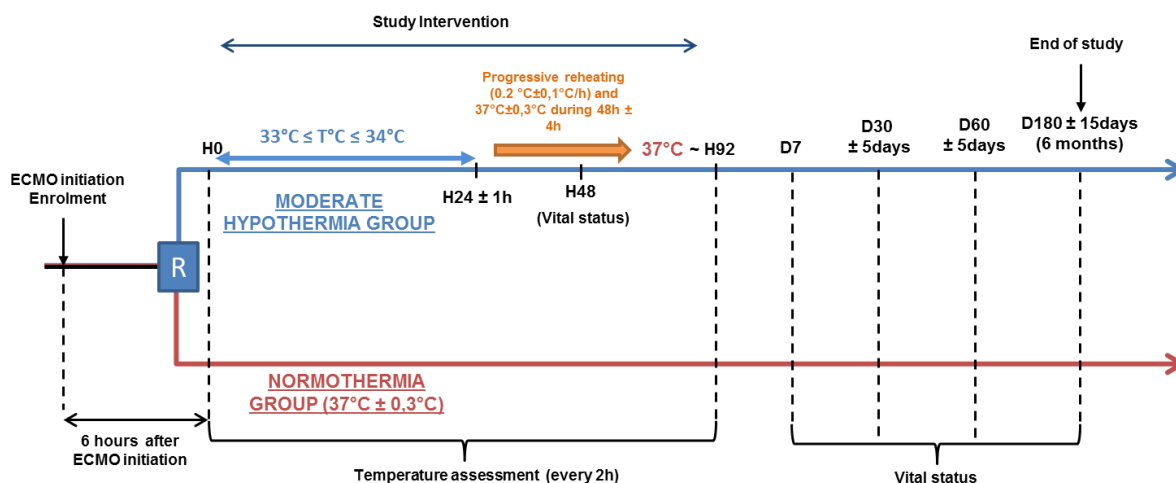
614 4.1 EXPERIMENTAL STUDY DESIGN

615 A multicenter, prospective, controlled, randomized (moderate hypothermia during 24 hours \pm

616 1h versus normothermia), comparative open trial will be conducted on two parallel groups of patients

617 with CS treated with VA-ECMO.

618



619
620

621 4.1.1 Common management for all patients before and during

622 intervention

623 For all patient enrolled in the study, VA-ECMO will be initiated in accordance to the local

624 practice with flow settings to ensure sufficient tissue perfusion.

625

626 **With the exception of temperature control, all other diagnostic, therapeutic and**

627 **weaning procedures will be done according to the current standard of care at the tertiary CV**

628 **center and at the discretion of the investigator.**

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

632 4.1.2 Heater-Cooler Unit and temperature control for all patients

633 Each circuit will be associated with a device able to control temperature used in this study in

634 conformity of the device CE Label such as "Heater-Cooler Unit HCU 35 from Maquet compagny".

635 These devices are available in each center. This device allows a perfect control and hold of the target

636 temperature. The water tank for the patient circuits is divided into two parts to ensure quick

637

638 temperature adjustments at the outlets. In addition, it has exceptional cooling capacity through its fast
639 ice-building technique using highly effective cooling plates and a powerful compressor. In our study
640 each center will use his local heater-cooler unit to control temperature (described in Appendix B).

641

642 4.1.3 Temperature assessment method

643

644 During therapeutic hypothermia, all centers monitor central temperature. Central temperature will be
645 measured in each group in accordance with local practice (e.g bladder catheter, oesophageal
646 probe...)

647 In both group, temperature will be measured every two hours during intervention (time during the first
648 92 hours at the allocated group (cf figure in chapter 4.1).

649

650 4.1.4 Inclusion and randomization of patient

651

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

655

656 After eligibility verification, complete clinical examination and inform consent process (cf chapter 13.2),
657 patient will be randomized. The patients will be placed on moderate hypothermia ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$)
658 or maintained on normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) during 24 hours \pm 1h according to the group.

659

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

665 4.1.5 Moderate hypothermia group

666

667 Moderate hypothermia will be induced as soon as possible **during the first 6 hours**
668 **(preferably 4 hours) after VA-ECMO initiation (H0) and randomization.** Moderate hypothermia will
669 be induced using the heat controller of the VA-ECMO circuit. Temperature will be maintained between
670 $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$ during 24 hours \pm 1h followed by a progressive reheating ($0.2 \pm 0.1^{\circ}\text{C}/\text{hour}$) to reach
671 37°C . Temperature at $37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$ will be maintained during 48 hours \pm 4h after having reached 37
672 $^{\circ}\text{C}$.

673

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

677

678 4.1.6 **Normothermia group**

679
680 The extracorporeal life support organization (ELSO) recommends "Temperature can be
681 maintained at any level by adjusting the temperature of the water bath. Temperature is usually
682 maintained close to 37° C." Therefore the temperature will be maintained at 37 °C ± 0.3°C under VA-
683 ECMO.

685 4.1.7 **Discontinuation of experimental study intervention (moderate
686 hypothermia group)**

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

692 4.1.8 **Prohibited treatment for the subject participation**

693 None, all medications or treatments are authorized.

695 4.1.9 **Follow up after intervention (H48, day 7, day 30 (± 5 days), day 60 (±
696 5 days), Day 180 (± 15 days) (end of the study) after randomization
697 for all patient)**

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

702 **4.2 FLOWCHART**

	Inclusion	Randomization (a)	After randomization					
			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)

704
705 a) During the first 6 hours (preferably 4 hours) after VA-ECMO implementation
706 b) Induced as soon as possible during the first 6 hours (preferably 4 hours) after VA-ECMO
707 implementation and randomization
708 LT : life threatening

709

710 **4.3 BIAS CONSIDERATION**

711

712 4.3.1 **Randomization procedure**

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

715 **Treatments arms :**

716

717 • **Experimental group:** Patients with CS allocated to a strategy of moderate hypothermia
718 (33°C ≤ T°C ≤ 34°C) associated with usual care.

719 • **Control group:** Patients with CS allocated to a strategy of normothermia (37 °C ± 0.3°C)
720 associated with usual care.

721

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

724

725 4.3.2 **Replacement procedures for patients**

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

728

729 **4.4 STUDY PERIOD**

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

731 Anticipated duration of recruitment: **36 months**

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

733 **4.5 TERMINATION RULES**

734

735 4.5.1 **Patient Premature termination**

736

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

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

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

742 4.5.2 **Exclusion period**

743

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

746

747 4.5.3 **Follow-up after end of study**

748

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

750 **4.6 DATA LIST NOT AVAILABLE IN THE PATIENT FILE**

751

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

753 **5 STUDY POPULATION**

754 **5.1 PARTICIPATING CENTERS**

755

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

758 **5.2 PATIENT SCREENING AND ENROLMENT**

759

760 All intubated patients with CS supported with VA-ECMO will be screened.

761 Patients with CS treated with VA-ECMO in the intensive care unit meeting all of the inclusion and non-
762 inclusion criteria will be enrolled in the study (emergency consent process of chapter 13.2).

763 Reasons for non-eligibility will be listed in a dedicated screening log file.

764 **5.3 INCLUSION CRITERIA**

765

766 - Age \geq 18 years

767 - Intubated patients with cardiogenic shock treated with VA-ECMO

768 - Patient affiliated to social security plan

769 **5.4 NON-INCLUSION CRITERIA**

770

771 - VA-ECMO after cardiac surgery for heart/lung transplantation or left or biventricular assist
772 device implantation

773 - VA-ECMO for acute poisoning with cardio-toxic drugs

774 - Pregnancy

775 - Uncontrolled bleeding (bleeding despite medical intervention (surgery or drugs))

776 - Indication of therapeutic hypothermia for cardiac arrest

777 - Resuscitation >30 minutes

778 - Cerebral deficit with fixed dilated pupils

779 - Participation in another biomedical research

780 - Patient moribund on the day of randomization

781 - Irreversible neurological pathology

782 - Minor patients

783

784 - Patients under tutelage

785

786 **6 METHODS USED FOR THE EVALUATION OF EFFICACY**

787 Cf chapter 3

788 **7 SAFETY ASSESSMENT**

789 **7.1 DESCRIPTION OF SAFETY ASSESSMENT PARAMETERS, METHOD AND**
790 **CALENDAR USED FOR THE EVALUATION OF SAFETY**

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

795
796 In particular, glycaemia, blood gas and coagulation will be followed up and the occurrence of
797 shivering, modifications in blood gas management, hyperglycemia, electrocardiographic changes, mild
798 coagulopathy and increased sensitivity to infection will all be recorded as adverse events.

799 Uncontrolled bleeding and coagulation disorders that require blood cells or platelet transfusion will be
800 considered as serious events.

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

802

803 All adverse events between inclusion and D7 will be recorded.

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

806

807 **7.2 REPORTING AND TRANSMISSIONS OF SAE/R**

808 **7.2.1 Definitions:**

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

812

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

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

821

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

825

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

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

833

834 Unexpected serious adverse effect (article R.1123-39 of the French Public Health Code):

835 Any adverse effect, of which the nature, the severity or the progression does not concord with the
836 information in the submissions to the ethics committee (Comité de Protection des Personnes, CPP)
837 and the competent authority.

838

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

842

843 7.2.2 List of expected adverse events suspected

844

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

- 848 - Shivering
- 849 - Modifications in blood gas management
- 850 - Hyperglycemia
- 851 - Electrocardiographic changes
- 852 - Mild coagulopathy
- 853 - Increased sensitivity to infection

854

855 Therefore, we will record in the patient's e-CRF the occurrence of hyperglycemia (appreciated by the
856 amount of insulin), nosocomial infection and hemorrhagic disorder (number of packed red cell
857 transfused).

858 We will consider as **serious adverse events** in the hypothermia group the occurrence of uncontrolled
859 bleeding. In this case, hypothermia will be stopped and resumed as soon as the bleeding is controlled
860 for a total duration of 24 hours.

861

862

863 7.2.3 Serious adverse events/ reactions and new facts reporting

864

- 865 - As soon as an investigator becomes aware of a SAE/R or a new fact, he/she advises the
866 sponsor without delay by faxing the SAE/R declaration form at **03 83 32 33 44**.
- 867 - If it is a an *unexpected serious adverse reactions* (USAR) or if it is a new fact, the sponsor will
868 contact the investigator in order to prepare an initial report which will be forwarded to the
869 ANSM, the CPP and to the coordinating investigator within 7 days in case of death or life
870 threatening SAE, otherwise within 15 days. An additional information will be forwarded within 7
871 days of death or life-threatening SAE.
- 872 - When the event is not resolved at the time of fax transmission, the investigator must send a
873 supplementary report to document the changes or to update the missing data.
- 874 - If it is an *expected serious adverse effect*, the sponsor will compile it for the drafting of annual
875 safety reports.
- 876 - *Expected non-serious adverse reactions* will be briefly described by the investigator on the
877 summary sheet dedicated to this effect in the data collection notebook.
- 878

879 7.2.4 **Non-serious adverse events/ reactions reporting**

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

883

884 7.2.5 **Adverse event/reaction monitoring**

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

- 886 - If the event is not serious, evolution/changes will be noted on the relevant page of the
887 case report form in the designated section reserved for this purpose.
- 888 - If the event is serious, a SAE/R follow-up will be sent to the sponsor.
- 889

890 7.2.6 **Safety report**

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

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

898

899 **8 ORGANIGRAM AND FEASIBILITY**

900 **8.1 PROJECT ORGANIZATION SCHEME**

901 **8.1.1 Steering Committee**

902

903 *Role*

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

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

911

912 The Steering committee will be comprised of:

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

918

919 **8.1.2 Data safety monitoring board (DSMB)**

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

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

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

927

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

931

932 **9 FEASIBILITY**

933

934 Hypothermia induction during VA-ECMO does not require any additional device or supplementary
935 catheter insertion since central temperature is easily controlled with the circuit heat controller.

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

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

941 **10 DATA MANAGEMENT AND STATISTICS**

942 **10.1 DATA MANAGEMENT**

943 10.1.1 **Electronic Case report form**

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

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

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

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

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

960

961 **11 DATA ANALYSIS AND STATISTICAL DETERMINATION**

962 **11.1 DESCRIPTION OF ANTICIPATED STATISTICAL ANALYSIS METHODS**

963 11.1.1 **Statistical analysis for the primary endpoint**

964
965 The differences between the 2 study groups (i.e. intervention and controls) in the risk
966 of all-cause mortality at day 30 following randomization will be studied using the Chi-2 test. To
967 illustrate the association, both an odd-ratio and a hazard ratio will be provided. In addition, survival
968 curves using the Kaplan-Meier method will be constructed.

969

970 11.1.2 **Statistical analysis for the secondary endpoints**

971

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

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

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

990
991 Chi-square tests (or Fisher exact test in case of insufficient number of expected patients in on
992 of the 2x2 cell) will be performed for the outcomes mentioned below:

- 993 - Pulmonary, blood and VA-ECMO cannulae infections

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

995 **11.2 SAMPLE SIZE CONSIDERATION**

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

999 The objective of the study is to demonstrate the superiority of the treatment with VA-ECMO plus
1000 moderate hypothermia as compared to VA-ECMO alone on mortality.

1001 Therefore, considering a total event risk (for the primary endpoint) of 50 % in the control group, a
1002 sample size of **N = 167 patients/group** will detecting a 15% absolute difference in favor the VA-
1003 ECMO group using a chi-square test with a 80 % power and considering a two-sided global alpha level
1004 of 5% using the LanDe Mets method with O'BrienFleming boundary for one interim analysis (efficacy
1005 and futility) after inclusion of 2/3 of the patients.

1006 **11.3 DEGREES OF STATISTICAL SIGNIFICANCE**

1007 A bilateral p value lower than 4.9% will be considered significant for the final analysis. A p
1008 value threshold lower than 5% is mandatory given the planned interim analyses to ensure a global
1009 alpha level at 5%.

1010 **11.4 PLANNED INTERIM ANALYSES (IF APPLICABLE)**

1011 One interim analysis for efficacy/futility will be performed after inclusion of 2/3 of the patients.

1012 **11.5 STATISTICAL CRITERIA FOR STUDY TERMINATION**

1013 A p-value threshold of 0.001 will be used for this interim analysis as calculated with the LanDe
1014 Mets method with O'BrienFleming boundary.

1015 **11.6 METHOD FOR ADDRESSING MISSING, INVALID OR UNUSED DATA**

1016 For the primary outcome, we do not expect missing variables. All-cause 30 days mortality is a
1017 straightforward outcome that does not require detailed information. Yet, in the unlikely case of missing
1018 vital status at 30 days, patients with missing data will be analyzed with the last observation being
1019 carried forward. In a sensitivity analysis, the worst case scenario method will be used (i.e. all patients
1020 with incomplete follow-up data died in the intervention group and died in the no intervention group).

1021 **11.7 MANAGEMENT OF AMENDMENTS TO THE ANALYSIS PLAN OF THE INITIAL**
1022 **STRATEGY**

1023 No amendments are expected. Amendments can be decided by the steering committee.

1024 **11.8 SELECTION OF SUBJECTS TO BE INCLUDED IN THE ANALYSIS**

1025 As per intention to treat analysis, every randomized patients will be included in the analysis.

1026 **12 CONTROL AND QUALITY ASSURANCE**

1027 **12.1 ACCESS TO SOURCE DATA AND DOCUMENTS**

1028 The sponsor is responsible for obtaining the agreement of all parties involved in the study so
1029 as to guarantee direct access to all study sites, source data, source documents, and reports so that
1030 the sponsor may control data quality and perform an audit.

1031
1032 Investigators accept to give access to all relevant data and records to the sponsor (Sponsor's
1033 monitors, auditors, the Sponsor's Quality Assurance representatives) and all authorized Sponsor
1034 personnel, and regulatory authorities, under strict confidentiality condition and in compliance to the
1035 French regulatory.

1036 **12.2 STUDY MONITORING**

1037 Monitoring will be performed by the sponsor (Department of Research and Innovation CHRU
1038 de Nancy) during the study to ensure that compliance with the Protocol and applicable regulations is
1039 maintained, that data are collected in a timely, accurate and complete manner and that the investigator
1040 continues to have sufficient staff and facilities to conduct the study safely and effectively.

1041 Details of the monitoring visits will be work out in the sponsor monitoring plan.

1042 **13 ETHICAL CONSIDERATIONS AND REGULATIONS**

1043 **13.1 REGULATORY AND ETHICAL CONSIDERATIONS**

1044 Before initiating a trial, according to the French local regulation, the sponsor (CHRU Nancy)
1045 should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics
1046 Committee (IRB/IEC) and authorization from the French Health Authorities for the research.

1047
1048 The sponsor and investigators commit that this research is conducted according to the protocol and
1049 his procedures, to the French local regulation (law n ° 2004-806 of August 9, 2004), as well as in
1050 agreement with Good Clinical Practices (I.C.H. version 4 of May 1, 1996 and Decision of November
1051 24, 2006) and the Helsinki Declaration (Ethical Principles for Medical Research Involving Human
1052 Subjects, Tokyo 2004).

1053 **13.2 INFORMED CONSENT PROCESS**

1054 Before collecting the patient's consent, the investigator will give complete information about the
1055 proposed study.

1056
1057 In the particular context of this protocol, the persons include in this research may not be able to
1058 receive information about the study and give their consent before the implementation of the protocol
1059 due to their medical condition.

1060 In this case, if a member of the patient's family (or support person defined in Article L.1111-6 -
1061 Appendix 5) is present, this person will be informed and consent will be gathered.

1062 In the absence of a family member or support person, the investigator will include the patient in the
1063 study and will gather the consent of the family member or support person as soon as possible.

1064 The patient will be asked to give his/her consent for the continuation of the trial when his/her condition
1065 will allow.

1066
1067 Patient, family member or support person, is free to refuse participation in the study and may at any
1068 time and for whatever reason withdraw its consent.

1069
1070 The consent form will be signed in two originals copy by the subject and the investigator and a
1071 member of the family / support person if applicable:

1072 - An exemplary will be given to the subject or family member / support person if applicable

1073 - An exemplary will be retained and archived by the investigator

1074
1075

1076 **13.3 PROTOCOL AMENDMENT**

1077 Any change or addition to the protocol can only be made in a written protocol amendment
1078 (modification of an inclusion criterion, extending the inclusion period, participation of new centers ...)

1079 that must be approved by the sponsor, French Health Authorities and the IRB/IEC prior to
1080 implementation.

1081 **13.4 PATIENT DATA CONFIDENTIALITY**

1082 Throughout the study, confidentiality shall be observed, at all times, by all parties involved,
1083 and all data shall be secured against unauthorized access.

1084 Confidentiality of each subject shall be preserved in reports and any publication of the results.

1085 Only authorized Sponsor staff and regulatory authorities may have access to these confidential files.

1086 The data collected during the study will be performed according to the French local regulation
1087 (Commission Nationale de l'Informatique et des Libertés (CNIL), in compliance with the MR001
1088 methodology)

1089 **13.5 ARCHIVING STUDY DOCUMENTS AND STUDY DATA**

1090 All study documents including patient's identification list and signed informed consent should be keep
1091 for at least 15 years. For each patient, documentation must clearly specify the following:

- 1092 • Participation of the patient in the study (patient and study's identification),
- 1093 • Concomitant treatments or medications,
- 1094 • Any visit to the hospital, particularly those visits made for the sole purposes of the study,
- 1095 • Serious adverse events (SAEs).

1096 **13.6 AUDIT AND INSPECTION**

1097 Audits or inspections may be performed at any time by persons mandated by the sponsor and
1098 independent of those in charge of the study or by French Health Authority respectively.

1099 Investigators accept to give access to all relevant data and records to the auditors and inspector. If an
1100 inspection of the clinical site is requested by the French Health Authority, the investigator must inform
1101 the sponsor immediately that this request has been made.

1102 **14 INSURANCE**

1103 **14.1 INSURANCE**

1104 The sponsor has subscribed an insurance for the duration of the study guaranteeing its own civil
1105 liability as well as that of any stakeholder involved in the conducting of the study, regardless of the
1106 nature of existing ties between the stakeholders and the sponsor.

1107 **15 PUBLICATION POLICY**

1108 **15.1 FINAL RESEARCH REPORT**

1109 The final report of the research will be written collaboratively by the coordinator and the
1110 biostatistician mandated for this search. This report will be submitted to each of the investigators for
1111 review. Once a consensus has been reached, the final version must be endorsed with the signature of

1112 each of the investigators and sent to the sponsor as early as possible after the effective end of the
1113 research.

1114

1115 Data is the property of the sponsor. The conditions for data transfer of all or part of the study database
1116 are decided by the study sponsor.

1117

1118 “CHRU Nancy” should be mentioned as sponsor of this study.

1119 The publications resulting from this work will be labeled by « The study was supported by a grant from

1120 the French Ministry of Health (Programme de Recherche Hospitalier National 2015) »

1121 **16 APPENDIX**

1122 **Appendix A: Common management for all included patients treated with VA-**
1123 **ECMO before and during study intervention**

1124
1125 **1. ECMO initiation;**
1126

1127 Venous-Arterial ECMO (VA-ECMO) support will be used. The extracorporeal system will consist of
1128 polyvinyl chloride tubing, a membrane oxygenator, a centrifugal pump, and percutaneous arterial and
1129 venous femoral cannulae. An oxygen/air blender will be used to ventilate the membrane oxygenator.
1130 An 7-10-Fr cannula will be inserted distally into the superficial femoral artery to prevent severe leg
1131 ischemia. Heparin boluses at the time of VA-ECMO implantation will be discouraged however a low
1132 dose bolus is permitted according to the experience of the ECMO team.

1133 **2. Initial parameter settings for VA-ECMO**
1134

1135 The pump flow will be set to 3.5-5 l/min, to provide adequate systemic perfusion. Pump flow might
1136 be reduced in case of cessation of LV ejection or major pulmonary edema. Percentage of oxygen
1137 contained in the ventilating gaseous air–oxygen mixture will be adjusted to obtain PaO₂ between 65
1138 and 90 mmHg and/or arterial oxygen saturation >90%. The membrane ventilation will be adjusted to
1139 maintain PaCO₂ between 40 and 45 mmHg.

1140 **3. VA-ECMO monitoring (extracorporeal circuit, anticoagulation, possible complications)**
1141

1142 The VA-ECMO circuit will be monitored several times daily by the medical and nursing team
1143 caring for the patient and at least once every 48 hours by a perfusionist. Circuit and cannula
1144 surveillance is intended to verify the correct functioning of the device and early screening for
1145 complications (leg ischemia, fibrin deposits or clots on the VA-ECMO membrane, clots in the cannulae
1146 or in the pump, bleeding or signs of inflammation or cutaneous infection at the cannula insertion sites,
1147 unexpected drop of the VA-ECMO outflow, appearance of clinical or biological signs of intravascular
1148 hemolysis). Should any of these complications occur, a medical–surgical consultation will be held to
1149 discuss the best therapeutic approach to take.

1150 Anticoagulation will be obtained with non-fractionated heparin to a target aPTT of 55-70 sec or
1151 heparinemia (antiXa activity) between 0.2 and 0.3 IU/ml. A bolus of heparin is not encouraged at the
1152 time of circuit implantation. Should severe bleeding occur that is not immediately controllable by
1153 specific treatment, heparin will be discontinued.

1154 Intravascular hemolysis will be sought should unexpected dark urine be excreted or in the case of
1155 obvious circuit dysfunction. It is recommended that plasma free hemoglobin be measured every 48
1156 hours and immediately if hemolysis linked to the circuit is suspected.

1157 The membrane and VA-ECMO circuit will be changed in the following situations: massive intravascular
1158 hemolysis linked to the device, severe thrombopenia linked to the circuit, clots preventing the pump
1159 and/or lines from functioning properly or systemic defibrination.

1160 The hemoglobin threshold for red cells transfusion will be 9-10 g/dl (may be decreased to 7-8 g/dl if
1161 the patient is stabilized and does not have residual myocardial ischemia). Platelet transfusion will be
1162 discouraged except when severe thrombopenia is associated by bleeding complications or when
1163 platelet count will be <20 G/L.

1164 Connecting an extrarenal dialysis circuit to the VA-ECMO circuit will be permitted under strict
1165 supervision of perfusionnists.

1166 **4. Intra-aortic balloon pump (IABP) support in addition to VA-ECMO**

1167 An IABP will be inserted according to the physician choice in the contralateral femoral artery. A
1168 strategy of liberal use of IABP has been associated with less pulmonary edema and better LV
1169 unloading in patients with severe LV dysfunction under VA-ECMO.
1170

1171 **5. Weaning criteria and ECMO weaning**

1172 Weaning from VA-ECMO should not be attempted in the first 48 hours. Before a first weaning trial,
1173 the patient should be hemodynamically stable, with baseline mean arterial pressure (MAP) > 60
1174 mmHg in the absence or at low doses of vasoactive agents and pulsatile arterial waveform maintained
1175 for at least 24 hours. The weaning will be conducted under echocardiographic monitoring. The ECMO
1176 flow will be decreased progressively to a minimum of 1–1.5 L/min. If mean blood pressure is
1177 constantly > 60 mmHg during the trial, the VA-ECMO flow rate will be returned to its baseline value.
1178 VA-ECMO removal will be considered if the patient does not have end-stage cardiac disease, tolerates
1179 the full weaning, and has LVEF \geq 20–25%, aortic velocity-time integral \geq 12 cm and lateral mitral
1180 annulus peak systolic velocity of \geq 6 cm/s under minimal VA-ECMO support.
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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 (polyméthylpentène)	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	
Montpellier	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	

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Centre Hospitalier Régional Universitaire de Nancy

Direction de la Recherche et de l'Innovation

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Clinical Trial Protocol

N° ID RCB N°2016-A00377-44

Code Promoteur : PHRCN2015/HYPOECMO-LEVY/YB

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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

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Version n°7.1 du 25/04/2018

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LIST OF ABBREVIATIONS

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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

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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°7.1 du 25/04/2018
TYPE OF STUDY	Biomedical research
NUMBER OF RECRUITING CENTER	20
RATIONALE /BACKGROUND	<p>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.</p> <p>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.</p> <p>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.</p> <p>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).</p> <p>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.</p> <p>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.</p>
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	<p><u>Evaluation of the impact of moderate hypothermia on:</u></p> <ul style="list-style-type: none"> - 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;

	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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 $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) during 24 hours \pm 1h versus normothermia $36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$, comparative open trial will be conducted on two parallel groups of patients with cardiogenic shock treated with VA-ECMO.
STUDY TREATMENTS/STRATEGIES PROCEDURES	<p>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.</p> <p>After inclusion and randomization (by CleanWeb® software), the patients according to the group allocated will be placed on moderate hypothermia ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) during 24 hours \pm 1h or maintained on normothermia ($36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$).</p> <p>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 $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$ during 24 hours \pm 1h followed by a progressive reheating ($0.2 \pm 0.1^{\circ}\text{C}/\text{h}$) to reach 37°C. Temperature at $37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$ will be maintained during 48 hours \pm 4h after having reached 37°C.</p> <p>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.</p> <p>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 $36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$.</p>

	<p>In both group, temperature will be measured every two hours during intervention (time during the first 92 hours at the allocated group).</p> <p>Follow up (vital status and cause of death) at D30 ± 5 days, D60 ± 5 days and D180 ± 15 days for all the patients.</p>
MAIN INCLUSION CRITERIA	<ul style="list-style-type: none"> - Age ≥ 18 years - Intubated patients with cardiogenic shock treated with VA-ECMO - Patient affiliated to social security plan
NON-INCLUSION CRITERIA	<ul style="list-style-type: none"> - 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	<p>All intubated patients with cardiogenic shock supported with VA-ECMO will be screened.</p> <p>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).</p>
EXCLUSION PERIOD	<p>Individuals cannot participate simultaneously in other biomedical Research for the duration of the study. There is no exclusion period.</p>
ACT REQUIRED LOGISTIC	<p>Randomization</p>
STUDY SIZE	<p>N= 334 patients</p> <p>We considered that mortality in cardiogenic patients supported with VA-ECMO will be 50% (based both on ELSO data, Combes data (<i>Crit Care Med.</i> 2008 May;36(5):1404-11) and study principal investigator's personal data (database of 150 patients)</p> <p>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.</p> <p>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.</p> <p>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.</p>
STUDY PERIOD	<p>Duration of participation of each patient: 6 months (D180)</p> <p>Anticipated duration of recruitment: 36 months</p> <p>Anticipated total duration of the study (statistical analysis included): 49 months</p>
STATISTICAL ANALYSIS OF THE DATA	<p>Statistical analysis for the primary endpoint:</p> <p>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.</p>

	<p>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 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 one of the 2x2 cell) will be performed for categorical outcomes other than those mentioned above and odd-ratios will be provided for illustration purposes.</p>
<p>FEASIBILITY OF THE PROJECT</p>	<p>Hypothermia induction during VA-ECMO does not require any additional device or supplementary catheter insertion. During therapeutic hypothermia, all centers monitor central temperature. Central temperature will be measured in each group in accordance with local practice (e.g bladder catheter, oesophageal probe...).</p> <p>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.</p> <p>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.</p> <p>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 experienced 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.</p>
<p>POTENTIAL IMPACT</p>	<p>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 %.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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</p>

	<p>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.</p>
FUNDING	<i>PHRC National 2015</i>

1381

1382 **1 SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION OF THE**
1383 **RESEARCH**

1384 **1.1 BACKGROUND**

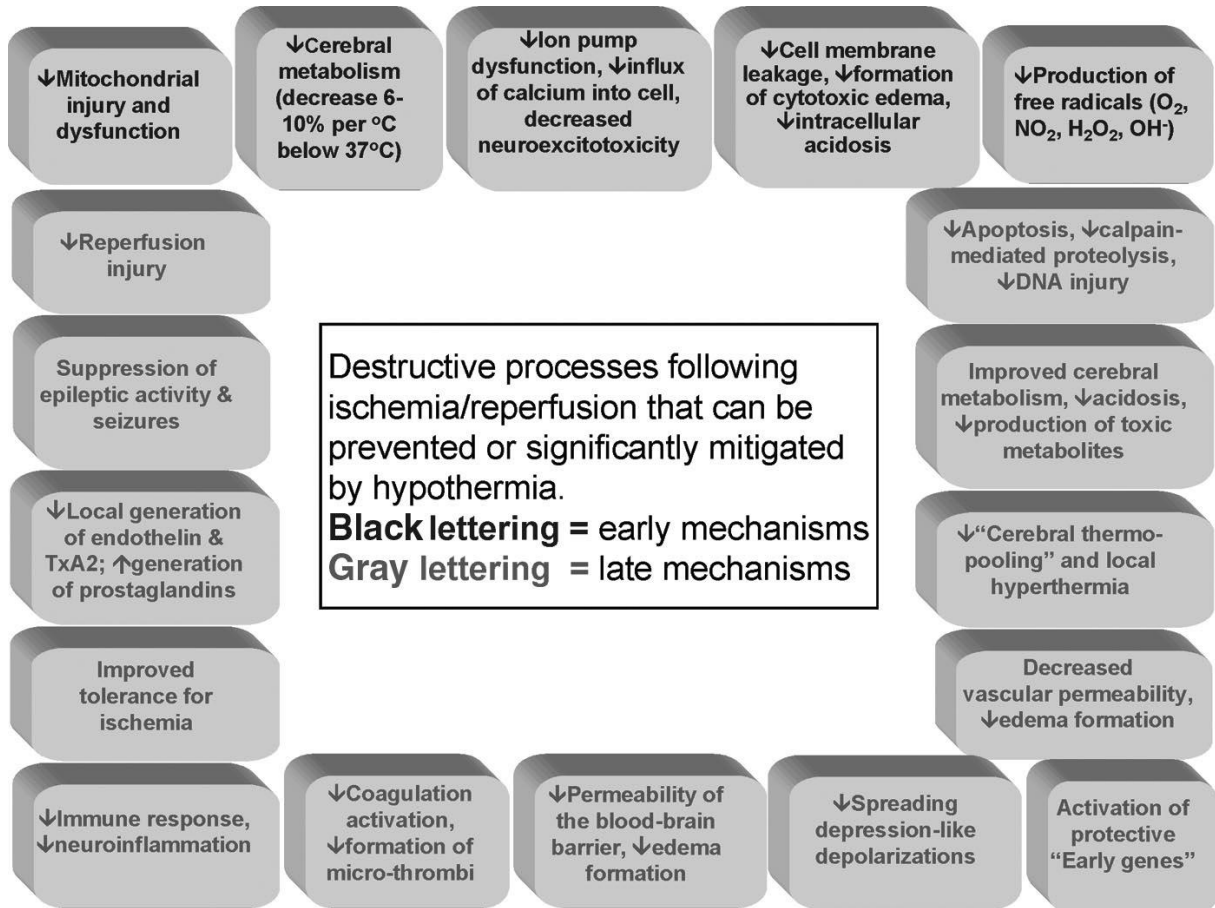
1385 Cardiogenic shock (CS) is generally defined by cardiac index <2.2 l/min/m², hypotension,
1386 elevated pulmonary capillary wedge pressure, and end-organ hypoperfusion. The leading cause of CS
1387 is myocardial infarction (MI)[1]. CS affects approximately 5% to 7% of patients with MI. Mortality in CS
1388 remains high. For example, for CS complicating MI, mortality is still 50 % [1, 2]. Importantly, long-term
1389 outcome for 1-year survivors of CS is similar to that of non-shock acute MI survivors. That points the
1390 importance of improving short-term survival, which remains unacceptably low. This should place the
1391 focus on very early reperfusion in MI to prevent shock and novel therapies targeting patients with CS.
1392 Efforts to improve early survival are only made more important by the observation that survivors will
1393 likely enjoy good quality of life; most will be in New York Heart Association functional class I or II at 1
1394 year of follow-up [3]. Further improving short-term outcomes has proven challenging. Recent attempts
1395 to inhibit inflammatory cytokine and nitric oxide-mediated systemic inflammatory response syndrome
1396 pathways in CS have yielded disappointing results. Unfortunately, there have been few recent
1397 advances in the treatment of cardiogenic shock on the exception of ExtraCorporeal Membrane
1398 Oxygenation (ECMO). As recently suggested, therapeutic hypothermia is a possibility to treat
1399 cardiogenic shock [4]. Therapeutic hypothermia is widely available and has become a standard
1400 component of treatment for out-of-hospital ventricular tachycardia/ventricular fibrillation arrest. It also
1401 has wide-ranging systemic effects that might be particularly advantageous when considering the
1402 systemic manifestations of cardiogenic shock [5].

1403 We hypothesized the following: first, the properties of therapeutic hypothermia that protect the
1404 brain and the heart and promote recovery after cardiac arrest will have similar effects on other vital
1405 organs and may improve short-term mortality; and second, therapeutic hypothermia merits further
1406 study as a potential novel treatment for cardiogenic shock patients treated with ECMO.

1407 **1.2 RATIONAL: CELLULAR AND ANIMAL MODELS**

1408 Hypoperfusion in the setting of CS leads to multiple end-organ damage and dysfunction that
1409 contributes to morbidity and mortality. Hypothermia decreases metabolic rate 5% to 7% per degree
1410 reduction of body temperature, and it decreases oxygen consumption, carbon dioxide production, and
1411 glucose consumption [5]. In addition, hypothermia affects the cardiovascular (CV) system in multiple
1412 ways, many of which could be potentially beneficial in CS, especially in a post-MI setting. In dogs,
1413 reduction of body temperature to 34°C in conjunction with vasodilator therapy results in increased
1414 contractility and external work of the left ventricle without increasing myocardial oxygen consumption
1415 [6]. In a dog model of post-MI CS, treatment with hypothermia to 32°C reduced heart rate, left
1416 ventricular (LV) end-diastolic pressure, systemic oxygen consumption, and estimated myocardial
1417 oxygen consumption while maintaining cardiac output and improving survival [7]. This study was
1418 validated recently in a porcine model of post-MI CS showing that animals treated with hypothermia
1419 had increased mean arterial pressure, stroke volume, pH, and mixed venous oxygen saturation with

1420 decreased heart rate. Mortality was also improved in the hypothermia group (0% mortality in the
 1421 hypothermia group vs. 63% in the control group) [8]. The inotropic effects of hypothermia seem to be
 1422 at least partially related to an increase in action potential duration, calcium transients, sarcoplasmic
 1423 reticulum calcium stores, and the fractional release of calcium in individual cardiac myocytes.



1424

1425 *Figure 1. Potential cerebral and systemic effects of moderate hypothermia (from Polderman KH, Critical Care*
 1426 *Medicine 2009)*

1427 Results of animal models further suggest that therapeutic hypothermia may reduce
 1428 ischemia/reperfusion injury after urgent revascularization for acute MI. In dogs, hypothermia beginning
 1429 30 min after left anterior descending coronary artery occlusion and continued through reperfusion 3
 1430 hours later improved cardiac function during occlusion, blunted hemodynamic derangements during
 1431 reperfusion, and reduced infarct size at 7 days [9]. In sheep, in addition to greater immediate
 1432 myocardial salvage, LV systolic function was improved at 8 weeks in animals treated with therapeutic
 1433 hypothermia [10].

1434 Hypothermia has additional outcomes outside its direct CV effects that may benefit patients with post-
 1435 MI cardiogenic shock [11] (for review see reference 4). Accumulation of oxygen free radicals and an
 1436 intense inflammatory response are hallmarks of myocardial ischemia and systemic hypoperfusion in
 1437 post-MI cardiogenic shock. Hypothermia impairs neutrophil and macrophage phagocytic function and
 1438 production of many proinflammatory cytokines. Therefore, therapeutic hypothermia could decrease the

1439 severity of myocardial injury and dysfunction associated with MI. Furthermore, hypothermia attenuates
1440 ischemia/reperfusion injury in other organ systems and reduces endothelial cell apoptosis and
1441 systemic oxidative stress. Hypothermia also increases urine output, likely via reduction in fluid
1442 resorption beyond the mid-distal tubule in the kidney, an effect that could prove beneficial in post-MI
1443 cardiogenic shock patients with difficult-to-manage volume status.

1444 The Figure 1 identifies potential pathways leading to or mediating the systemic effects of CS and
1445 where preclinical data suggest therapeutic hypothermia may modulate these effects.

1446

1447 Concerning VA-ECMO, Han et al [12] investigated in a rodent model the role of core body temperature
1448 in hypothermic protection after cardiac arrest. In these experiments, hypothermic ECMO was found to
1449 be significantly better than normothermic ECMO since hypothermia trended toward better 72-h
1450 survival. Finally, we have demonstrated (Critical Care Medicine, submitted) in a porcine model of CS
1451 treated with VA-ECMO) that hypothermia when compared to normothermia leads to a marked
1452 decrease in vasopressor and fluid use and to a better myocardial function. The potential beneficial
1453 effects of moderate hypothermia are summarized in figure 2

1454

1455 **From bench to bedside : Important points and consequences for the HYPO-ECMO study.**

1456 Studies on mechanisms underlying hypothermia's protective effects point to four key factors
1457 determining success or failure of cooling treatment. These are:

1458 e) Speed of induction of hypothermia; outcomes in animal experiments are far better when
1459 cooling is initiated rapidly after injury [13]. ***In HYPO-ECMO study we will use an early and
1460 fast cooling.***

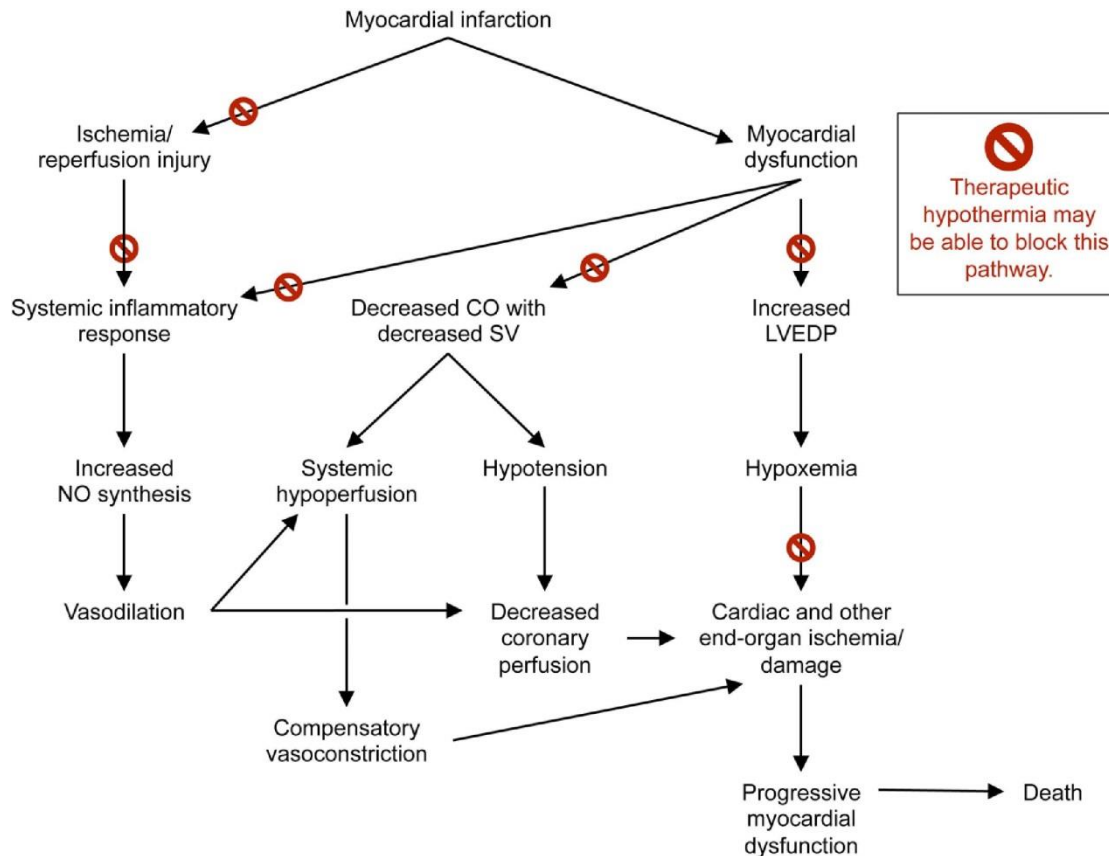
1461 f) Duration of cooling (depending on the severity of the initial injury and the time interval until
1462 target temperature is reached). ***In HYPO-ECMO study we will use 24 hours which is the
1463 most common duration used for cardiac arrest patients.***

1464 g) Speed of rewarming (this should be slow lest the destructive processes be reinitiated; this
1465 happens frequently if rewarming speeds are high). ***In HYPO-ECMO study the patient will be
1466 rewarmed in 24 hours (0.2±0.1°C/h) follow by 48 hours of maintained normothermia.***

1467 h) Proper management of side effects. Side effects include immunosuppression with increased
1468 infection risk, cold diuresis and hypovolemia, electrolyte disorders, insulin resistance, and mild
1469 coagulopathy. Targeted interventions are required to effectively manage these side effects.
1470 ***Specific management based on the literature for these potential side effects will be
1471 propose in HYPO-ECMO study (cf chapter 1.4.2)***

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1475 *Figure 2: Potential effects of hypothermia in cardiogenic shock (from Stegman BM, J Am Coll Cardiol 2012)*

1476

1477 1.3 HUMAN STUDIES OF HYPOTHERMIA

1478 1.3.1 In non-complicated myocardial infarction.

1479 One study in humans showed decreased infarct size among patients with anterior infarcts
 1480 treated with therapeutic hypothermia who reached a temperature of <35°C at time of reperfusion [14].
 1481 In this study, cooling was well tolerated, with no hemodynamic instability or increase in arrhythmia.
 1482 Nine patients experienced mild episodic shivering. Major adverse cardiac events occurred in 0% vs.
 1483 10% (p = NS) of treated versus control patients. The median infarct size was slightly smaller in
 1484 patients who received cooling compared with the control group (2% vs. 8% of the left ventricle, p =
 1485 0.80).

1486 More recently, a pilot study [15] of 20 patients with acute MI undergoing endovascular cooling and
 1487 cold saline infusion to ensure body temperature of <35°C at time of reperfusion. Twenty patients with
 1488 acute MI scheduled to undergo primary percutaneous coronary intervention were enrolled in this
 1489 prospective, randomized study. After 4 ± 2 days, myocardium at risk and infarct size were assessed by
 1490 cardiac magnetic resonance using T2-weighted imaging and late gadolinium enhancement imaging,
 1491 respectively. A core body temperature of <35°C (34.7 ± 0.3°C) was achieved before reperfusion
 1492 without significant delay in door-to-balloon time (43 ± 7 minutes versus 40 ± 6 minutes, hypothermia
 1493 versus control, P=0.12). Despite similar duration of ischemia (174 ± 51 minutes versus 174 ± 62

1494 minutes, hypothermia versus control, $P=1.00$), infarct size normalized to myocardium at risk was
1495 reduced by 38% in the hypothermia group compared with the control group ($29.8 \pm 12.6\%$ versus 48.0
1496 $\pm 21.6\%$, $P=0.041$). This was supported by a significant decrease in both peak and cumulative release
1497 of Troponin T in the hypothermia group ($P=0.01$ and $P=0.03$, respectively). The authors concluded that
1498 the protocol demonstrates the ability to reach a core body temperature of $<35^{\circ}\text{C}$ before reperfusion in
1499 all patients without delaying primary percutaneous coronary intervention and that combination
1500 hypothermia as an adjunct therapy in acute MI may reduce infarct size at 3 days as measured by MR

1501 1.3.2 In myocardial infarction complicated by Cardiogenic Shock non treated 1502 with VA-ECMO

1503
1504 There are only a few case reports and case series of hypothermia in patients with CS, mostly
1505 limited to pediatric and adult cardiac surgery patients whose postoperative courses were complicated
1506 by CS [16, 17] and none were from patients with CS in the acute MI setting. It is also important to
1507 recognize that these are reports of highly selected cases in which treatment was nonrandomized and
1508 concurrent therapy was uncontrolled. Only a well-designed randomized clinical trial can provide
1509 evidence sufficient to support clinical practice in post-MI patients.

1510
1511 In general, whether in infants or children, when hypothermia is added to conventional therapy in
1512 patients with refractory shock after cardiothoracic surgery, it resulted in decreases in heart rate and
1513 increases in mean arterial pressure and urine output with improved clinical stability. Therapeutic
1514 hypothermia has been reported in only three case series in adult patients with refractory heart failure.

1515
1516 Yahagi et al [16] reported 10 adult patients experienced post-cardiac surgery cardiogenic shock that
1517 was refractory to medical therapy, including multiple vasopressors and intra-aortic balloon pumping;
1518 the use of external cooling along with cold gastric lavage to a temperature of 34.5°C was associated
1519 with an increase in cardiac index (1.9 ± 0.3 to 2.2 ± 0.3), mixed venous saturation ($55 \pm 7\%$ to $64 \pm$
1520 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
1521 mean arterial pressure, heart rate, systemic vascular resistance, or pH. Eight of 10 patients survived to
1522 discharge. This study did not provided controls, but the expected mortality of patients in such condition
1523 is $>50\%$.

1524
1525 Zobel et al [18] reported the effects of moderate hypothermia in 20 patients admitted in CS after
1526 resuscitation from cardiac arrest. Patients were matched with a historical normothermic group by
1527 means of propensity score. Moderate therapeutic hypothermia was associated with a significant
1528 decrease in heart rate from 74 to 64 beats per minute. Despite the reduction in heart rate, cardiac
1529 index remained unchanged under moderate therapeutic hypothermia likely due to an increase in
1530 ejection fraction from $43 \pm 4\%$ to $55 \pm 4\%$. Mean arterial pressure increased rapidly from 75 ± 2 mmHg
1531 to 84 ± 3 mmHg ($p = .001$) upon induction of hypothermia paralleled by an initial increase in systemic
1532 vascular resistance. Accordingly, patients with moderate therapeutic hypothermia required lower
1533 cumulative doses of vasopressors and inotropes. They concluded that in CS moderate therapeutic

1534 hypothermia provides circulatory support and an increase in systemic vascular resistance that leads to
1535 reduced vasopressor use and may result in lower oxygen consumption.

1536
1537 Finally, Schmidt-Schweda [19] in 12 patients in CS found that hypothermia consistently decreased
1538 heart rate, and increased stroke volume, cardiac index and cardiac power output. Metabolic and
1539 electrocardiographic parameters remained constant during cooling.

1540
1541 Patients with signs of CS after cardiac arrest who underwent cooling provide another possible source
1542 of information, although little is currently available. In one study [20], 28 of 56 patients who were
1543 cooled after cardiac arrest also had CS, although it was not reported how many of these patients had
1544 acute MI concurrent with the cardiac arrest. Among the CS patients, after 24 to 48 h of therapeutic
1545 hypothermia, cardiac index increased from 1.5 ± 0.26 to 2.3 ± 0.371 . In addition, heart rate decreased
1546 among CS patients but to a lesser extent than among patients without shock; mean arterial pressure
1547 increased in patients with CS whereas it decreased in patients without initial signs of shock.

1548
1549 **To summarize, preliminary data demonstrated that moderate hypothermia during cardiogenic**
1550 **shock is well tolerated and improves hemodynamic parameters.**

1551
1552 **Finally, to the best of our knowledge, there have been no published randomized human studies**
1553 **of therapeutic hypothermia in post-MI cardiogenic shock treated with VA-ECMO. We found only**
1554 **one ongoing clinical trial (NCT01890317) to test the effects of moderate hypothermia in CS**
1555 **following MI. Importantly, in this study, patients will not be treated with VA-ECMO.**

1556 **1.4 POTENTIAL RISKS AND BENEFITS**

1557 **1.4.1 Expected patient or public health benefit**

1558
1559 **Potential advantages of adding moderate hypothermia to VA-ECMO:** Moderate
1560 hypothermia improves cardiac function and attenuates ischemia/reperfusion injury in other organ
1561 systems and reduces endothelial cell apoptosis and systemic oxidative stress. CS patients treated with
1562 ECMO have severe cardiac failure, associated with severe ischemia-reperfusion injury and pro-
1563 inflammatory profile leading to increased NO production and subsequent severe vasoplegia and
1564 multiple organs failure. Therefore, adding hypothermia in the very early phase of ECMO may alleviate
1565 the deleterious effects of ischemia-reperfusion. Moreover, moderate hypothermia is well tolerated.
1566 Finally, we intend to identify an absolute difference in the risk of death of 15%. In the field of
1567 cardiovascular medicine, the trials are usually intending to identify a 15% reduction of relative risk,
1568 usually translating in 5% reduction of absolute risk. The risk difference we intend to identify is
1569 consequently highly clinically relevant. Yet, even if this effect size is large, it appears congruous with
1570 the strong preclinical and clinical evidence we provide.

1571
1572 The annual incidence of AMI (Acute Myocardial Infarction) is estimated at 100–150 per 100,000
1573 inhabitants in France and 5-8% of AMI patients will develop cardiogenic shock. Therefore, the annual

1574 incidence for cardiogenic shock following MI is 12 per 100,000 inhabitants. It was recently found that
1575 cardiogenic shock was secondary to AMI in 68 % [21]. Interestingly, in this study, post cardiac surgery
1576 cardiogenic shock patients were not included. Therefore, the annual incidence of all causes of CS
1577 might be estimated at 18-20 per 100,000 inhabitants (including MI, myocarditis, cardiomyopathy and
1578 shock post cardiac surgery) in France with a mortality rate of 50 %.

1579 Reducing the death rate by 15% would save up to 1860 lives in France. This decrease in death rate
1580 might be accompanied by a reduction in the duration of ICU and hospital stays, therefore reducing the
1581 costs associated with the care of these critically ill patients. Better long-term outcomes might also be
1582 expected.

1583 This issue is important because ECMO use during CS management is still increasing worldwide and it
1584 is now urgent to determine the best approach to optimize such promising therapy. Recent papers
1585 demonstrated that the use of ECMO has increased rapidly, whereas rates of in-hospital mortality have
1586 decreased. These changes have taken place in the context of declining hospital costs associated with
1587 ECMO.

1588 Finally, lessons from the SHOCK study [22] demonstrate that an efficient treatment of cardiogenic
1589 shock may be associated with a delay improvement in mortality. In the SHOCK study, emergency
1590 revascularization did not significantly reduce overall mortality at 30 days. However, after six months
1591 there was a significant survival benefit. Therefore, we will also study the effects of moderate
1592 hypothermia on mortality at 180 days.

1593 1.4.2 Risks

1594 The induction of moderate hypothermia induces numerous changes throughout the body. The
1595 most important physiological changes and side effects, and their consequences for patient
1596 management, are discussed below.

1597 Moderate hypothermia is/might be associated with shivering, modifications in blood gas management,
1598 hyperglycemia, electrocardiographic changes, mild coagulopathy and increased sensitivity to infection
1599 [5].

1600 Since moderate hypothermia is widely used for resuscitated patients after cardiac arrest, strategies
1601 have been developed to minimize these potential side effects. Finally, moderate hypothermia was
1602 used for patients with resuscitated cardiac arrest treated with ECMO and none particular side effects
1603 have been described [23].

1604

1605 Management of physiological effects of hypothermia ***based on the literature [5]:***

1606 e) The tolerance to hypothermia will be ensured with the cautious use of **sedation and**
1607 **eventually with the use of a paralyzing agent in cases of shivering**. Use of a developed
1608 shivering assessment scale will be proposed for this purpose [23] .

1609

1610 f) **Management of blood gas:** Blood gas values are temperature dependent, and if blood gas
1611 are warmed to 37°C before analysis (as is common in most laboratories), Po₂ and Pco₂ will be
1612 overestimated and pH underestimated in hypothermic patients. **For accurate temperature**
1613 **correction, blood gas will be analyzed at the patient's real temperature.**

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- g) **Glycemia management:** 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.

- h) **Coagulation:** 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.

1653 Finally, comparatively to drug/new device research, hypothermia is inexpensive and very simple to
1654 implement in real life. Therefore, the only cost for society will be the grant for the study.
1655

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- 1733

1734

1735 **3 STUDY OBJECTIVES**

1736 In this chapter, and accordingly to the literature, moderate hypothermia is definite as a
1737 temperature between $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$. Normothermia is definite as a temperature at $36^{\circ}\text{C} \leq T^{\circ}\text{C}$
1738 $\leq 37^{\circ}\text{C}$.
1739

1740 **3.1 PRIMARY OBJECTIVE**

1741 The study objective is to determine whether early moderate hypothermia ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) is
1742 superior to normothermia $36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$ in patients with cardiogenic shock treated with VA-ECMO
1743 with respect to 30-day mortality.

1744 **3.2 SECONDARY OBJECTIVES**

1745 Evaluation of the impact of moderate hypothermia on:

- 1746 - Mortality during hospitalization and up to 180 days
- 1747 - VA-ECMO weaning time
- 1748 - Adverse cardiovascular events
- 1749 - Necessity of fluid and vasopressor (norepinephrine, epinephrine)
- 1750 - Lactate clearance
- 1751 - Duration of organ failure
- 1752 - Mechanical ventilation support use
- 1753 - Renal replacement therapy use
- 1754 - Duration of ICU stay and total duration of hospitalization
- 1755 - The risk of bleeding
- 1756 - The risk of Sepsis (pulmonary, blood, venous lines, VA-ECMO cannulaes)

1757 **3.3 STUDY OUTCOME MEASURES**

1758 **3.3.1 Primary endpoints**

1759 All-cause mortality at day 30 following randomization (i.e. 30 day mortality)

1760 **3.3.2 Secondary endpoints:**

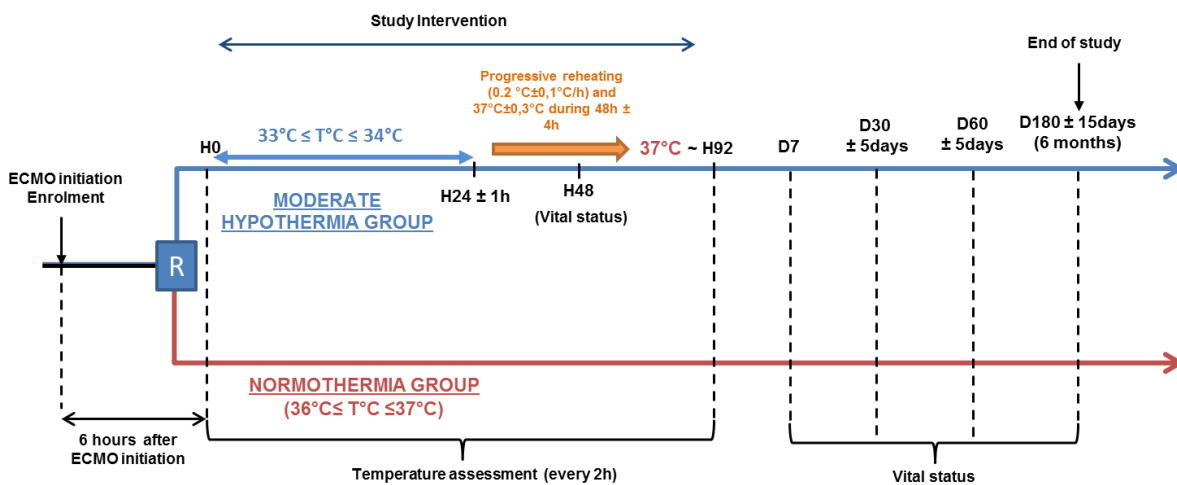
- 1761 - All-cause mortality at 48 hours and day 7, 60, 180
- 1762 - VA-ECMO duration
- 1763 - Composite endpoint of death, cardiac transplant, escalation to LVAD, stroke at days 30, 60,
1764 180
- 1765 - Cumulated amount of administered fluids and duration of vasopressors use in ICU
- 1766 - Duration to normalization of lactate
- 1767 - Number of days alive without organ failure(s), defined with the SOFA score and its
1768 components (respiratory, liver, coagulation and renal), between inclusion, D7 and D30
- 1769 - Duration of mechanical ventilation and the number of days between inclusion and day 30/
1770 60/ day 180, alive without mechanical ventilation
- 1771 - Number of days alive without renal replacement therapy, and the number of days, between
1772 inclusion and day 30, day 60 and day 180, without renal replacement therapy

- 1773 - Duration of ICU stay, of hospitalization
- 1774 - 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
- 1775
- 1776 - Infection probability: pulmonary, blood and VA-ECMO cannulae

1777 4 STUDY DESIGN AND PROCEDURES

1778 4.1 EXPERIMENTAL STUDY DESIGN

1779 A multicenter, prospective, controlled, randomized (moderate hypothermia during 24 hours ±
 1780 1h versus normothermia), comparative open trial will be conducted on two parallel groups of patients
 1781 with CS treated with VA-ECMO.



1782
 1783
 1784

1785 4.1.1 Common management for all patients before and during 1786 intervention

1787 For all patient enrolled in the study, VA-ECMO will be initiated in accordance to the local
 1788 practice with flow settings to ensure sufficient tissue perfusion.
 1789

1790 **With the exception of temperature control, all other diagnostic, therapeutic and**
 1791 **weaning procedures will be done according to the current standard of care at the tertiary CV**
 1792 **center and at the discretion of the investigator.**

1793
 1794
 1795

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

1796 4.1.2 Heater-Cooler Unit and temperature control for all patients

1797 Each circuit will be associated with a device able to control temperature used in this study in
 1798 conformity of the device CE Label such as “Heater-Cooler Unit HCU 35 from Maquet compagny”.
 1799 These devices are available in each center. This device allows a perfect control and hold of the target
 1800 temperature. The water tank for the patient circuits is divided into two parts to ensure quick
 1801 temperature adjustments at the outlets. In addition, it has exceptional cooling capacity through its fast
 1802

1803 ice-building technique using highly effective cooling plates and a powerful compressor. In our study
1804 each center will use his local heater-cooler unit to control temperature (described in Appendix B).

1805
1806 Temperature management (hypothermia, normothermia or reheating) will be performed using the heat
1807 controller of the VA-ECMO circuit and other classical temperature management if necessary (external
1808 or internal technique).

1809 4.1.3 Temperature assessment method

1810
1811 During therapeutic hypothermia, all centers monitor central temperature. Central temperature will be
1812 measured in each group in accordance with local practice (e.g bladder catheter, oesophageal
1813 probe...)

1814 In both group, temperature will be measured every two hours during intervention (time during the first
1815 92 hours at the allocated group (cf figure in chapter 4.1).

1816 1817 4.1.4 Inclusion and randomization of patient

1818
1819 The inclusion and randomization of the patient will be performed after VA-ECMO indication
1820 and implementation. Inclusion and study intervention will be performed as soon as possible **during**
1821 **the first 6 hours (preferably 4 hours) after VA-ECMO initiation.**

1822
1823 After eligibility verification, complete clinical examination and informed consent process (cf chapter 13.2),
1824 patient will be randomized. The patients will be placed on moderate hypothermia ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$)
1825 or maintained on normothermia $36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$ during 24 hours \pm 1h according to the group.

1826
1827 Data collected (nonspecific to the study) at inclusion and during ICU stay after randomization :
1828 demographic data, medical history, SOFA score, biological data (Arterial Lactate, ASAT, ALAT, urea,
1829 creatinine, coagulation parameters..), amount of paralyzing agent and sedative, amount of insulin...),
1830 concomitant drugs, treatments (fluid amount, vasopressors, inotropes, echocardiography at inclusion
1831 performed before study intervention (echocardiography data result from usual care...))...

1832 4.1.5 Moderate hypothermia group

1833
1834 Moderate hypothermia will be induced as soon as possible **during the first 6 hours (preferably 4**
1835 **hours) after VA-ECMO initiation (H0) and randomization.** Moderate hypothermia will be induced
1836 using the heat controller of the VA-ECMO circuit and other classical temperature management if
1837 necessary (external or internal technique). Temperature will be maintained between $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$
1838 during 24 hours \pm 1h followed by a progressive reheating ($0.2 \pm 0.1^{\circ}\text{C}/\text{hour}$) to reach 37°C .
1839 Temperature at $37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$ will be maintained during 48 hours \pm 4h after having reached 37°C .

1840
1841 **The potential physiological effects of hypothermia and their managements based on literature**
1842 **are described in chapter 1.4.2. Their managements will be done according to the local practice**
1843 **and to the discretion of investigator.**

1844

1845 4.1.6 Normothermia group

1846

1847 The extracorporeal life support organization (ELSO) recommends "Temperature can be maintained at
1848 any level by adjusting the temperature of the water bath. Temperature is usually maintained close to
1849 37° C." A large amount of patients that need VA-ECMO experiment a cardiac arrest before ECMO
1850 implantation. Concerning the patients with cardiac arrest it is now recommended to maintain the
1851 patients between 33 and 36 degrees. Therefore,the temperature will be maintained at
1852 Therefore the temperature will be maintained at 36°C≤ T°C ≤37°C under VA-ECMO.

1853 4.1.7 Discontinuation of experimental study intervention (moderate
1854 hypothermia group)

1855 In the moderate hyperthermia group, in cases of uncontrolled bleeding (bleeding despite
1856 medical intervention (surgery or drugs)), moderate hypothermia will be stopped and resumed as soon
1857 as the bleeding is controlled for a total duration of 24 hours ± 1h of moderate hypothermia. Under VA-
1858 ECMO, rhythms disturbances are not an indication to stop moderate hypothermia.

1859

1860 4.1.8 Prohibited treatment for the subject participation

1861 None, all medications or treatments are authorized.

1862

1863 4.1.9 Follow up after intervention (H48, day 7, day 30 (± 5 days), day 60 (±
1864 5 days), Day 180 (± 15 days) (end of the study) after randomization
1865 for all patient)

1866

1867 Vital status (and date/cause of death) will be collected for all patients and if necessary
1868 obtained by the investigator or his staff by contacting the patient, the family or his/her primary care
1869 physician.

1870 4.2 FLOWCHART

1871

	Inclusion	Randomization (a)	After randomization					
			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)

1872

- 1873 b) During the first 6 hours (preferably 4 hours) after VA-ECMO implementation
1874 c) Induced as soon as possible during the first 6 hours (preferably 4 hours) after VA-ECMO
1875 implementation and randomization
1876 LT : life threatening
1877

1878 **4.3 BIAS CONSIDERATION**

1879

1880 4.3.1 Randomization procedure

1881 Randomization will be performed after enrolment using a centralized on-line randomization
1882 system (Cleanweb™) available 24h/24h.

1883 **Treatments arms :**

1884

1885 • **Experimental group:** Patients with CS allocated to a strategy of moderate hypothermia
1886 (33°C ≤ T°C ≤ 34°C) associated with usual care.

1887 • **Control group:** Patients with CS allocated to a strategy of normothermia 36°C ≤ T°C ≤ 37°C
1888 associated with usual care.

1889

1890 Randomization will be stratified on the center. The randomization plan will be devised by Centre
1891 investigation Clinique 1433 module Plurithématique de Nancy, France.

1892

1893 4.3.2 Replacement procedures for patients

1894 All patients non randomized will be replaced to reach 334 patients (167 patients in each
1895 group) (cf chapter 11.8)

1896

1897 **4.4 STUDY PERIOD**

1898 Duration of participation of each patient: **6 months (D180)**

1899 Anticipated duration of recruitment: **36 months**

1900 Anticipated total duration of the study (statistical analysis included): **49 months**

1901 **4.5 TERMINATION RULES**

1902

1903 4.5.1 Patient Premature termination

1904

1905 Any subject can stop his participation to the research at any time and for any reason.

1906 The investigator can permanently end a subject's participation in the research for any reason that
1907 affects the subject's safety or which would be in the subject's best interests.

1908 If a subject leaves the research prematurely, data relating to the subject can be used unless an
1909 objection was recorded when the subject signed the consent form.

1910 4.5.2 Exclusion period

1911

1912 Patient cannot participate simultaneously in other biomedical research during the research. There is
1913 no exclusion period.

1914

1915 4.5.3 **Follow-up after end of study**
1916
1917 Patient will be follow up in accordance with the current standard of care.

1918 **4.6 DATA LIST NOT AVAILABLE IN THE PATIENT FILE**
1919

1920 All medical data will be available in the patient medical file.

1921 **5 STUDY POPULATION**

1922 **5.1 PARTICIPATING CENTERS**
1923

1924 Patients will be enrolled in 17 ECMO French centers. All centers are well trained for VA-
1925 ECMO.

1926 **5.2 PATIENT SCREENING AND ENROLMENT**
1927

1928 All intubated patients with CS supported with VA-ECMO will be screened.

1929 Patients with CS treated with VA-ECMO in the intensive care unit meeting all of the inclusion and non-
1930 inclusion criteria will be enrolled in the study (emergency consent process cf chapter 13.2).

1931 Reasons for non-eligibility will be listed in a dedicated screening log file.

1932 **5.3 INCLUSION CRITERIA**
1933

- 1934 - Age \geq 18 years
1935 - Intubated patients with cardiogenic shock treated with VA-ECMO
1936 - Patient affiliated to social security plan

1937 **5.4 NON-INCLUSION CRITERIA**
1938

- 1939 - VA-ECMO after cardiac surgery for heart transplantation or heart - lung transplantation or left
1940 or biventricular assist device implantation
1941 - VA-ECMO for acute poisoning with cardio-toxic drugs
1942 - Pregnancy
1943 - Uncontrolled bleeding (bleeding despite medical intervention (surgery or drugs))
1944 - Implantation of VA-ECMO under cardiac massage with a duration of cardiac massage \geq 45
1945 minutes
1946 - Out of hospital refractory cardiac arrest
1947 - Cerebral deficit with fixed dilated pupils
1948 - Participation in another interventional research involving therapeutic modifications
1949 - Patient moribund on the day of randomization
1950 - Irreversible neurological pathology
1951 - Minor patients
1952
1953 - Patients under tutelage

1954

1955 **6 METHODS USED FOR THE EVALUATION OF EFFICACY**

1956 Cf chapter 3

1957 **7 SAFETY ASSESSMENT**

1958 **7.1 DESCRIPTION OF SAFETY ASSESSMENT PARAMETERS, METHOD AND** 1959 **CALENDAR USED FOR THE EVALUATION OF SAFETY**

1960 In both group, the VA-ECMO implementation and monitoring will be done in accordance with the
1961 current standard of care. All adverse events will be documented during this study from medical
1962 examinations, biological and imaging exams if necessary and will be compiled in the electronic case
1963 report form (eCRF).

1964

1965 In particular, glycaemia, blood gas and coagulation will be followed up and the occurrence of
1966 shivering, modifications in blood gas management, hyperglycemia, electrocardiographic changes, mild
1967 coagulopathy and increased sensitivity to infection will all be recorded as adverse events.

1968 Uncontrolled bleeding and coagulation disorders that require blood cells or platelet transfusion will be
1969 considered as serious events.

1970 In normothermia group, no additional risk linked to research is expected.

1971

1972 All adverse events between inclusion and D7 will be recorded.

1973 After D7, only serious life-threatening and fatal adverse events will be recorded until the end of the
1974 follow-up of the patient.

1975

1976 **7.2 REPORTING AND TRANSMISSIONS OF SAE/R**

1977 **7.2.1 Definitions:**

1978 **Adverse event (AE)** (article R.1123-39 of the French Public Health Code): Any harmful event
1979 occurring in a person participating in a biomedical study, whether or not this event is in relation or not
1980 with the study or the product studied.

1981

1982 **Serious adverse event (SAE)** (article R.1123-39 of the French Public Health Code and ICH E2B
1983 guide). Any adverse event that:

- 1984 ✓ results in death,
- 1985 ✓ is life-threatening,
- 1986 ✓ requires hospitalization or prolongation of existing hospitalization,
- 1987 ✓ results in persistent or significant incapacity/disability,
- 1988 ✓ or any other medically important condition,
- 1989 ✓ and when regarding a medicinal product, whatever the administered dose.

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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.

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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.

2068 **8 ORGANIGRAM AND FEASIBILITY**

2069 **8.1 PROJECT ORGANIZATION SCHEME**

2070 **8.1.1 Steering Committee**

2071

2072 *Role*

2073 The Steering Committee initiates the project and is responsible for writing and validating the
2074 observation notebooks. Its members initially determine the methodology and decide during the trial the
2075 responses to unforeseen events, monitors the course of the project, especially concerning safety and
2076 side effects.

2077 Committee members define the general organization and course of the project and coordinate the
2078 information. They oversee the analysis of data and the writing of scientific documents derived from the
2079 research project.

2080

2081 The Steering committee will be comprised of:

- 2082 - Prof Bruno LEVY (Intensivist – CHRU Nancy, France)
- 2083 - Prof Alain Combes (intensivist – APHP-la Pitié Salpêtrière, France)
- 2084 - Dr Nicolas GIRERD (cardiologist – CHRU Nancy, France)
- 2085 - Dr Fabrice VANHUYSE (Cardiovascular surgeon – CHRU Nancy, France)
- 2086 - Prof Patrick ROSSIGNOL (Nephrologist, Professor in Therapeutic –CHRU Nancy, France)

2087

2088 **8.1.2 Data safety monitoring board (DSMB)**

2089 The DSMB will be responsible for the review of the study data in order to identify any potential
2090 safety issues. Based on the safety data, the DSMB may recommend modifications to the protocol (e.g.
2091 amendments, termination of the study) and, when needed, the DSMB will decide on stoppage rules.

2092 Members of this board are independent of the study. The DSMB will be composed of two intensivists
2093 and a biostatistician or methodologist.

2094 The chairman of the DSMB will inform the Steering Committee members in writing whether or not any
2095 safety issues are identified during DSMB meetings or telephone conferences.

2096

2097 The DSMB will review aggregate SAEs at 6 months intervals. At this time, the DSMB will recommend
2098 to the HYPO-ECMO steering committee and sponsor to a) continue the study as scheduled, b)
2099 suspend enrolment, or c) obtain more information before a recommendation can be made.

2100

2101 **9 FEASIBILITY**

2102

2103 Considering the main objective, the HYPO-ECMO trial will be a pragmatic study in order to facilitate
2104 patient inclusion and monitoring.

2105 HYPO ECMO project is included in the large clinical network F-CRIN (French Clinical Research
2106 Infrastructure Network) INI CRCT (Cardiovascular and Renal Clinical Trialists coordinated by Prof.
2107 Rossignol www.inicrct.org<<http://www.inicrct.org>>).

2108 **10 DATA MANAGEMENT AND STATISTICS**

2109 **10.1 DATA MANAGEMENT**

2110 10.1.1 **Electronic Case report form**

2111 Data management will be carried out by the “Centre d’Investigation Clinique 1433,
2112 Plurithématique department, CHRU-Nancy”. Data collection for this study will be made via an
2113 electronic Case Report Form (eCRF).

2114 Each patient will be identified on the eCRF with his/her initials (first letter of the name and first letter of
2115 the surname), birth date (month and year) and an identification number indicating his/her rank of
2116 inclusion into the study. Investigators must not provide other personal information about the patients to
2117 the staff in charge of the data management and data analysis (i.e full names and last known
2118 addresses).

2119 The investigator or a qualified designee from the site should complete the eCRF as soon as the data
2120 are available. The data manager in charge of the study will provide access codes as well as guidance
2121 for the completion of e-CRF.

2122 As a matter of regulations, the investigator is responsible for the accuracy and authenticity of all
2123 clinical data entered onto eCRFs. Each page of the completed eCRFs must be reviewed for accuracy
2124 by the investigator, corrected as necessary, and e-signed.

2125 The investigator’s e-signature serves to attest that the investigator has reviewed the information
2126 contained on the eCRF and is true and accurate.

2127

2128 **11 DATA ANALYSIS AND STATISTICAL DETERMINATION**

2129 **11.1 DESCRIPTION OF ANTICIPATED STATISTICAL ANALYSIS METHODS**

2130 11.1.1 **Statistical analysis for the primary endpoint**

2131
2132 The differences between the 2 study groups (i.e. intervention and controls) in the risk
2133 of all-cause mortality at day 30 following randomization will be studied using the Chi-2 test. To
2134 illustrate the association, both an odd-ratio and a hazard ratio will be provided. In addition, survival
2135 curves using the Kaplan-Meier method will be constructed.

2136

2137 11.1.2 **Statistical analysis for the secondary endpoints**

2138
2139 For the secondary analysis of a) all-cause mortality at 48 hours and day 7, 60, 180, b) the
2140 composite endpoint of death, cardiac transplant, escalation to LVAD, stroke at days 30, 60, 180 the
2141 same analysis strategy will be performed as for the primary endpoint.

2142 Unpaired t-test will be performed, after checking for normality of the variable's distribution, for the
2143 outcomes mentioned below. Importantly, In case of non-normal distributions (which is highly likely for
2144 all duration data), non-parametric tests will be performed.

- 2145 - VA-ECMO duration
- 2146 - cumulated amount of administered fluids and duration of vasopressors use
- 2147 - duration to normalization of lactate
- 2148 - Number of days alive without organ failure(s), defined with the SOFA score and its
2149 components (respiratory, liver, coagulation and renal), between inclusion, D7 and D30
- 2150 - duration of mechanical ventilation and the number of days, between inclusion and day 30/
2151 day 60/ day 180 , alive without a mechanical ventilation
- 2152 - number of days alive without renal replacement therapy, and the number of days, between
2153 inclusion and day 30/ day 60/ day 180, without renal replacement therapy
- 2154 - duration of ICU stay, of hospitalization
- 2155 - number of severe and moderate bleeding complications (gusto-definition) and number of
2156 packed red blood cells transfused under VA-ECMO

2157
2158 Chi-square tests (or Fisher exact test in case of insufficient number of expected patients in on
2159 of the 2x2 cell) will be performed for the outcomes mentioned below:

- 2160 - Pulmonary, blood and VA-ECMO cannulae infections

2161 To illustrate the association, an odd-ratio will be provided.

2162 **11.2 SAMPLE SIZE CONSIDERATION**

2163 We considered that mortality in cardiogenic patients supported with VA-ECMO will be 50%
2164 (based both on ELSO data, Combes data (*Crit Care Med.* 2008 May;36(5):1404-11) and study principal
2165 investigator's personal data (database of 150 patients)

2166 The objective of the study is to demonstrate the superiority of the treatment with VA-ECMO plus
2167 moderate hypothermia as compared to VA-ECMO alone on mortality.

2168 Therefore, considering a total event risk (for the primary endpoint) of 50 % in the control group, a
2169 sample size of **N = 167 patients/group** will detecting a 15% absolute difference in favor the VA-
2170 ECMO group using a chi-square test with a 80 % power and considering a two-sided global alpha level
2171 of 5% using the LanDe Mets method with O'BrienFleming boundary for one interim analysis (efficacy
2172 and futility) after inclusion of 2/3 of the patients.

2173 **11.3 DEGREES OF STATISTICAL SIGNIFICANCE**

2174 A bilateral p value lower than 4.9% will be considered significant for the final analysis. A p
2175 value threshold lower than 5% is mandatory given the planned interim analyses to ensure a global
2176 alpha level at 5%.

2177 **11.4 PLANNED INTERIM ANALYSES (IF APPLICABLE)**

2178 One interim analysis for efficacy/futility will be performed after inclusion of 2/3 of the patients.

2179 De-identified hospitalization reports will be collected from the associated centers. These reports will be
2180 centralized at the CIC-P of the CHRU of Nancy and will be submitted to a reading committee.

2181 **11.5 STATISTICAL CRITERIA FOR STUDY TERMINATION**

2182 A p-value threshold of 0.001 will be used for this interim analysis as calculated with the LanDe
2183 Mets method with O'BrienFleming boundary.

2184 **11.6 METHOD FOR ADDRESSING MISSING, INVALID OR UNUSED DATA**

2185 For the primary outcome, we do not expect missing variables. All-cause 30 days mortality is a
2186 straightforward outcome that does not require detailed information. Yet, in the unlikely case of missing
2187 vital status at 30 days, patients with missing data will be analyzed with the last observation being
2188 carried forward. In a sensitivity analysis, the worst case scenario method will be used (i.e. all patients
2189 with incomplete follow-up data died in the intervention group and died in the no intervention group).

2190 **11.7 MANAGEMENT OF AMENDMENTS TO THE ANALYSIS PLAN OF THE INITIAL** 2191 **STRATEGY**

2192 No amendments are expected. Amendments can be decided by the steering committee.

2193 **11.8 SELECTION OF SUBJECTS TO BE INCLUDED IN THE ANALYSIS**

2194 As per intention to treat analysis, every randomized patients will be included in the analysis.

2195 **12 CONTROL AND QUALITY ASSURANCE**

2196 **12.1 ACCESS TO SOURCE DATA AND DOCUMENTS**

2197 The sponsor is responsible for obtaining the agreement of all parties involved in the study so
2198 as to guarantee direct access to all study sites, source data, source documents, and reports so that
2199 the sponsor may control data quality and perform an audit.

2200
2201 Investigators accept to give access to all relevant data and records to the sponsor (Sponsor's
2202 monitors, auditors, the Sponsor's Quality Assurance representatives) and all authorized Sponsor
2203 personnel, and regulatory authorities, under strict confidentiality condition and in compliance to the
2204 French regulatory.

2205 **12.2 STUDY MONITORING**

2206 Monitoring will be performed by the sponsor (Department of Research and Innovation CHRU
2207 de Nancy) during the study to ensure that compliance with the Protocol and applicable regulations is
2208 maintained, that data are collected in a timely, accurate and complete manner and that the investigator
2209 continues to have sufficient staff and facilities to conduct the study safely and effectively.

2210 Details of the monitoring visits will be work out in the sponsor monitoring plan.

2211 **13 ETHICAL CONSIDERATIONS AND REGULATIONS**

2212 **13.1 REGULATORY AND ETHICAL CONSIDERATIONS**

2213 Before initiating a trial, according to the French local regulation, the sponsor (CHRU Nancy)
2214 should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics
2215 Committee (IRB/IEC) and authorization from the French Health Authorities for the research.

2216

2217 The sponsor and investigators commit that this research is conducted according to the protocol and
2218 his procedures, to the French local regulation (law n ° 2004-806 of August 9, 2004), as well as in
2219 agreement with Good Clinical Practices (I.C.H. version 4 of May 1, 1996 and Decision of November
2220 24, 2006) and the Helsinki Declaration (Ethical Principles for Medical Research Involving Human
2221 Subjects, Tokyo 2004).

2222 **13.2 INFORMED CONSENT PROCESS**

2223 Before collecting the patient's consent, the investigator will give complete information about the
2224 proposed study.

2225

2226 In the particular context of this protocol, the persons include in this research may not be able to
2227 receive information about the study and give their consent before the implementation of the protocol
2228 due to their medical condition.

2229 In this case, if a member of the patient's family (or support person defined in Article L.1111-6 -
2230 Appendix 5) is present, this person will be informed and consent will be gathered.

2231 In the absence of a family member or support person, the investigator will include the patient in the
2232 study and will gather the consent of the family member or support person as soon as possible.

2233 The patient will be asked to give his/her consent for the continuation of the trial when his/her condition
2234 will allow.

2235

2236 Patient, family member or support person, is free to refuse participation in the study and may at any
2237 time and for whatever reason withdraw its consent.

2238

2239 The consent form will be signed in two originals copy by the subject and the investigator and a
2240 member of the family / support person if applicable:

2241 - An exemplary will be given to the subject or family member / support person if applicable

2242 - An exemplary will be retained and archived by the investigator

2243

2244 Particular case:

2245 Given the studied pathology (cardiogenic choc), the prognosis for survival of the patient included in
2246 emergency setting is threatened and the death probability stays high.

2247

2248 If the patient died after inclusion in emergency setting and no support person is written in the medical
2249 file or support person can't be contacted by investigator, consent must be gathered from a family

2250 member. If the patient does not have a family or if the investigator can't contact the family or if the
2251 investigator can't contact again family after obtaining an oral agreement from a family member, the
2252 investigator will have to write all the steps taken in the medical file and note his inability to contact the
2253 family.

2254
2255 The inclusion of the patient in the protocol and the use of the data are possible without signed consent
2256 if all these 3 conditions are met:

2257 - The patient died after inclusion in emergency setting without family or support person, properly
2258 documented in the medical file by the investigator.

2259
2260 - no support person is noted in the medical file or the inability to contact support person or to contact
2261 again support person after obtaining an oral agreement in spite of the implemented efforts properly
2262 documented by investigator in the medical file.

2263
2264 - the inability to contact family member or to contact again family member after obtaining an oral
2265 agreement in spite of the implemented efforts properly documented by investigator in the medical file.

2266 .
2267

2268 **13.3 PROTOCOL AMENDMENT**

2269 Any change or addition to the protocol can only be made in a written protocol amendment
2270 (modification of an inclusion criterion, extending the inclusion period, participation of new centers ...)
2271 that must be approved by the sponsor, French Health Authorities and the IRB/IEC prior to
2272 implementation.

2273 **13.4 PATIENT DATA CONFIDENTIALITY**

2274 Throughout the study, confidentiality shall be observed, at all times, by all parties involved,
2275 and all data shall be secured against unauthorized access.

2276 Confidentiality of each subject shall be preserved in reports and any publication of the results.

2277 Only authorized Sponsor staff and regulatory authorities may have access to these confidential files.

2278 The data collected during the study will be performed according to the French local regulation
2279 (Commission Nationale de l'Informatique et des Libertés (CNIL), in compliance with the MR001
2280 methodology)

2281 **13.5 ARCHIVING STUDY DOCUMENTS AND STUDY DATA**

2282 All study documents including patient's identification list and signed informed consent should be keep
2283 for at least 15 years. For each patient, documentation must clearly specify the following:

- 2284 • Participation of the patient in the study (patient and study's identification),
- 2285 • Concomitant treatments or medications,
- 2286 • Any visit to the hospital, particularly those visits made for the sole purposes of the study,
- 2287 • Serious adverse events (SAEs).

2288 **13.6 AUDIT AND INSPECTION**

2289 Audits or inspections may be performed at any time by persons mandated by the sponsor and
2290 independent of those in charge of the study or by French Health Authority respectively.

2291 Investigators accept to give access to all relevant data and records to the auditors and inspector. If an
2292 inspection of the clinical site is requested by the French Health Authority, the investigator must inform
2293 the sponsor immediately that this request has been made.

2294 **14 INSURANCE**

2295 **14.1 INSURANCE**

2296 The sponsor has subscribed an insurance for the duration of the study guaranteeing its own civil
2297 liability as well as that of any stakeholder involved in the conducting of the study, regardless of the
2298 nature of existing ties between the stakeholders and the sponsor.

2299 **15 PUBLICATION POLICY**

2300 **15.1 FINAL RESEARCH REPORT**

2301

2302 The final report of the research will be written collaboratively by the coordinator and the
2303 biostatistician mandated for this search. This report will be submitted to each of the investigators for
2304 review. Once a consensus has been reached, the final version must be endorsed with the signature of
2305 each of the investigators and sent to the sponsor as early as possible after the effective end of the
2306 research.

2307

2308 Data is the property of the sponsor. The conditions for data transfer of all or part of the study database
2309 are decided by the study sponsor.

2310

2311 "CHRU Nancy" should be mentioned as sponsor of this study.

2312 The publications resulting from this work will be labeled by « The study was supported by a grant from
2313 the French Ministry of Health (Programme de Recherche Hospitalier National 2015) »

2314 16 APPENDIX

2315 Appendix A: Common management for all included patients treated with VA- 2316 ECMO before and during study intervention

2317 2318 **6. ECMO initiation;**

2319 Venous-Arterial ECMO (VA-ECMO) support will be used. The extracorporeal system will consist of
2320 polyvinyl chloride tubing, a membrane oxygenator, a centrifugal pump, and percutaneous arterial and
2321 venous femoral cannulae. An oxygen/air blender will be used to ventilate the membrane oxygenator.
2322 An 7-10-Fr cannula will be inserted distally into the superficial femoral artery to prevent severe leg
2323 ischemia. Heparin boluses at the time of VA-ECMO implantation will be discouraged however a low
2324 dose bolus is permitted according to the experience of the ECMO team.
2325

2326 **7. Initial parameter settings for VA-ECMO**

2327 The pump flow will be set to 3.5-5 l/min, to provide adequate systemic perfusion. Pump flow might
2328 be reduced in case of cessation of LV ejection or major pulmonary edema. Percentage of oxygen
2329 contained in the ventilating gaseous air–oxygen mixture will be adjusted to obtain PaO₂ between 65
2330 and 90 mmHg and/or arterial oxygen saturation >90%. The membrane ventilation will be adjusted to
2331 maintain PaCO₂ between 40 and 45 mmHg.
2332

2333 **8. VA-ECMO monitoring (extracorporeal circuit, anticoagulation, possible complications)**

2334 The VA-ECMO circuit will be monitored several times daily by the medical and nursing team
2335 caring for the patient and at least once every 48 hours by a perfusionist. Circuit and cannula
2336 surveillance is intended to verify the correct functioning of the device and early screening for
2337 complications (leg ischemia, fibrin deposits or clots on the VA-ECMO membrane, clots in the cannulae
2338 or in the pump, bleeding or signs of inflammation or cutaneous infection at the cannula insertion sites,
2339 unexpected drop of the VA-ECMO outflow, appearance of clinical or biological signs of intravascular
2340 hemolysis). Should any of these complications occur, a medical–surgical consultation will be held to
2341 discuss the best therapeutic approach to take.
2342

2343 Anticoagulation will be obtained with non-fractionated heparin to a target aPTT of 55-70 sec or
2344 heparinemia (antiXa activity) between 0.2 and 0.3 IU/ml. A bolus of heparin is not encouraged at the
2345 time of circuit implantation. Should severe bleeding occur that is not immediately controllable by
2346 specific treatment, heparin will be discontinued.

2347 Intravascular hemolysis will be sought should unexpected dark urine be excreted or in the case of
2348 obvious circuit dysfunction. It is recommended that plasma free hemoglobin be measured every 48
2349 hours and immediately if hemolysis linked to the circuit is suspected.

2350 The membrane and VA-ECMO circuit will be changed in the following situations: massive intravascular
2351 hemolysis linked to the device, severe thrombopenia linked to the circuit, clots preventing the pump
2352 and/or lines from functioning properly or systemic defibrination.

2353 The hemoglobin threshold for red cells transfusion will be 9-10 g/dl (may be decreased to 7-8 g/dl if
2354 the patient is stabilized and does not have residual myocardial ischemia). Platelet transfusion will be
2355 discouraged except when severe thrombopenia is associated by bleeding complications or when
2356 platelet count will be <20 G/L.

2357 Connecting an extrarenal dialysis circuit to the VA-ECMO circuit will be permitted under strict
2358 supervision of perfusionnists.

2359 **9. Intra-aortic balloon pump (IABP) support in addition to VA-ECMO**

2360 An IABP will be inserted according to the physician choice in the contralateral femoral artery. A
2361 strategy of liberal use of IABP has been associated with less pulmonary edema and better LV
2362 unloading in patients with severe LV dysfunction under VA-ECMO.
2363

2364 **10. Weaning criteria and ECMO weaning**

2365 Weaning from VA-ECMO should not be attempted in the first 48 hours. Before a first weaning trial,
2366 the patient should be hemodynamically stable, with baseline mean arterial pressure (MAP) > 60
2367 mmHg in the absence or at low doses of vasoactive agents and pulsatile arterial waveform maintained
2368 for at least 24 hours. The weaning will be conducted under echocardiographic monitoring. The ECMO
2369 flow will be decreased progressively to a minimum of 1–1.5 L/min. If mean blood pressure is
2370 constantly > 60 mmHg during the trial, the VA-ECMO flow rate will be returned to its baseline value.
2371 VA-ECMO removal will be considered if the patient does not have end-stage cardiac disease, tolerates
2372 the full weaning, and has LVEF \geq 20–25%, aortic velocity-time integral \geq 12 cm and lateral mitral
2373 annulus peak systolic velocity of \geq 6 cm/s under minimal VA-ECMO support.
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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 (polyméthylpentène)	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	
Montpellier	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	

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2393 Effects of Induced Moderate HYPOthermia on mortality in Cardiogenic Shock Patients Rescued by
2394 veno-arterial ExtraCorporeal Membrane Oxygenation (ECMO)
2395 HYPO ECMO STUDY
2396 N° ID RCB N°2016-A00377-44
2397
2398 c) Summary of changes
2399

2400 Version 1.0 du 04/03/2016

2401 Version 2.0 du 21/09/2016

2402

Page ou n° chapitre	Protocole version 1.0 du 04/03/2016	Page ou n° chapitre	Protocole version 2.0 du 21/09/2016
SUMMARY RATIONALE /BACKGROUND	The HYPO-ECMO trial will test the hypothesis that moderate hypothermia (temperature between $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) associated with VA-ECMO support results in a reduction in 30-day mortality in comparison with the normothermia group ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$)	SUMMARY RATIONALE /BACKGROUND	The HYPO-ECMO trial will test the hypothesis that moderate hypothermia (temperature between $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) associated with VA-ECMO support results in a reduction in 30-day mortality in comparison with the normothermia group ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) $36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$
SUMMARY MAIN OBJECTIVE	The study objective is to determine whether early moderate hypothermia ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) is superior to normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) in patients with cardiogenic shock treated with VA-ECMO with respect to 30-day mortality.	SUMMARY MAIN OBJECTIVE	The study objective is to determine whether early moderate hypothermia ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) is superior to normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) ($36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$) in patients with cardiogenic shock treated with VA-ECMO with respect to 30-day mortality.
SUMMARY SECONDARY ENDPOINTS	<ul style="list-style-type: none"> - Number of days alive without organ failure(s), defined with the SOFA score and its components (respiratory, liver, coagulation and renal), between inclusion and D30 - Duration of mechanical ventilation and the number of days between inclusion and day 30/ day 60, alive without mechanical ventilation - Number of days alive without renal replacement therapy, and the number of days, between inclusion and day 30 and day 60, without renal replacement therapy 	SUMMARY SECONDARY ENDPOINTS	<ul style="list-style-type: none"> - 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 and day 60 and D180, without renal replacement therapy
SUMMARY STUDY DESIGN	A multicenter, prospective, controlled, randomized (moderate hypothermia $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) during 24 hours \pm 1h versus normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) , comparative open trial will be conducted on two parallel groups of patients with cardiogenic shock treated with VA-ECMO.	SUMMARY STUDY DESIGN	A multicenter, prospective, controlled, randomized (moderate hypothermia $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) during 24 hours \pm 1h versus normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) $36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$, comparative open trial will be conducted on two parallel groups of patients with cardiogenic shock treated with VA-ECMO.
SUMMARY STUDY TREATMENTS/STRATEGIES PROCEDURES	After inclusion and randomization (by CleanWeb® software), the patients according to the group allocated will be placed on moderate hypothermia ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) during 24 hours \pm 1h or maintained on normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) 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. Temperature will be maintained between $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$	SUMMARY STUDY TREATMENTS/STRATEGIES PROCEDURES	After inclusion and randomization (by CleanWeb® software), the patients according to the group allocated will be placed on moderate hypothermia ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) during 24 hours \pm 1h or maintained on normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) ($36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$). 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

	<p>during 24 hours \pm 1h followed by a progressive reheating ($0.2\pm 0.1^{\circ}\text{C}/\text{h}$) to reach 37°C. Temperature at $37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$ will be maintained during 48 hours \pm 4h after having reached 37°C.</p> <p>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.</p> <p>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." Therefore the temperature will be maintained at $37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$.</p>		<p>internal technique). Temperature will be maintained between $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$ during 24 hours \pm 1h followed by a progressive reheating ($0.2\pm 0.1^{\circ}\text{C}/\text{h}$) to reach 37°C. Temperature at $37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$ will be maintained during 48 hours \pm 4h after having reached 37°C.</p> <p>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.</p> <p>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 $36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$ $37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$.</p>
SUMMARY NON-INCLUSION CRITERIA	<ul style="list-style-type: none"> - Uncontrolled bleeding (bleeding despite medical intervention (surgery or drugs)) - Indication of therapeutic hypothermia for cardiac arrest - Resuscitation >30 minutes 	SUMMARY NON-INCLUSION CRITERIA	<ul style="list-style-type: none"> - Uncontrolled bleeding (bleeding despite medical intervention (surgery or drugs)) - Indication of therapeutic hypothermia for cardiac arrest - Resuscitation >30 minutes
3 STUDY OBJECTIVES	In this chapter, and accordingly to the literature, moderate hypothermia is definite as a temperature between $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$. Normothermia is definite as a temperature at $37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$.	3 STUDY OBJECTIVES	In this chapter, and accordingly to the literature, moderate hypothermia is definite as a temperature between $33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$. Normothermia is definite as a temperature at $36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$ $37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$.
3.1 Primary objective	The study objective is to determine whether early moderate hypothermia ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) is superior to normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) in patients with cardiogenic shock treated with VA-ECMO with respect to 30-day mortality.	3.1 Primary objective	The study objective is to determine whether early moderate hypothermia ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) is superior to normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) $36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$ in patients with cardiogenic shock treated with VA-ECMO with respect to 30-day mortality.
3.3.2 Secondary objective	<ul style="list-style-type: none"> - Number of days alive without organ failure(s), defined with the SOFA score and its components (respiratory, liver, coagulation and renal), between inclusion, and D30 - Duration of mechanical ventilation and the number of 	3.3.2 Secondary objective	<ul style="list-style-type: none"> - 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

	<p>days between inclusion and day 30/ day 60 alive without mechanical ventilation</p> <ul style="list-style-type: none"> - Number of days alive without renal replacement therapy, and the number of days, between inclusion and day 30, and day 60, without renal replacement therapy 		<p>without mechanical ventilation</p> <ul style="list-style-type: none"> - Number of days alive without renal replacement therapy, and the number of days, between inclusion and day 30, and day 60 and day 180, without renal replacement therapy
4.1 Experimental study design	Schema de l'étude	4.1 Experimental study design	Modification du schéma portant sur la T°C du groupe normothermie : normothermia group ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) $36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$
4.1.2 Heater cooler unit and temperature control for all patients	<p>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".</p> <p>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).</p>	4.1.2 Heater cooler unit and temperature control for all patients	<p>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".</p> <p>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).</p> <p>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).</p>
4.1.4 Inclusion and randomization of patient	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 ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) or maintained on normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) during 24 hours \pm 1h according to the group.	4.1.4 Inclusion and randomization of patient	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 ($33^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 34^{\circ}\text{C}$) or maintained on normothermia ($37^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$) $36^{\circ}\text{C} \leq T^{\circ}\text{C} \leq 37^{\circ}\text{C}$ during 24 hours \pm 1h according to the group.
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.	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).
4.1.6	The extracorporeal life support organization (ELSO)	4.1.6	The extracorporeal life support organization (ELSO) recommends

Normothermia group	recommends "Temperature can be maintained at any level by adjusting the temperature of the water bath. Temperature is usually maintained close to 37° C." The temperature will be maintained at Therefore the temperature will be maintained at 37 °C ± 0.3°C under VA-ECMO.	Normothermia group	"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 37 °C ± 0.3°C 36°C ≤ T°C ≤ 37°C under VA-ECMO.
4.3.1 Randomization procedure	<ul style="list-style-type: none"> Control group: Patients with CS allocated to a strategy of normothermia (37 °C ± 0.3°C) associated with usual care. 	4.3.1 Randomization procedure	<ul style="list-style-type: none"> Control group: Patients with CS allocated to a strategy of normothermia (37 °C ± 0.3°C) 36°C ≤ T°C ≤ 37°C associated with usual care.
5.4 Non inclusion criteria	<ul style="list-style-type: none"> - Uncontrolled bleeding (bleeding despite medical intervention (surgery or drugs)) - Indication of therapeutic hypothermia for cardiac arrest - Resuscitation >30 minutes 	5.4 Non inclusion criteria	<ul style="list-style-type: none"> - Uncontrolled bleeding (bleeding despite medical intervention (surgery or drugs)) - Indication of therapeutic hypothermia for cardiac arrest - Resuscitation >30 minutes
9. Feasibility	Hypothermia induction during VA-ECMO does not require any additional device or supplementary catheter insertion since central temperature is easily controlled with the circuit heat controller. Moreover, considering the main objective, the HYPO-ECMO trial will be a pragmatic study in order to facilitate patient inclusion and monitoring.	9. Feasibility	Hypothermia induction during VA-ECMO does not require any additional device or supplementary catheter insertion since central temperature is easily controlled with the circuit heat controller. Moreover, considering the main objective, the HYPO-ECMO trial will be a pragmatic study in order to facilitate patient inclusion and monitoring.
11.1.2 statistical analysis for the secondary endpoints	<ul style="list-style-type: none"> - Number of days alive without organ failure(s), defined with the SOFA score and its components (respiratory, liver, coagulation and renal), between inclusion and D30 - duration of mechanical ventilation and the number of days, between inclusion and day 30/ day 60, 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, without renal replacement therapy 	11.1.2 statistical analysis for the secondary endpoints	<ul style="list-style-type: none"> - Number of days alive without organ failure(s), defined with the SOFA score and its components (respiratory, liver, coagulation and renal), between inclusion and 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

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2404 Version 2.0 du 21/09/2016

2405 Version 3.0 du 03/02/2017

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Synopsis Number of recruiting center	17	Synopsis Number of recruiting center	47 18
Synopsis Main non inclusion criteria - VA-ECMO after cardiac surgery for heart/lung transplantation or left or biventricular assist device implantation - Resuscitation >30 minutes	Synopsis Main non inclusion criteria - VA-ECMO after cardiac surgery for heart transplantation or heart + - lung transplantation or left or biventricular assist device implantation - Resuscitation >30 minutes Implantation of VA-ECMO under cardiac massage with a duration of cardiac massage > 30 minutes
Chap 5.4 Non inclusion criteria - VA-ECMO after cardiac surgery for heart/lung transplantation or left or biventricular assist device implantation - Resuscitation >30 minutes	Chap 5.4 Non inclusion criteria - VA-ECMO after cardiac surgery for heart transplantation or heart + - lung transplantation or left or biventricular assist device implantation - Resuscitation >30 minutes Implantation of VA-ECMO under cardiac massage with a duration of cardiac massage > 30 minutes

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2408 Version 3.0 du 03/02/2017

2409 Version 4.0 du 31/05/2017

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synopsis, non Inclusion criteria	<ul style="list-style-type: none"> - 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 > 30 minutes - Cerebral deficit with fixed dilated pupils - Participation in another biomedical research - Patient moribund on the day of randomization - Irreversible neurological pathology - Minor patients - Patients under tutelage 	synopsis, non Inclusion criteria	<ul style="list-style-type: none"> - 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 > 30 minutes ≥ 45 minutes - Out of hospital refractory cardiac arrest - Cerebral deficit with fixed dilated pupils - Participation in another biomedical research interventional research involving therapeutic modifications - Patient moribund on the day of randomization - Irreversible neurological pathology - Minor patients - Patients under tutelage
5.4 non Inclusion criteria	<ul style="list-style-type: none"> - 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 > 30 minutes - Cerebral deficit with fixed dilated pupils - Participation in another biomedical research - Patient moribund on the day of randomization - Irreversible neurological pathology - Minor patients - Patients under tutelage 	5.4 non Inclusion criteria	<ul style="list-style-type: none"> - 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 > 30 minutes ≥ 45 minutes - Out of hospital refractory cardiac arrest - Cerebral deficit with fixed dilated pupils - Participation in another biomedical research interventional research involving therapeutic modifications - Patient moribund on the day of randomization - Irreversible neurological pathology - Minor patients - Patients under tutelage

2411 Version 4.0 du 31/05/2017

2412 Version 5.0 du 04/07/2017

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synopsis	NUMBER OF RECRUITING CENTER 18	synopsis	NUMBER OF RECRUITING CENTER 48 19

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2417 Version 5.0 du 04/07/2017

2418 Version 6.0 du 01/09/2017

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13.2	<p>Before collecting the patient's consent, the investigator will give complete information about the proposed study.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>The patient will be asked to give his/her consent for the continuation of the trial when his/her condition will allow.</p> <p>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.</p> <p>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:</p>	13.2	<p>Before collecting the patient's consent, the investigator will give complete information about the proposed study.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>The patient will be asked to give his/her consent for the continuation of the trial when his/her condition will allow.</p> <p>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.</p> <p>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:</p>

	<ul style="list-style-type: none"> - 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 		<ul style="list-style-type: none"> - 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 <p>Particular case:</p> <p>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.</p> <p>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.</p> <p>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:</p> <ul style="list-style-type: none"> - The patient died after inclusion in emergency setting without family or support person, properly documented in the medical file by the investigator.
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			<p>- 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.</p> <p>- 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.</p>
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2422 Version 7.0 du 06/11/2017

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synopsis	NUMBER OF RECRUITING CENTER 19	synopsis	NUMBER OF RECRUITING CENTER 19 20

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Page ou n°chapitre	Protocole version 7.0 du 06/11/2017	Page ou n° chapitre	Protocole version 7.1 du 25/04/2018
Synopsis STUDY SIZE	<p>N= 334 patients We considered that mortality in cardiogenic patients supported with VA-ECMO will be 50% (based both on ELSO data, Combes data (<i>Crit Care Med.</i> 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.</p>	Synopsis STUDY SIZE	<p>N= 334 patients We considered that mortality in cardiogenic patients supported with VA-ECMO will be 50% (based both on ELSO data, Combes data (<i>Crit Care Med.</i> 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.</p> <p>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.</p>
Planned interim analyses Page 33	One interim analysis for efficacy/futility will be performed after inclusion of 2/3 of the patients.	Planned interim analyses Page 33	<p>One interim analysis for efficacy/futility will be performed after inclusion of 2/3 of the patients.</p> <p>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.</p>

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2434 2 a) Original and final statistical analysis plan

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2439

HYPO ECMO Statistical analysis plan
11/01/2021
Validated before database lock
K Duarte / N Girerd

2440 **17 STUDY ENDPOINTS**

2441

2442 **17.1 PRIMARY ENDPOINT**

2443 All-cause mortality at day 30 will be the primary outcome variable of this analysis.

2444

2445 **17.2 SECONDARY ENDPOINTS**

2446 Secondary endpoints will be tested in a hierarchical fashion [1] as listed in the following Table:

2447

2448 **Table 1: Secondary endpoints and hierarchical testing order**

Hierarchical Testing Order	Secondary Endpoint
1	Composite endpoint of death, cardiac transplant, escalation to LVAD, stroke at day 30
2	All-cause mortality at day 180
3	Composite endpoint of death, cardiac transplant, escalation to LVAD, stroke at day 180
4	All-cause mortality at day 60
5	Composite endpoint of death, cardiac transplant, escalation to LVAD, stroke at day 60
6	All-cause mortality at day 7
7	All-cause mortality at 48 hours
8	VA-ECMO duration
9	Cumulated amount of administered fluids
10	Duration of vasopressors use in ICU
11	Duration to normalization of lactate
12	Number of days alive without organ failure(s), defined with the SOFA score and its components (respiratory, liver, coagulation and renal), between inclusion and day 7
13	Number of days alive without organ failure(s), defined with the SOFA score and its components (respiratory, liver, coagulation and renal), between inclusion and day 30
14	Duration of mechanical ventilation
15	Number of days of mechanical ventilation between inclusion and day 30
16	Number of days of mechanical ventilation between inclusion and day 60
17	Number of days of mechanical ventilation between inclusion and day 180
18	Duration of ICU stay
19	Duration of hospitalization
20	Number of severe and moderate bleeding complications estimated using the BARC classification under VA-ECMO
21	Number of packed red blood cells transfused under VA-ECMO
22	Pulmonary infections
23	Blood infections
24	VA-ECMO cannulae infections
25	Lactate clearance at day 1
26	Lactate clearance at day 2
27	Lactate clearance at day 3
28	Lactate clearance at day 4
29	Lactate clearance at day 5
30	Lactate clearance at day 6
31	Lactate clearance at day 7

2449

2450 **18 STATISTICAL ANALYSIS**

2451

2452 **18.1 SAMPLE SIZE CONSIDERATION**

2453 We anticipated that mortality in cardiogenic patients supported with VA-ECMO will be 50% (based both on
2454 ELSO data, Combes data (Crit Care Med. 2008 May;36(5):1404–11), as well as personal data from the study's
2455 principal investigator (database of 150 patients)).

2456 Considering a total event risk (for the primary endpoint) of 50% in the control group, a sample size of n=167
2457 patients/group will detect a 15% absolute difference in favour of the VA-ECMO group using a chi-square test
2458 with an 80% power and considering a two-sided global alpha level of 5% using the LanDe Mets method with
2459 O'Brien-Fleming boundary for one interim analysis after inclusion of two-third of the patients.
2460

2461 **18.2 GENERAL CONSIDERATIONS**

2462 All analyses will be performed using SAS software version 9.4 (SAS Institute, Cary, NC,
2463 USA) and R software version 4.0.3 (the R foundation for Statistical Computing).
2464

2465 **18.3 CONTINUOUS VARIABLES**

2466 Continuous variables will be described by the number of non-missing values, mean and standard deviation. The
2467 normality of the distributions will be assessed. In case of violation of normality, the continuous variables will be
2468 described by the median and interquartile range (1st quartile and 3rd quartile).
2469

2470 **18.4 CATEGORICAL VARIABLES**

2471 Categorical variables will be summarized by the observed frequencies and the percentages relative to the total
2472 number of non-missing items.
2473

2474 **18.5 DESCRIPTION OF STATISTICAL ANALYSIS OF PRIMARY AND SECONDARY**
2475 **ENDPOINTS**

2476 As per intention to treat analysis, every randomized patient will be included in the analysis of primary and
2477 secondary endpoints.
2478

2479 **18.5.1 Analysis of the primary endpoint**

2480 The differences between the two study groups (ie, intervention and controls) relative to the risk of all-cause
2481 mortality at day 30 will be studied using logistic regression adjusted for the postcardiotomy setting, prior cardiac
2482 arrest, prior MI, age, vasopressor dose, SOFA score and lactate at randomisation. Resulting associations will be
2483 illustrated by means of Kaplan-Meier survival curves, and a similarly adjusted HR will also be provided as well
2484 as crude estimates of ORs and HRs.
2485

2486 One interim analysis for efficacy/futility was performed after inclusion of 2/3 of the patients.

2487 To maintain an overall type I error rate of 5% (two-sided), a bilateral p-value lower than 4.9% will be considered
2488 significant for the final analysis.
2489

2490 For the primary outcome, we do not expect missing variables. All-cause 30 day mortality is a straightforward
2491 outcome that does not require detailed information. Yet, in the unlikely case of missing vital status at 30 days,
2492 patients with missing data will be analyzed with the last observation being carried forward. In a sensitivity
2493 analysis, the worst case scenario method will be used (i.e. all patients with incomplete follow-up data died in the
2494 intervention group and died in the no intervention group).
2495

2496 An interaction analysis will be performed using the following list of possible predictive markers: postcardiotomy
2497 setting, prior cardiac arrest, prior MI, age, vasopressor dose, SOFA score and lactate at randomisation.
2498

2499 **18.5.2 Analysis of the secondary endpoints**

2500 Secondary endpoints will be tested in a hierarchical fashion and are listed in Table 1 (page 1). A hierarchical
2501 testing procedure will be implemented in the order shown in this table until the p-value exceeded 0.049 [1].
2502

2503 For the secondary analysis of a) all-cause mortality at 48 hours and at days 7, 60, 180, and b) the composite
2504 endpoint of death, cardiac transplant, escalation to LVAD, stroke at days 30, 60, 180, the same analysis strategy
2505 will be performed as for the primary endpoint.

2506
2507 An unpaired t-test will be performed, after testing of the variables for normality of distribution of continuous
2508 outcomes. Linear regression adjusted for the same variables as those depicted in the primary endpoint analysis
2509 will also be performed. Importantly, in case of non-normal distributions, non-parametric tests will be used.

2510
2511 Chi-square tests (or Fisher's exact test in the event of an insufficient number of expected patients in the 2×2 cell)
2512 will be performed for categorical outcomes other than those described above and odd-ratios will be provided for
2513 illustrative purposes.

2514

2515 **18.6 REFERENCE**

2516 [1] Harrington, D. et al. New guidelines for statistical reporting in the journal. N. Engl. J. Med. 381, 286 (2019).

2517