

**Évaluation de la StO<sub>2</sub> musculaire au cours de la phase précoce d'une assistance circulatoire = Assessment of muscle StO<sub>2</sub> in the early phase of extracorporeal life support**

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UNIVERSITÉ JOSEPH FOURIER  
FACULTÉ DE MÉDECINE DE GRENOBLE

ANNÉE : 2011

N°

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LA PHASE PRECOCE D'UNE ASSISTANCE  
CIRCULATOIRE**

**Assessment of muscle StO<sub>2</sub> in the early phase of extracorporeal  
life support**

Thèse présentée pour l'obtention du doctorat en médecine

**DIPLÔME D'ETAT**

**Dirigée par le Dr BEDAGUE Damien**

Par : **HAUTEFEUILLE Serge**  
Né le : 28/07/1980 à MONACO

THÈSE SOUTENUE PUBLIQUEMENT À LA FACULTÉ DE  
MÉDECINE DE GRENOBLE

Le 4 avril 2011

Devant le jury composé de

**Président du jury :**

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## **A notre Maître, Directeur de thèse,**

Monsieur le Docteur Damien Bedague,

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Monsieur le Professeur Jean-François Payen,

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A Thomas, Nicolas, Caroline, Florence, Stéphane, Valentine, nous avons tous suivi notre chemin (médecin, chirurgien, magistrat, ingénieur). Ces années passées auprès de vous resteront parmi les plus belles années de ma vie.

**Assessment of muscle StO<sub>2</sub> in the early phase of extracorporeal life support**

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## **LIST OF ABBREVIATIONS**

ECLS: ExtraCorporeal Life Support

NIRS: Near-InfraRed Spectroscopy

StO<sub>2</sub>: Tissue Oxygen Saturation

VOT: Vascular Occlusive Test

IABP: Intra Aortic Balloon Pump

SOFA: Sequential Organ Failure Assessment

ScvO<sub>2</sub>: Central venous oxygenation saturation

OPS: Orthogonal Polarisation Spectral imaging

RS: Reperfusion Slope

OS: Occlusion Slope

StO<sub>2</sub>min: minimum tissue oxygen saturation

CRP: C reactive protein

SIRS: Systemic Inflammatory Response Syndrome

ICU: Intensive Care Unit



# I - INTRODUCTION

Extracorporeal Life support (ECLS) is a technique gaining interest, mainly due to technological advances in the device, the oxygenator and its biocompatibility. The use of ECLS for cardiogenic shock refractory to medical treatment is attractive due to its ability to provide ventricular support to recovery, or to serve as a bridge to ventricular assist device or cardiac transplantation.

Considering the critical state of the patients who are candidates for this device, there is no doubt that ECLS can be life-saving. However, we observed in our institution that 43% of the patients receiving ECLS died of multiple organ failure [1]. Another study reported the incidence of multiple organ failure during ECLS to be 42% [2].

ECLS management is currently based on clinical and haemodynamic parameters including mean arterial pressure, cardiac output, urinary output and central venous oxygen saturation (ScvO<sub>2</sub>). However, these parameters are not useful for early detection of tissue hypoperfusion. The classic biological markers of tissue ischemia (pH, base excess, arterial lactate) are rather late markers of ischemia. Furthermore, their values are influenced by other intercurrent factors such as hepatic clearance and adrenergic drugs [3]. In cases of severe circulatory deficiency, regional territories such as cerebral, hepatic, and coronary territories are preferentially perfused at the expense of muscle, skin and splanchnic circulations. Therefore, continuous non-invasive oxygen tissue monitoring of these less well-perfused territories at the bedside would be of interest to identify early on those patients at risk of altered microperfusion.

Severe alteration of the microcirculation, the key organ providing gas and nutrient exchange to all tissues, leads to multiple organ failure. We know that patients with cardiogenic shock, even if the cardiac output is restored, may not survive. Thus restoring the macrohaemodynamics alone may fail to save the patient [4].

During recent years, new bedside monitoring tools have been developed for investigating the microcirculation.

Near-infrared technology (NIRS) is one of them. It is a non-invasive tool that uses the different absorption properties of haemoglobin and desoxyhaemoglobin of light for different wavelength ranges in the near infrared spectrum. Haemoglobin, myoglobin and oxidized cytochrome are the 3 chromophores that absorb near infrared light (680-800 nm) in a biologic tissue. The two latter ones are of negligible importance [5]. According to the Beer-Lambert law, the NIRS signal monitors only vessels less than 1 mm in diameter, because the

high concentration of blood in arteries and veins makes photon emergence unlikely. This technology therefore enables one to evaluate the microvascular oxygen saturation denoted tissular oxygen saturation (StO<sub>2</sub>).

In addition to the continuous StO<sub>2</sub> measurement, a vascular occlusive test can be performed in order to indirectly evaluate muscle oxygen consumption and microcirculatory response to a hypoxic stimulus induced by a transient interruption of blood flow. The vascular occlusive test (VOT) combined with NIRS has already been studied during sepsis and septic shock [6, 9], and in patients with heart failure [10]. In septic shock, an alteration of the VOT parameters was found compared to findings in sepsis and healthy volunteers [6, 7]. The persistence of this alteration was related to outcome, suggesting an ongoing endothelial dysfunction for non-survivors despite a restored macrohaemodynamic perfusion [9]. Peripheral muscle microcirculation assessed by VOT was also impaired in patients with an end-stage cardiac failure and partially reversed by inotropics drugs [10].

StO<sub>2</sub> and VOT under ECLS with a non-pulsatile flow are largely unknown. Therefore, we conducted a prospective observational study to characterize the StO<sub>2</sub> and VOT parameters for patient receiving ECLS for refractory cardiogenic shock.

## **II - MATERIALS AND METHODS**

The study protocol was approved as a routine care by the local ethics committee. An information form was given to each patient or his or her next of kin.

### **A - Study population**

Patients hospitalized in the 11-bedded cardiothoracic intensive care unit of a teaching hospital after insertion of arterio-venous extracorporeal life support (ECLS) for refractory cardiogenic shock refractory to standard therapies, with or without prior cardiac arrest, were enrolled.

Patients were excluded if they were under 18 years of age, had cardiogenic shock secondary to sepsis, were pregnant, or could not be fitted with a StO<sub>2</sub> device on their thenar eminence.

## **B - ECLS management**

The decision to initiate ECLS was always taken by the ECLS team. In our institution, the inclusion criteria for ECLS support were cardiogenic shock not responding to multiple inotropic agents and/or intraaortic balloon pump (IABP) counterpulsation and cardiac failure when being weaned off cardiopulmonary bypass (CPB). ECLS for refractory cardiac arrest followed the guidelines proposed by our French intensive care society [11]. The ECLS cannulas were either inserted percutaneously or by using a surgical approach whereby the cardiac surgeon catheterised the femoral vessels using a modified Seldinger technique under direct vision. The ECLS system consisted of a portable centrifugal pump (Rotaflow, Jostra-Maquet, Orléans, France) with polyvinyl chloride tubing, a hollow-fiber membrane oxygenator (Quadrox) and arterial and venous femoral armed cannulas (Medtronic, Vienna, Austria). The extracorporeal circuit is heparin coated with Bioline Coating (Maquet, Jostra Medizintechnik AG, Hirrlingen, Germany). Before cannula insertion, patients received a heparin bolus of 50-100 UI/Kg. Heparin was not administered to patients with clinical or laboratory evidence of coagulopathy or those receiving thrombolytic drugs or GPIIb/IIIa inhibitors. The circuit was primed with 6% hydroxyethyl starch 130/0.4 (Voluven®) solution. All ECLS circuits had a heat exchanger. The initial ECLS flow, vasopressor and fluid requirement was set to maintain stable haemodynamics, mean arterial pressure  $\geq 65$  mmHg, arterial oxygen saturation  $\geq 95\%$ , mixed venous oxygen saturation  $\geq 70\%$ , and urine output  $\geq 0.5$  ml/kg/h. The patient had a protective ventilation strategy. The fractional inspired oxygen concentration for ECLS and the gas flow were adjusted according to the results of the arterial blood gas analysis.

All patients had a central venous line in the superior cava territory and an arterial catheter for continuous pressure monitoring. Low doses of inotropic agents were administered in order to maintain left ventricular ejection and prevent pulmonary oedema, left ventricle blood stasis and intracardiac thrombosis.

In order to improve neurological outcome in patients with a prior cardiac arrest, mild hypothermia was induced for 12 hours with a target temperature between 33°C to 34 °C [12, 13].

The management of patients was left to the ICU team without interference in their usual treatment procedures. StO<sub>2</sub> values and VOT curve analysis were not used to guide therapeutic decisions made by the ICU team.

## **C - StO<sub>2</sub> measurements**

The tissue oxygen saturation (StO<sub>2</sub>) was measured by a tissue spectrometer (*Inspectra Model 650, Hutchinson Technology Inc., Hutchinson, MN, USA*). The maximum depth of the tissue volume sampled is estimated to be equal to the distance between the sending and receiving fibres of the probe. We used a probe with an interoptode distance of 15 mm. The probe was placed on the thenar eminence to minimise the effect of fat and oedema on near-red light absorption [14, 15]. The probe was not placed on the same side of the existing radial arterial catheter. The StO<sub>2</sub> was recorded every 3 sec for 48 hours. Data were collected afterwards by an Inspectra software program (*Hutchinson, MN, USA*).

The vascular occlusion test (VOT) was performed by placing a sphygmomanometer cuff around the arm. A rapid inflation of 50 mmHg over the systolic arterial pressure was applied for 3 minutes. The sphygmomanometer was then rapidly deflated.

The VOT curves obtained were subsequently analysed by the Inspectra software version 4.0 running on MatLabs 7.0 software (*Math Works Inc, Natick, Mass, USA*). The first degree slope of the haemoglobin desaturation during stagnant limb ischemia was used to extrapolate the oxygen consumption rate named occlusion slope (%/min). The oxygen reperfusion rate named reperfusion slope (%/sec) was measured as the first degree slope of the increase of StO<sub>2</sub> after the release of the brachial artery occlusion. The vascular reactivity of the respective tissue microcirculation was estimated as the area (units/min) under the StO<sub>2</sub> curve above baseline values.

## **D - Study protocol**

Patients were enrolled following ECLS implantation 2 hours after optimizing the haemodynamics. The NIRS probe was placed on the skin of the thenar eminence. Care was taken to avoid any pressure over the probe which could have artificially produced an ischemic area under the probe.

Demographic data collected included age, sex, weight, height (to calculate the body mass index and the corporeal surface) and comorbidities. The indication for ECLS was noted. The Simplified Gravity index II was calculated on admission [16], Sequential Organ Failure Assessment (SOFA) was calculated daily [17]. The StO<sub>2</sub> was measured continuously during

48 hours. At H2, H12, H24 and H48 from the ECLS implantation, we carried out a vascular occlusive test.

The clinical and haemodynamic parameters measured immediately prior to the VOT were: mean arterial pressure, ECLS pump flow, gas exchange flow, doses of catecholamine drugs, central temperature (measured in the bladder) and urine output. Biological data collected included arterial blood gases, arterial blood lactate, haemoglobin concentration, central venous saturation, creatinine, bilirubin, prothrombin time and activated partial thromboplastin time. Procalcitonin and C protein reactive were also measured.

Patients were followed up to 28 days after the inclusion. In the event of death, mortality analysis was undertaken.

### **III - DATA ANALYSIS**

Descriptive statistics are expressed as median with the extreme range. Because deaths occurred during the study period, analysis for statistical significance of temporal changes during the study period was performed using the random effect linear model. Nonparametric Mann–Whitney tests were used for intergroup analysis. Correlations were performed using the random effect linear model.

Statistical significance was established at  $p < 0.05$ .

All statistical analyses were performed using Stat version 11.0 software (Stata Corp., College Station, TX)

### **IV - RESULTS**

#### **A - Patients**

A total of 25 patients were studied. Baseline characteristics, including the indication for ECLS, are shown in table 1. Eight patients (32%) died within the first 7 days, all due to multiple organ failure. One patient died between H2 and H12, 3 patients between H24 and H48 and the other 4 patients between day 2 and day 7. Five of these 8 patients had ECLS for cardiac arrest, 2 required support several hours after cardiectomy, the remaining patient developed cardiogenic shock following myocardial infarction. 14 patients (56%) had died by day 28.

**Table 1 : Demographic data**

---

Age (years)	64 (30-81)
Gender: F/M	3/22
Body mass index ( m.kg <sup>-2</sup> )	25 (18 – 36)
Arterial hypertension	11
Dyslipidemia	6
Non insulin dependent Diabetes	5
Corporeal surface (m <sup>2</sup> )	1.85 (1.42 – 2.2)
IGS II	49 (11- 89)
SOFA H2	9 (3 – 17)
SOFA H24	9 (5 – 16)
SOFA H48	9.5 (3 – 17)
ECLS indication :	
- cardiac arrest	9
- postcardiotomy	5
- acute myocardial infarction	5
- decompensated heart failure	5
- cardiotope intoxication	1

---

*Data expressed as median (minimum, maximum value)*

Haemodynamic data are presented in table 2. No evolution over time during the study period was found for the mean arterial pressure, the ECLS parameters, norepinephrine and dobutamine requirements or the arterial oxygen saturation. Urine output decreased and central temperature increased over time ( $p < 0.05$ ). Looking at survivors vs. non survivors, no significant differences were found at each time measurement for mean arterial pressure, indexed pump flow or norepinephrine doses. The temperatures of non-survivors were significantly lower at H2 [survivors median 35.7 °C vs. non survivors median 33.4 °C;  $p = 0.007$ ] but no difference was observed at H12 [36°C vs. 36°C], H24 [36.8 °C vs. 36.3 °C] and H48 [36.5°C vs. 36.3°C].

**Table 2: clinical and haemodynamic data**

	<b>H2</b>	<b>H12</b>	<b>H24</b>	<b>H48</b>
Mean arterial Pressure (mmHg)	71 (50-88)	72 (61-98)	69 (51-96)	68 (51-90)
<b>Indexed Pump flow ( l/mn/m2)</b>	<b>2.1 (1.4-3)</b>	<b>2.2 (1.4-3)</b>	<b>2.1 (1.6-3.2)</b>	<b>2.3 (1.5-3.1)</b>
Gas flow ( l/mn)	4 (2- 7)	4 ( 2.5- 10)	4 (2.5 – 10)	4 ( 3- 6.5)
<b>Norepinephrine(dose in µg/kg /mn)</b>	<b>0.33 (0-2.8)</b>	<b>0.1 (0-2.2)</b>	<b>0.14 (0-1.8)</b>	<b>0.07 (0-1.6)</b>
Dobutamine ( dose in µg/kg/mn)	2.95 (0-10)	2.75 (0-6.4)	2.7 (0-7.6)	2.64 (0-12.4)
<b>O2 saturation (%)</b>	<b>99 (84-100)</b>	<b>98.5 (82-100)</b>	<b>98 (93-100)</b>	<b>97.9 (94-100)</b>
Temperature (Celsius) *	35.1 (30.4-37.8)	35.6 (34.7-37.9)	36.5 (33.6-38.4)	36.5 (35.2-38)
<b>Diuresis (ml/h)*</b>	<b>105 (0-550)</b>	<b>64 (0-372)</b>	<b>53 (0-300)</b>	<b>55 (0-360)</b>

*Data expressed as median (minimum, maximum value). \*: significant evolution over time, p<0.05*

Biologic data are shown in table 3. Central venous oxygenation saturation (ScvO<sub>2</sub>) and lactate decreased over time in the study population (p< 0.05), whereas pH increased over time (p<0.05). No difference was observed between survivors and non survivors for arterial pH. For lactate, only the value at H2 was significantly higher for non-survivors (p<0.05) but not at H12, H24 or H48. There was a trend to increased ScvO<sub>2</sub> for the non-survivor group during the first day which however only attained significance at H12 [median non survivors vs. survivors: H2: 78(49-95) vs. 71(55-90) p=0.15; H12: 77.8 %( 67-91) vs. survivors 70.2% (40- 81) p=0.03; H24: 72(70-89) vs. 69(45-89) p=0.21]. The biological markers of inflammation (procalcitonin and C- protein reactive) increased over time (p< 0.05). No statistical differences were observed between survivors and non-survivors for the inflammatory markers. Haemoglobin concentration decreased during the first 48 hours (P<0.05). Haemoglobin concentration showed no differences between both groups and was considered adequate.

**Table 3: biological data**

	<b>H2</b>	<b>H12</b>	<b>H24</b>	<b>H48</b>
ScvO2 (%) *	<b>74.5</b> (49-94)	<b>73</b> (60-90)	<b>71.3</b> (45-89)	<b>67.5</b> (62-82)
Lactate (mmol/l) *	<b>5.6</b> (1.2-15.7)	<b>2.5</b> (1.2-17)	<b>1.9</b> (1-19)	<b>1.6</b> (1.1-3.8)
pH *	<b>7.33</b> (6.78-7.53)	<b>7.39</b> (7.1-7.5)	<b>7.45</b> (6.92-7)	<b>7.47</b> (7.36-7.5)
Procalcitonin *	<b>0.51</b> (0-13.7)	<b>4.4</b> (0.1-45)	<b>4.6</b> (0.3-93)	<b>3.44</b> (0.3-96)
CRP *	<b>36.5</b> (0-256)	<b>66</b> (5-260)	<b>136.5</b> (22-299)	<b>144</b> (29-394)
Haemoglobin *	<b>99.5</b> (63-137)	<b>100.5</b> (69-147)	<b>95</b> (70-130)	<b>88</b> (70-110)
Creatinin	<b>138</b> (61-462)	<b>174</b> (49-391)	<b>171</b> (44-440)	<b>161</b> (43-539)

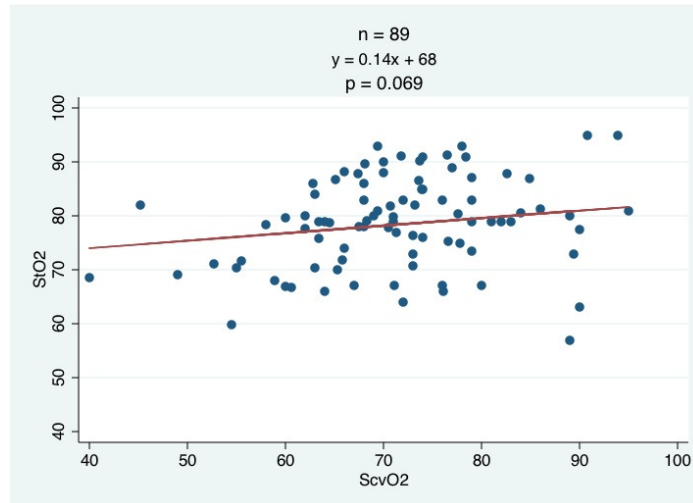
*Data expressed as median (minimum, maximum value), \*: significant evolution over time ( $p < 0.05$ ); CRP: C-reactive protein; ScvO2: central venous oxygen saturation*

### **B - Baseline StO2 characteristics**

Baseline StO2 are shown on table 4. There was no evolution over time for the StO2 in the study population. We found a wide variation of StO2 values, ranging from 56% to 95%. Next, we searched for correlations between the StO2 and other variables reflecting hypoperfusion. No correlation was found between StO2 and lactate ( $r^2 = 0.0004$ ), mean arterial pressure ( $r^2 = 0.002$ ) or norepinephrine requirements ( $r^2 = 0.01$ ). StO2 values were not statistically different between the survivors and non-survivors at any time measurement during the study. Note that no correlation was observed between basal StO2 and central temperature ( $r^2 = 0.001$ ). No correlation was neither observed between StO2 and ScvO2 ( $r^2 = 0.02$ ) (Figure 1).



**Figure 1: Correlation between StO2 and ScvO2 by pooling data**



### C - VOT characteristics

For the VOT parameters (Table 4), we observed a significant increase over time for the occlusion slopes and for the reperfusion slopes in the overall study population using the random linear effect ( $p < 0.05$ ). StO2min decreased across time ( $p < 0.05$ ). There was no significant evolution over time for hyperaemia.

**Table 4: StO2 characteristics**

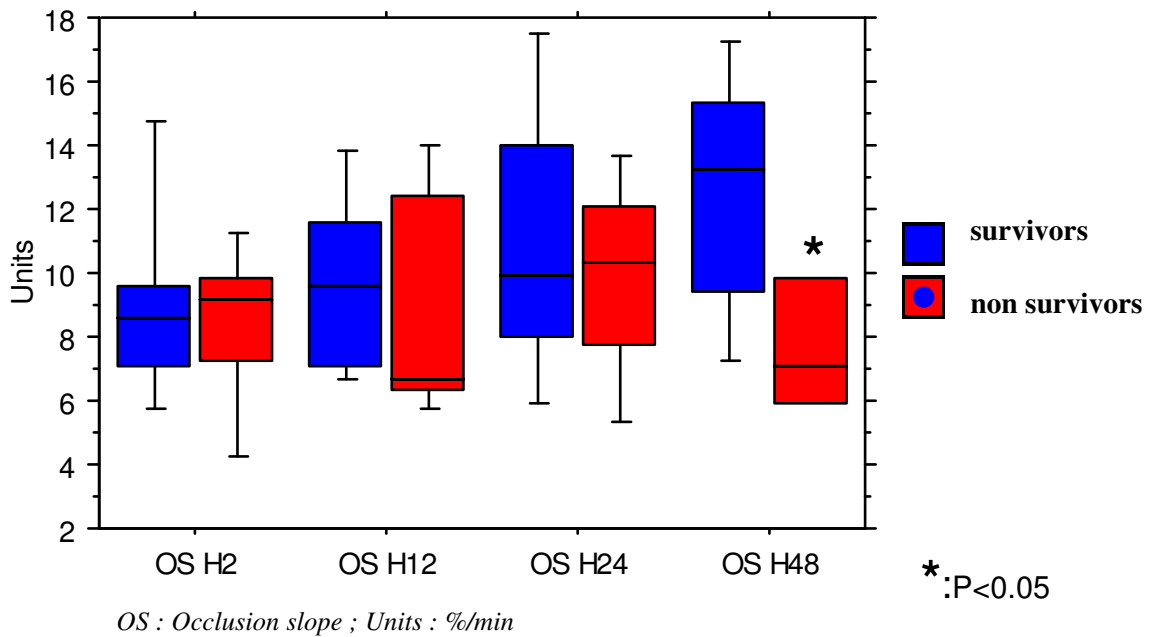
	<b>H2</b>	<b>H12</b>	<b>H24</b>	<b>H48</b>
<b>StO2 Baseline (%)</b>	<b>78,9</b> (63-95)	<b>78,1</b> (66-95)	<b>79,5</b> (56-91,2)	<b>79</b> (66-90)
<b>OS (U/min) *</b>	<b>8,8</b> (0.4-15.8)	<b>8,8</b> (5.4-14,4)	<b>9,9</b> (5.6-15.6)	<b>11.7</b> (6.4-15.9)
<b>RS (U/s) *</b>	<b>1.84</b> (0.1-6.3)	<b>2.6</b> (0.1-4.8)	<b>2.1</b> (0.7-6.8)	<b>2.9</b> (0.17-5.3)
<b>Hyperaemia(U/min)</b>	<b>13.8</b> (0-45)	<b>12</b> (0 - 48.5)	<b>13.3</b> (1.1-50)	<b>13 .1</b> (1-45)
<b>StO2min *</b>	<b>47.5</b> (22- 74)	<b>48</b> (25-74)	<b>44</b> (12- 67)	<b>41</b> (15-60)

*Data expressed as median (minimum, maximum value), \*: significant evolution across time ( $p < 0.05$ ). OS: Occlusion slope; RS: Reperfusion Slope; StO2min: Minimum StO2*

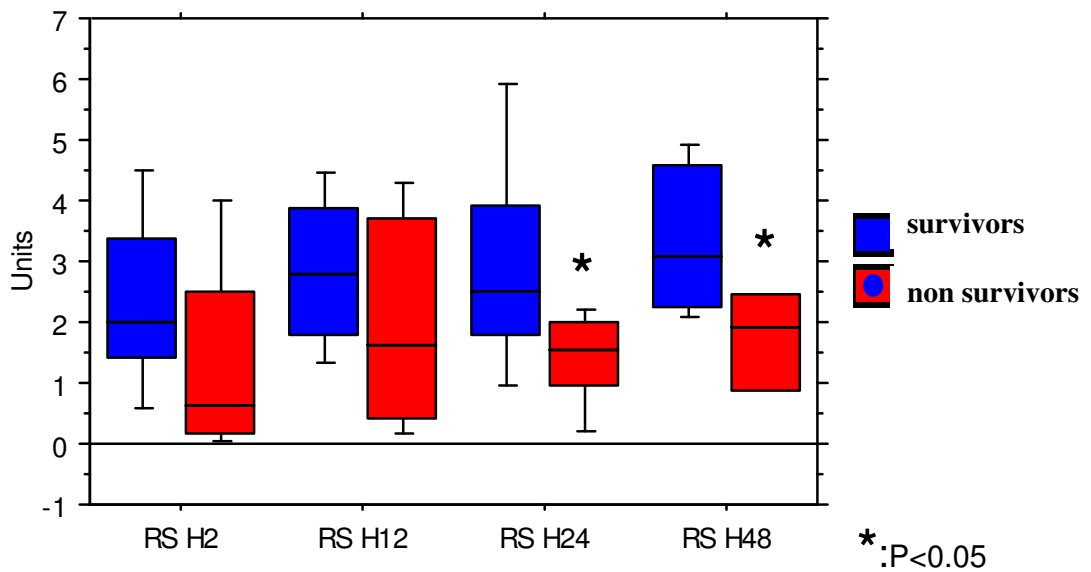
Afterwards, we looked for differences in the occlusion and reperfusion slopes between the survivors and the non-survivors.

Evolution of the occlusion slopes over time is not the same for the two groups ( $p=0.02$ ). The occlusion slopes increased for survivors but not for non-survivors. Regarding the reperfusion slopes, there is a trend towards increased slopes over time for survivors compared with non-survivors, which failed to reach significance ( $p=0.088$ ). In our cohort, we did not observe a significant difference for the occlusion slopes between survivors and non-survivors except at H48 ( $p= 0.04$ ) (Figure 2). Although there were no differences between survivors versus non-survivors for the reperfusion slope at H2 and H12, non-survivors had significantly lower values of the reperfusion slope at H24 compared to the survivors [median 1.35 %/seconds (0.01-2.25) vs. 2.5 %/seconds (0.74 to 6.8),  $p=0.03$ ] and at H48 [ median 1.9 %/seconds ( 0.17-2.7) vs. 3,08 %/seconds (1,2 – 5.3) ,  $p=0.02$ ] (Figure 3).

**Figure 2: Occlusion slopes for survivors and non survivors by day 7**



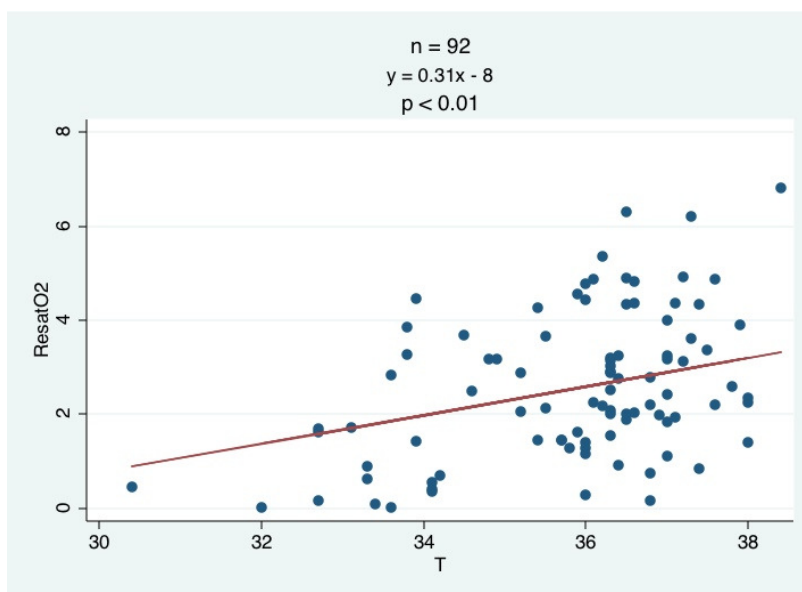
**Figure 3: reperfusion slopes for survivors and non survivors by day 7**



RS: Reperfusion Slope; Units: %/sec

No correlation was observed between reperfusion slope and lactate ( $r^2= 0.025$ ) or with mean arterial pressure ( $r^2=0.001$ ). We found a weak correlation between reperfusion slope and central temperature ( $r^2= 0.1$ ).

**Figure 4: Correlation between reperfusion slope and temperature**



## V - DISCUSSION

Although ECLS restores macrohaemodynamics, some patients succumb to multiple organ dysfunction, suggesting that the tissue perfusion is also dependant on the microcirculation. Microcirculatory dysfunction following a severe shock state probably plays a fundamental role. The microcirculation during ECLS is not well known. *Jung C et al.* showed that microflow in the vessels of the sublingual mucosa observed by orthogonal polarization spectral imaging (OPS) was restored after interruption of the ECLS for oxygenator exchange [18]. This suggests that the microcirculation is indeed dependant of the macrocirculation but the evolution of the microcirculation during ECLS with a nonpulsatile flow has not yet been investigated. Among other non-invasive bedside techniques recently developed, muscle NIRS technology has been used to study the microcirculation during sepsis and severe traumatology. To our knowledge, this is the first observational study that analyses muscle StO<sub>2</sub> and VOT with NIRS technology during the early phase of ECLS.

The first finding, not evident prior to the study, is that StO<sub>2</sub> on the thenar eminence with VOT measurement is feasible for patients receiving ECLS with a non-pulsatile flow. The StO<sub>2</sub> values and VOT curves obtained were similar to other studies in traumatology and sepsis using the same interoptode distance [8, 19, 20, 21]. The muscle NIRS technology is able to measure the oxyhaemoglobin and desoxyhaemoglobin without needing a pulsatile signal, so a continuous flow under ECLS does not alter the measures of the muscle oxygen saturation. Furthermore, blood flow is known to be non-pulsatile in the microvessels even when the flow is pulsatile.

The primary objective of our study was to evaluate the usefulness of basal StO<sub>2</sub> monitoring for detecting hypoperfusion during ECLS. In our cohort, we found a median StO<sub>2</sub> of 79 %. Crookes and al reported a mean StO<sub>2</sub> of 87+/- 6% among 707 healthy volunteers with values ranging from as low as 50% to as high as 97% [22]. The median StO<sub>2</sub> values appeared lower in our ECLS cohort. Nevertheless, baseline StO<sub>2</sub> failed to distinguish the severity of hypoperfusion for patients receiving ECLS for cardiogenic shock. We observed a wide range of values for the basal StO<sub>2</sub> (56 % to 95%). This distribution was not correlated with tissue hypoperfusion. Even though we observed a progressive evolution of lactate and pH over time, suggesting an improvement of tissue perfusion under ECLS, StO<sub>2</sub> did not vary with time. No correlation was observed between lactate and StO<sub>2</sub> ( $r^2= 0.01$ ). Furthermore, we did not observe any difference for the StO<sub>2</sub> values between the survivors and the non-survivors by day 7. These results suggest that the continuous StO<sub>2</sub> measurement on the

thenar muscle is a poor marker of hypoperfusion for a patient receiving ECLS for refractory cardiogenic shock, moreover, does not appear to add any clinically relevant information. In comparison, basal StO<sub>2</sub> seems more pertinent for traumatic shock and cardiogenic failure. In a large study conducted on traumatic shock patients, Cohn and al showed that values underneath 75% of StO<sub>2</sub> were associated with a worse outcome [23]. In another study looking at patients with chronic heart failure, StO<sub>2</sub> values in end stage chronic heart failure were lower than for healthy volunteers and increased after inotropic drugs [10]. It should be noted that none of their patients had severe cardiogenic shock. Studies performed in sepsis show contradictory results. Some studies did not observe different values between septic patients and healthy volunteers [6, 7, 20] whereas others did find a difference [8, 9]. Creteur et al. found no difference in basal StO<sub>2</sub> values between sepsis and septic shock patients. [9]. Payen, D et al. also reported no difference between survivors and non-survivors in septic shock. [24]. The failure of basal StO<sub>2</sub> to detect hypoperfusion might be linked to the fact that the ratio between oxyhaemoglobin and desoxyhaemoglobin obtained with the NIRS technology from muscle is classically named tissue oxygen saturation (StO<sub>2</sub>) but it represents a mixed vascular saturation of arterioles, capillaries and venules which represent 10%, 20%, 70% respectively of the muscle capillary bed [25]. This is the distribution that has been described under physiologic conditions. In shock states, especially in distributive shock secondary to sepsis or severe SIRS (like our patients under ECLS), the distribution of these different compartments are unknown. We could theorise that the arteriolar compartment may be more important in shocked patients hence maintaining artificially high values of StO<sub>2</sub>. Furthermore, in severe endothelial dysfunction, StO<sub>2</sub> can remain high and falsely reassuring, because of cytopathic hypoxia or microvascular shunting resulting in low consumption.

Alteration in oxygen extraction during ECLS for severe cardiogenic shock is suggested in our cohort by the relatively high values of ScvO<sub>2</sub> during the first 24 hours with significant higher ScvO<sub>2</sub> for non survivors by day 7 on H12. We observed, concomitant-with the high values of ScvO<sub>2</sub>, high lactates levels suggesting a severe oxygen extraction dysfunction in the early phase of ECLS for severe cardiogenic shock.

Basal StO<sub>2</sub> has been proposed to monitor the ScvO<sub>2</sub> since it reflects predominantly the O<sub>2</sub> saturation of the venule. Podbregar et al. found a good correlation between StO<sub>2</sub> and SvO<sub>2</sub> for cardiogenic shock but not in septic patients [26]. In sepsis, other studies confirm the absence of correlation between StO<sub>2</sub> and ScvO<sub>2</sub> [24]. In our study, we did not find any correlation between StO<sub>2</sub> and ScvO<sub>2</sub>. StO<sub>2</sub> for patients receiving ECLS for cardiogenic shock did not provide a good estimation of the ScvO<sub>2</sub>.

Because basal StO<sub>2</sub> monitoring gives limited information on microvascular perfusion, the information obtained from StO<sub>2</sub> measurements can be further enhanced by applying a dynamic challenge (transient ischemia by means of arteriovenous occlusion) that can indirectly evaluate oxygen consumption/metabolism and microcirculatory function. This technique has already been described elsewhere [27]. To summarize, after a rapid arterial occlusion, the StO<sub>2</sub> decrease, named occlusion slope, has been used extensively in the literature as an estimate of oxygen consumption rate of muscle tissue. The rate of StO<sub>2</sub> increase after cuff release reflects the resaturation rate, known as reperfusion slope, which depends on the integrity and the functionality of the vascular endothelium. It reflects mainly the capillary recruitment capacity after an ischemic challenge.

The main finding of our study is the gradual improvement over time of the two dynamic StO<sub>2</sub> parameters, occlusion slope and reperfusion slope. This suggests an improvement in oxygen consumption rate of the muscle and improved endothelial function even though the patients were receiving ECLS with non-pulsatile flow.

We observed a significant increase of the occlusion slope in the early phase of ECLS suggesting an improvement in muscle oxygen consumption under ECLS. Only the patients who survived improved their occlusion slope, thus showing their capacity of restoring the muscle oxygen consumption over time. The oxygen consumption rate estimated with the NIRS vascular occlusion technique has been evaluated in healthy subjects [28, 29] and in sepsis [7, 20, 8] with good reproducibility [28]. The oxygen consumption rate reflects the basic metabolism of skeletal muscle at rest, but is also influenced by the adequacy of microcirculation to provide necessary oxygen to the tissue. In septic patients, lower oxygen consumption rates were reported compared to healthy volunteers [7, 9, 20, 8]. This could be attributed either to lower oxygen consumption by the muscle tissue, due to mitochondrial dysfunction for example, or to impaired microcirculatory flow (functional and/or anatomical shunt) that deprives the tissue of the necessary oxygen.

In addition, the reperfusion slope also improved over time suggesting an improvement in endothelial function, and the capacity for capillary recruitment after an ischemic challenge during the early phase of ECLS for cardiogenic shock. Like the occlusion slopes, survivors showed a tendency to improve their reperfusion slopes compared to the non-survivors, which in our study failed to reach significance. Creteur et al. found similar results from a large study on septic shock [9]. Interestingly, we observed a significant difference for reperfusion slopes at H24 and H48 between non- survivors and survivors. Moreover, the only parameter distinguishing the survivors from the non survivors at H24 was the reperfusion

slope. Classical parameters of tissular perfusion like lactates, pH, vasoactive drugs and haemodynamic parameters, failed to discriminate between these two populations.

VOT with NIRS muscle technology could be of interest in optimizing the microcirculation of patients receiving ECLS.

Despite the small number of patients, we showed that muscle oxygen consumption and endothelial function following an ischemic challenge are able to improve during ECLS. Furthermore, we observed a tendency for different evolution over time between the survivors and the non-survivors. It is now well accepted by the medical community that severe cardiogenic shock causes a systemic inflammatory response (SIRS) which is characterized by a release in inflammatory mediators, a capillary and endothelial dysfunction leading to multiple organ dysfunctions[..]. Several studies have linked markers of SIRS with short-term mortality in cardiogenic shock [30, 31]. In our cohort, alteration in tissue oxygen extraction showed by the high ScvO<sub>2</sub> values associated with high lactate concentrations, increase in inflammatory markers over time and microcirculation alteration by VOT were observed. The data suggests that our patients receiving ECLS experienced a systemic inflammatory response syndrome known to affect the microcirculation. The need for ECLS support occurs after a profound cardiopulmonary collapse. This severe circulatory failure is associated with either ischemic or reperfusion organ injury or alterations in the inflammatory response leading to complement, neutrophil, platelet, and cytokine activation [32]. ECLS produces similar responses, and this undoubtedly compounds the initial insult [33]. Initiating ECLS before complete haemodynamic collapse is ideal, but in most cases the insult has already occurred. Even though ECLS restores macrohaemodynamics, microvascular dysfunction could persist and lead to organ failure. Recently, different therapies have been studied for septic patients in order to observe the response of the microcirculation evaluated by VOT parameters [34, 35, 36].

Finally, the effect of temperature is a matter of concern since we measured the muscle oxygenation at a peripheral site. It could be influenced by the vasoconstriction due to hypothermia. During sepsis, Creteur et al observed no correlation between reperfusion slopes and temperature [9]. However, patients remained in a narrow range of temperature. In our cohort, patients were more frequently hypothermic in the first hours after initiation of ECLS. Patient requiring ECLS for cardiac arrest were treated by moderate hypothermia for brain protection during the first 12 hours [12]. Patients also experienced moderate hypothermia during the initial hours because ECLS was rarely implemented in the ICU. Rapid temperature drops can occur before adding the heat exchanger into the circuit. No correlation was noted

between StO<sub>2</sub> and temperature in our study. Putman et al found no influence of temperature on basal StO<sub>2</sub> during cardiopulmonary bypass in cardiac surgery [37]. For the VOT slopes, we observed a weak correlation ( $r= 0.31$ ) between reperfusion slopes and temperature. Reperfusion slopes had a tendency to be lower when patient were moderately hypothermic. One could argue that temperature might have an influence on reperfusion slopes in moderate hypothermia. However, patients with the lowest temperature in our cohort are mainly post cardiac arrest ECLS, known to induce a severe endothelial dysfunction [38]. Furthermore, reperfusion slopes were significantly lower for non-survivors at H24, whereas temperature was the same between the two groups at this time. We cannot draw any conclusions in this study because it has not been designed to study the influence of temperature on StO<sub>2</sub> and VOT parameters.

### **Study limitation**

The first major limitation is the small number of patients included in our study. Furthermore, 8 deaths occurred by day 7, which is consistent with results from prior epidemiologic studies on ECLS survival complicated by multiple organ dysfunction (33 % mortality rate). The small number of non-survivors gives a limited power for statistical analysis between survivors and non-survivors. This limited number prevents us from drawing any definitive conclusion. The data suggest that VOT could be of interest for exploring the microcirculation and capillary dysfunction for patient under ECLS. This finding would need to be confirmed on a larger population.

The second limit is the heterogeneity of the study population. The purpose was to explore muscle StO<sub>2</sub> with VOT for patients receiving ECLS since it had never been done. So we decided to include a wide range of ECLS indications to have a first overview of StO<sub>2</sub> and VOT during ECLS. One could argue that including post cardiac arrest ECLS might be a bias in our study since it is probably a situation of ischemic-reperfusion with a severe endothelial dysfunction compared to other types of cardiogenic shock needing ECLS [38]. Looking at the 4 survivors by day 7 following a cardiac arrest, all had improved their reperfusion slopes. VOT seems pertinent even in this extreme hypoperfusion situation. Further research needs to be conducted on homogenous patient population receiving ECLS.

The third limit is the decision to place the probe on the hand without the arterial catheter to avoid any disturbance of thenar perfusion. After recovery of cardiac function during ECLS, it is possible that the Harlequin syndrome can alter the oxygenation on the



right hand. The side of the arterial catheter was left to the discretion of the intensivist so the probe could have been placed on either side. It is reasonable to think that the cardiac function has not yet fully recovered during the early phase of ECLS for severe cardiogenic shock, so the risk of a Harlequin syndrome would appear low in our study population.

## **VI – CONCLUSION**

Similar to other shock states, therapeutic efforts for patients receiving ECLS should address the microcirculation. NIRS applied to muscle has been recently developed to monitor the microcirculation at the bedside in intensive care. In this pilot study, we showed that muscle NIRS is feasible under ECLS. Basal StO<sub>2</sub> does not seem to provide any pertinent information for the monitoring of tissular perfusion in our cohort. Even though patients were receiving ECLS with non-pulsatile flow, muscle oxygen consumption and microvascular reactivity after an ischemic challenge estimated by muscle StO<sub>2</sub> improved over time and had a tendency to evolve differently between survivors and non-survivors. Muscle StO<sub>2</sub> with VOT could be a novel research tool for improving the management strategy of patients requiring ECLS by facilitating the optimisation of the microcirculation with appropriate modifications of ECLS pump flow, drugs and fluid administration.

## **Evaluation de la StO<sub>2</sub> musculaire au cours de la phase précoce d'une assistance circulatoire extra-corporelle**

### **RESUME**

Les patients traités par assistance circulatoire extra-corporelle ou ExtraCorporeal Life Support (ECLS) pour choc cardiogénique réfractaire sont à risque d'hypoperfusion tissulaire, processus physiopathologique qui conduit à des défaillances d'organes et au décès. L'élément clé de la réanimation initiale est donc la détection précoce et la correction de l'ischémie tissulaire. Or les marqueurs habituels hémodynamiques (pression artérielle, fréquence cardiaque, débits cardiaque et urinaire) et biologiques (lactate, pH artériel) sont pris en défaut pour apprécier l'ischémie tissulaire et ne prédisent pas correctement la survenue d'une défaillance d'organe. Il est actuellement possible de mesurer l'oxygénation tissulaire par la saturation tissulaire en oxygène (StO<sub>2</sub>) dans le muscle thénar, selon le principe de la spectroscopie en proche infrarouge, ou Near-infrared spectroscopy (NIRS). Un test d'occlusion artérielle peut y être associé. L'utilité de ces mesures est actuellement évaluée pour la réanimation du choc septique et en traumatologie grave ; sa pertinence chez les patients traités par ECLS pour un choc cardiogénique est inconnue.

Après accord du CPP, nous avons donc conduit une étude prospective observationnelle de soins courants afin de caractériser la StO<sub>2</sub> musculaire au cours de la phase précoce d'une ECLS pour choc cardiogénique réfractaire aux traitements médicaux.

Les patients étaient inclus 2 heures après la pose de l'ECLS, avec ou sans arrêt cardio-respiratoire préalable. La StO<sub>2</sub> était mesurée par un spectrophotomètre tissulaire en proche infrarouge (*Inspectra Model 650, Hutchinson Technology Inc., Hutchinson, MN, USA*) sur l'éminence thénar pendant 48 heures. Un test d'occlusion artérielle 50 mmHg au dessus de la pression artérielle systolique pendant 3 minutes avec un brassard à tension a été réalisé à H2, H12, H24 et H48. Les pentes d'occlusion, de reperfusion et l'aire sous la courbe de la réponse hyperhémique étaient alors calculées par un logiciel (*Inspectra analysis programme version 4.0 running on MatLabs 7.0 software, Math Works Inc, Natick, Mass, USA*). Au même temps, des paramètres hémodynamiques (PAM, débit de pompe, doses d'amines) et biologiques (saturation veineuse centrale, lactates, gaz du sang artériel, taux d'hémoglobine) étaient recueillis.

L'analyse statistique pour l'évolution temporelle a été conduite par un modèle linéaire à effet aléatoire. Les corrélations ont été réalisées avec le même modèle en regroupant les données de H2, H12, H24, H48. Un test non-paramétrique de Mann-Whitney était réalisé pour les comparaisons intergroupes. Le seuil de significativité a été fixé à 0,05.

25 patients [22H/3F ; 60,8 ans (30-80)] ont été inclus. 8 patients étaient décédés à J7. La StO<sub>2</sub> n'a pas évolué au cours du temps alors que les lactates et le pH ont diminué ( $p < 0,05$ ). Aucune différence significative pour la valeur de StO<sub>2</sub> à chaque temps entre le groupe des survivants et des non survivants à J7 n'a été décelée. Quant aux paramètres d'occlusion artérielle dynamique, une augmentation des pentes d'occlusion et de reperfusion au cours du

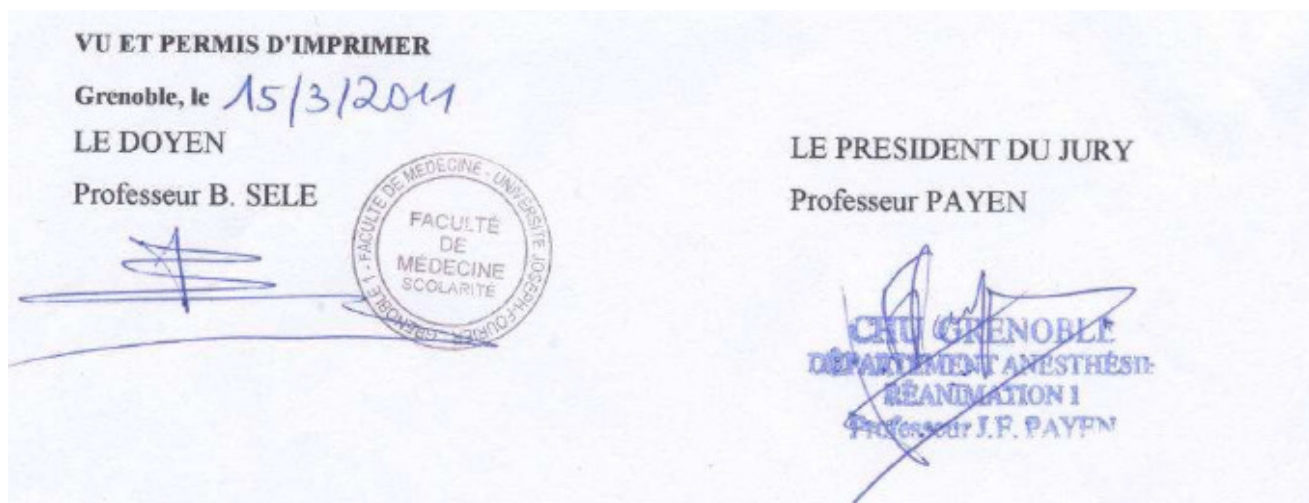
temps ( $p < 0,05$ ) est observée. De plus, nous retrouvons une différence d'évolution significative des pentes d'occlusion

entre les survivants et les non survivants à J7 ( $p < 0,05$ ). La même tendance pour les pentes de reperfusion est notée mais sans atteindre la significativité ( $p = 0,088$ ). Les pentes de reperfusion sont significativement plus basses à H24 ( $p = 0,03$ ) et H48 ( $p = 0,02$ ) pour les non survivants à J7.

Dans notre cohorte, la StO2 basale ne semble pas être un marqueur pertinent pour détecter précocement une ischémie tissulaire périphérique. Une amélioration du métabolisme musculaire sur l'effectif global, reflétée par la pente d'occlusion, au cours du temps sous ECLS est observée. Chez les non survivants, ces pentes d'occlusion ne semblent pas s'améliorer au cours du temps. La même tendance est observée avec les pentes de reperfusion, témoignant d'une amélioration de la capacité de recrutement capillaire après une épreuve d'ischémie. En comparant les survivants et les non survivants à J7, on observe une différence significative pour les pentes de reperfusion à H24 et H48, alors qu'aucun autre des paramètres hémodynamiques et biologiques n'a pu les discriminer.

L'exploration microcirculatoire au lit du patient en état de choc reste un axe de recherche fondamental pour limiter l'ischémie tissulaire responsable de défaillance multiviscérale même si la macrocirculation est restaurée. La microcirculation sous ECLS est encore mal connue. Notre travail montre la faisabilité de la StO2 musculaire avec un test dynamique au cours d'une ECLS. Alors que la StO2 basale ne semble pas apporter d'indice d'hypoperfusion, notre étude montre une amélioration des tests d'occlusion vasculaires, reflétant le métabolisme musculaire et la capacité de recrutement capillaire, pour des patients sous ECLS malgré un débit non pulsatile. De plus, seule la capacité de recrutement capillaire à H24 semble discriminer les non survivants à J7 alors que les paramètres d'hypoperfusion tissulaire classiques, comme le lactate, ne le font pas.

Cette étude observationnelle montre la faisabilité de la NIRS musculaire sous ECLS pour étudier la microcirculation. Elle ouvre la voie à de futures études cliniques évaluant l'effet de nos thérapeutiques sur la microcirculation sous ECLS.



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## **ANNEXE 1 : FORMULAIRE D'INFORMATION**

**Titre de l'étude : Mesure de l'oxygénation tissulaire (StO<sub>2</sub>) au cours des 48 premières heures d'une assistance circulatoire extra-corporelle (ECMO) pour choc cardiogénique.  
Etude de soins courants**

Madame, Monsieur,

L'état de santé de votre proche nécessite à l'heure actuelle une prise en charge médicale dans l'unité de réanimation cardio-vasculaire et thoracique du CHU de Grenoble. Parmi les soins qui lui sont prodigués figurent ceux qui permettent de maintenir un état circulatoire par la mise en place d'une assistance circulatoire extra-corporelle (ECMO). Ce traitement complexe est justifié quand les autres traitements habituels de la défaillance cardiaque ont échoué. Pour évaluer l'efficacité de l'ECMO, nous disposons de nombreux paramètres, cliniques et biologiques, mais ils peuvent être pris en défaut pour détecter précocement une insuffisance circulatoire périphérique.

Depuis quelques années, un appareil permet de mesurer la saturation tissulaire en oxygène (StO<sub>2</sub>) au niveau des muscles du pouce, et est disponible pour les équipes de réanimation. Le capteur collé sur la peau mesure en continu le degré d'oxygénation de ces muscles, et est relié à un moniteur doté du marquage CE. Ainsi, la mesure de StO<sub>2</sub> détecte rapidement une baisse locale d'oxygénation tissulaire, ce qui peut être un bon reflet de ce qui se passe dans la circulation générale. Des études ont été réalisées avec succès chez des patients ayant une infection grave (sepsis) et en traumatologie. Nous vous proposons d'évaluer l'intérêt de la mesure de StO<sub>2</sub> pour surveiller l'efficacité de l'ECMO. Notre hypothèse est que la mesure de StO<sub>2</sub> détecte une insuffisance circulatoire périphérique au cours de l'ECMO, de manière plus précoce que les paramètres habituels de surveillance. Les paramètres de surveillance sont consignés sur des fiches. Il s'agit donc d'une étude de soins courants. Cette étude est réalisée conformément à la Loi 2004-806 du 9 août 2004. Elle n'est proposée qu'aux patients affiliés à la sécurité sociale.

L'investigateur principal de cette étude est le Docteur Damien Bedague, Pôle d'Anesthésie-Réanimation, CHU Grenoble. Un comité de Protection des Personnes (CPP Sud Est II) a donné un avis favorable en date du 22/04/2009.

Nous garantissons que toutes les informations concernant votre proche resteront strictement confidentielles. Elles ne seront utilisées que par l'équipe médicale, les personnes dûment mandatées et par des représentants des autorités administratives. Les données recueillies seront informatisées. La base de données informatique sera réalisée selon les critères exigés par la commission nationale informatique et liberté. Vous pourrez exercer votre droit d'accès et de rectification de toutes les données concernant votre proche prévu par la loi informatiques et liberté auprès d'un médecin de votre choix. A tout moment, vous pouvez refuser le traitement des données de votre proche, quelles que soient vos raisons et sans supporter aucune responsabilité. Le fait de ne plus participer à cette recherche ne portera pas atteinte aux relations avec le médecin investigateur, ni compromettre les soins qui seront prodigués. Le médecin investigateur pourra interrompre la participation à l'étude s'il juge que cela est dans l'intérêt du patient.

## Annexe 2 : Cahier d'observation des patients

**Mesure de l'oxygénation tissulaire (StO<sub>2</sub>) au cours des 48 premières heures d'une assistance circulatoire extra-corporelle (ECMO) pour choc cardiogénique**

Nom (1 lettre) /\_/ Prénom (1 lettre) /\_/

Date de naissance /\_/ /\_/ /\_/

Sexe  F  M

Poids (Kg) : /\_/ /\_/ (estimé ou réel)

Taille (cm) : /\_/ /\_/

Antécédents :

Pose ECMO (H0) Date /\_/ /\_/ /\_/

Heure /\_/ / h /\_/ / mn

Indication ECMO :

Devenir à 3 jours :	vivant : OUI/NON	date du décès :
	ECMO : OUI/NON	Cause décès :
		date du sevrage :
Devenir à 7 jours :	vivant : OUI/NON	date du décès :
	ECMO : OUI/NON	Cause décès :
		date du sevrage :

	H 2	H 12	H 24	H 48
<b>PAS/PAD</b>				
<b>PAM</b>				
<b>FC</b>				
<b>Température (°C)</b>				
<b>Diurèse (ml/h)</b>				
<b>Débit sang ECMO</b>				
<b>Débit gaz ECMO</b>				
<b>EER UF</b>				
<b>DOBU (ml/h)</b>				
<b>NORADRE (mg/h)</b>				
<b>ADRE(mg/h)</b>				
<b>Cristalloïdes (ml)</b>				
<b>Colloïdes (ml)</b>				
<b>Transfusion (n CG)</b>				
<b>PSL (PFC ml/Plaq UI)</b>				



<b>PaO2 /FiO2</b>				
<b>PaCO2</b>				
<b>pH artériel</b>				
<b>SaO2</b>				
<b>SvcO2</b>				
<b>Lactate artériel</b>				
<b>BE</b>				
<b>Hémoglobine</b>				
<b>Hématocrite</b>				
<b>Plaquettes</b>				
<b>TP-TCA-Fibrinogène</b>				
<b>Protides</b>				
<b>Glycémie</b>				
<b>Créatinine</b>				
<b>Bilirubine</b>				
<b>TGO/TGP</b>				
<b>CRP</b>				
<b>Procalcitonine</b>				
<b>Score SOFA</b>				
<b>IGS II</b>				
<b>StO2 base</b>				
<b>StO2 min (3min occlusion)</b>				
<b>StO2 max (levée occlusion)</b>				
<b>Pente StO2 descente (% O2/s)</b>				
<b>Pente StO2 remontée (% O2/s)</b>				
<b>Delta StO2</b>				
<b>Delta THI</b>				
<b>Temps de réponse</b>				
<b>Aire sous la courbe désaturation</b>				
<b>Aire sous la courbe resaturation</b>				

### Annexe 3: Score SOFA (sequential organ failure assessment)

	1 point	2 points	3 points	4 points
Respiratoire :				
PaO <sub>2</sub> /FiO <sub>2</sub> (mmHg)	<400 et/ou VM	<300 et/ou VM	<200 et VM	<100 et VM
Cardiovasculaire :				
(amines en µg/kg/min)	PAM <70 mmHg	Dopa <5 ou Dobu	Dopa >5 ou Ad/Nad <0,1	Dopa >15 ou Ad/Nad >0,1
Neurologique :				
Score Glasgow	13-14	10-12	6-9	<6
Rénal :				
créat (µmol/l) ou diurèse	110-170	171-299	300-440 ou <500 ml/j	>440 ou <200 ml/j
Hépatique :				
bilirubine (µmol/l)	20-32	33-101	102-204	>204
Coagulation :				
plaquettes (G/l)	<150	<100	<50	<20

VM, ventilation mécanique. Dopa, dopamine. Dobu, dobutamine. Ad, adrénaline. Nad, noradrénaline. Créat, créatininémie.

Le score SOFA est la somme arithmétique de chaque défaillance d'organe, soit une étendue de 0 à 24 points.



## SERMENT D'HIPPOCRATE

Qui dias memorem laudes, repetamque fideles  
Ingenij dotes, Hippocratisque decus.  
Democriti auditor Phœbea, ô, Coë propago,  
Certius an quis te tradidit artis opes?

*En présence des Maîtres de cette Faculté, de mes chers condisciples et devant  
l'effigie d'HIPPOCRATE,*

*je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans  
l'exercice de la Médecine.*

*Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au  
dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.*

*Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma  
langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre  
les mœurs, ni à favoriser le crime.*

*Je ne permettrai pas que des considérations de religion, de nation, de race, de parti  
ou de classe sociale viennent s'interposer entre mon devoir et mon patient.*

*Je garderai le respect absolu de la vie humaine.*

*Même sous la menace, je n'admettrai pas de faire usage de mes connaissances  
médicales contre les lois de l'humanité.*

*Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants  
l'instruction que j'ai reçue de leurs pères.*

*Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.*

*Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.*

