Continuous monitoring of cerebral autoregulation in children supported by extracorporeal membrane oxygenation- a pilot study.

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Keywords: ECMO, cerebral autoregulation, acute neurological event, children

Word count: manuscript (3181 words); abstract (315 words)

Tables and figures : 2 tables, 4 figures, 1 Supplemental Digital Content-Figure, Supplemental Digital Content-Table

Trial Registration: ClinicalTrials.gov (NCT04282525, February 21, 2020) https://clinicaltrials.gov/ct2/results?cond=&term=NCT04282525&cntry=&state=&city=&dist=

Details page

1) We confirm that manuscript complies with all instructions to authors

2) We confirm that authorship requirements have been met and the final manuscript was approved by all authors

3) We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal

4) We confirm adherence to ethical guidelines as mentioned in the manuscript

5) Conflicts of interest

Dr. Joram has nothing to disclose.

Dr. Beqiri has nothing to disclose.

Dr. Pezzato has nothing to disclose.

Dr Moscatelli has nothing to disclose.

Dr. Robba has nothing to disclose.

Dr. Liet has nothing to disclose.

Dr. Chenouard has nothing to disclose.

Dr. Bourgoin has nothing to disclose.

Dr. Czosnyka reports personal fees from Cambridge Enterprise Ltd, UK, during the conduct of the study;

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Dr Léger has nothing to disclose.

Dr. Smielewski reports and receives part of licensing fees for the brain monitoring software ICM+ (Cambridge Enterprise Ltd, Cambridge, UK) used in this project.

Abstract (315 wds)

Objective

Cerebral Autoregulation (CA) impairment may pose a risk factor for neurological complications among children supported by Extra-Corporeal Membrane Oxygenation (ECMO). Our first objective was to investigate the feasibility of CA continuous monitoring during ECMO treatment and to describe its evolution over time. The second objective was to analyze the association between CA impairment and neurological outcome.

Design

Observational prospective study.

Patients and setting

Twenty nine children treated with veno-arterial or veno-venous ECMO in the PICU of Nantes University Hospital, France and the PICU of the IRCCS Giannina Gaslini Institute in Genoa, Italy.

Measurements

A correlation coefficient between the variations of regional cerebral oxygen saturation (rSO2) and the variations of mean arterial blood pressure (MAP) was calculated as an index of CA (cerebral oxygenation reactivity index, COx). A COx > 0.3 was considered as indicative of dysautoregulation. COx – MAP plots were investigated allowing determining optimal MAP (MAPopt) and limits of autoregulation: lower (LLA) and upper (ULA). Neurological outcome was assessed by the onset of an acute neurologic event (ANE) after ECMO start.

Results

We included 29 children (median age 84 days, weight 4.8 kg). MAPopt, LLA and ULA were detected in 90.8 % (84.3-93.3) of monitoring time. Mean COx was significantly higher during day 1 of ECMO compared to day 2 (0.1 (0.02-0.15) vs 0.01 (-0.05-0.1), p=0.002). Twelve children experienced ANE (34.5%). The mean COx and the percentage of time spent with a COx > 0.3 were significantly higher among ANE+ compared to ANE- patients (0.09 (0.01-0.23) vs 0.04 (-0.02-0.06), p=0.04 and 33.3% (24.8-62.1) vs 20.8% (17.3-23.7) p=0.001). ANE+ patients spent significantly more time with MAP below LLA (17.2% (6.5-32.9) vs 5.6% (3.6-9.9), p=0.02) and above ULA (13% (5.3-38.4) vs 4.2% (2.7-7.4), p=0.004) respectively.

Conclusions

CA assessment is feasible in pediatric ECMO. The first 24 hours following ECMO represent the most critical period regarding CA. Dysautoregulation is significantly more severe among patients who experience ANE.

Introduction

Extra-corporeal membrane oxygenation (ECMO) is a life support therapy for critically ill children presenting severe respiratory or hemodynamic failure or during cardiac arrest. These patients present a high risk of developing ischemic or hemorrhagic neurologic complications which lead to a significant morbidity and represent a substantial risk factor of mortality in this population *(1,2)*.

Cerebral autoregulation (CA) is a physiological protective mechanism aimed to maintain steady cerebral blood flow (CBF) over changes of mean cerebral perfusion pressure (CPP). In some cases mean arterial pressure (MAP) is considered instead of CPP, when intracranial pressure (ICP) is low and stable or cannot be monitored *(3)*. Even if CBF is not always directly monitored at the bedside, several surrogates can be used and a wide variety of indices of correlation between the variations of these surrogates and CPP or MAP have been validated *(4)*. In particular, in critically ill children, monitoring of the regional cerebral oxygen saturation (rSO2) is routinely available using near infrared spectrometry (NIRS). rSO2 is widely believed to reflect CBF slow fluctuations (0.005 to 0.05Hz), and the derived CA index is called Cerebral Oxygenation index (COx) *(5)*. In adults and children, CA may be disturbed in varying conditions including traumatic brain injury (TBI), perinatal asphyxia, cardiac surgery, cardiac arrest or sepsis and impaired CA is usually associated with unfavorable outcome *(4,6–10)*. Furthemore, some studies in healthy newborn lambs have shown an impact of ECMO itself on CA *(11,12)*.

In this overall context, CA impairment in critically ill patients treated by ECMO may be a key factor in the genesis of neurological complications. Recent preliminary studies using different methods have suggested an association with CA disorders and neurological outcome among children supported by ECMO *(13–15)*.

In this context, the aim of our pilot study was to investigate the feasibility of continuous monitoring of CA in children supported by ECMO and to descriibe its evolution overtime and its association with neurological outcome.

Methods

Study design

This prospective observational study was conducted from July 2018 to September 2019 in the respectively 12-bed and 20-bed surgical and medical Pediatric Intensive Care Units (PICU) of the University-affiliated hospital in Nantes, France and the IRCCS Giannina Gaslini Institute in Genoa, Italy.

Patients

Patients from 0 to 15 years treated by veno-arterial (VA) or veno-venous (VV) ECMO for hemodynamic or respiratory failure or during cardiac arrest resuscitation were included. The study was approved by the local Ethics Committees. Information of the parents was provided before inclusion. The only exclusion criterion for was a parental refusal. Clinical informations on medical history, clinical and biological parameters at PICU admission and during the PICU stay were collected prospectively.

Patient management under ECMO

Patients were treated according to the local practice of each center. After surgical or percutaneous cannulation, all the patients were placed on centrifugal pumps (Deltastream, Medos®, Germany, for Nantes and Centrimag, Thoratec Corporation®, Pleasanton, USA, for Genoa). For VA ECMO, cannulation was central through the ascending aorta and the right atrium, or peripheral through right carotid artery and right internal jugular vein or through femoral vessels depending on the indication and the age of the patient. For VV ECMO,

cannulation was through right internal jugular vein using double lumen cannulae (Avalon Elite®, Maquet, Germany) or through femoral vein and right internal jugular vein. Membrane oxygenator and circuitry were changed when fibrin deposition or thrombi had deleterious effects on blood oxygenation, platelet count or blood fibrinogen level decreased significantly or significant intravascular hemolysis appeared. In the two centers, heparin was the anticoagulation drug of choice. After a loading dose (50 to 100 UI/kg) at the time of cannulation, all patients were continuously infused with unfractionated heparin and the dose was adapted at least once a day according to the anti-Xa activity (targeting 0.3 to 0.5). Antithrombin III and platelet count measured at least once a day were maintained above 70% and 50 000/mm^3 respectively.

All children were sedated with a combination of midazolam and morphine, fentanyl or sufentanyl. Ketamine and dexmedetomidine were added if clinically indicated.

Arterial blood gas analysis was performed during the first hour following ECMO start and thereafter at least twice a day. Oxygenation was primarily managed adjusting FiO2 on the ECMO blender, targeting SpO2 from 88 to 97%. Gas flow in the blender was settled according to the blood gas measurement, targeting pH 7.30 to 7.45 and PaCO2 35 to 45 mmHg.

Autoregulation monitoring

Routine hemodynamic and cerebral monitoring devices were used for the study. The only project-specific addition to the standard monitoring setup was calculation of CA, blinded for all the clinicians including radiologists. Arterial blood pressure (ABP) was continuously monitored from an indwelling radial or femoral arterial catheter (MX700 for Nantes, MX800 for Genoa, Phillips®, Netherlands). NIRS pediatric sensors were placed at least on the left forehead (bilaterally in some patients) and rSO2 was continuously measured (INVOS 5100C, Medtronic®, Ireland). All signals were collected digitally, resampled at a frequency of 100 Hz and integrated using a laptop computer with ICM+ software (https://icmplus.neurosurg.cam.ac.uk, University of Cambridge, Cambridge Enterprise Ltd, Cambridge, UK). The same software was used to process ABP and rSO2 waveforms retrospectively as follows. Only the monitoring of left rSO2

and periods corresponding to the ECMO run were selected. For patients who experienced brain death, only monitoring prior to the clinical diagnosis of brain death was considered. Artefacts of ABP and rSO2 were manually identified and excluded for further analysis. MAP was calculated as the 10sec time averaged value of ABP. CA was assessed with the COx index, which uses variations in the rSO2 signal as a surrogate of changes in CBF. COx was calculated as a moving correlation coefficient between MAP and the mean rSO2 (thus filtering out high-frequency waves from pulse and respiration) from 300-s duration data segments, thereby utilizing 30 data points for each COx calculation, and was updated every minute. In case of CA impairment, COx approaches 1, indicating that the CBF is blood pressure passive, while when MAP is within the limits of CBF autoregulation, COx decreases. However, the absolute COx cutoff for CA impairment is not entirely established, especially in this particular condition, but is likely between 0.3 and 0.5 (5,16). We have followed (9) and chose the value of 0.3 as the autoregulatory threshold. With that, several different summary (per-patient) metrics of CA could be calculated including the mean value, the percentage time spent with a COx above 0.3, the area under the curve (AUC) of COx>0.3 during time. As CA monitoring duration differed from patient to patient, we normalized AUC by dividing it by the duration of the recording expressed in hours. Cox values were averaged for each day after ECMO start.

Assessment of optimal MAP, lower and upper limits of autoregulation

Optimal MAP (MAPopt), lower and upper limits of autoregulation (LLA and ULA respectively) were calculated using a multiwindow approach inspired by Depreitere *et al*., subsequently implemented in ICM+, investigated in a retrospective traumatic brain injury data set (17,18), and recently adjusted for prospective bedside use by Beqiri *et al.* (19). In this study, we adapted the algorithm to our clinical population and to the signals available, therefore only an overview of the approach is given below, highlighting the main differences with the algorithm as described by Beqiri *et al*. At each time point, 36 COx-MAP plots were generated from past data windows of increasing duration ranging from 2 to 8 hours, using incremental steps of 10 min. The data points were divided into groups corresponding to MAP bins of 2 mmHg length within 20–120

mmHg range of MAP values and where each MAP bin must represent at least 2% of the total data count. For each bin, mean (Fisher transformed) COx and MAP values were used to fit a second order polynomial describing the theoretical U-shape, with its nadir determining MAPopt, and with LLA and ULA defined by the MAP values at COx = 0.3 (figure 1). This process was repeated for each progressively longer data window. Individual results were filtered using a set of quality control criteria and the accepted values were combined using weighted average operation. The calculations were repeated every minute and the resulting time series were finally subjected to an exponentially weighted average filter of 2 hours of duration forming the MAPopt, LLA and ULA time trends. The missing data limit of the calculation was set at 75%, therefore at least 2 hours of data were necessary to generate the first MAPopt value. As shown in supplemental digital content-figure 1, this method allowed building continuous curves of MAPopt, ULA and LLA. The feasibility of the methodology was assessed using a metric of the percentage of MAP monitored time when MAPopt, LLA and ULA were available. The difference between median MAP and MAPopt was calculated continuously (ΔMAPopt = median MAP-MAPopt). The percentage of time spent with a MAP more than 5 mmHg below (ΔMAPopt<-5mmHg), more than 5 mmHg above (ΔMAPopt>5 mmHg), or close to (ΔMAPopt = -5 to 5 mmHg) MAPopt was calculated for each patient. Percentage of time below LLA and above ULA and AUC of MAP below LLA and above ULA were also calculated and these values were averaged for each day after ECMO start.

Neurological outcome

No specific clinical or neuroimaging assessment protocol was introduced during the study. For neonates and children with open fontanels, head ultra-sound (HUS) was performed during the pre-ECMO period if possible, every day during the ECMO run and at least once after ECMO discharge. When available, patients in the two PICUs were monitored by continuous amplitude integrated electroencephalography (aEEG) and/or discontinuous electroencephalography (EEG). For all patients, in case of any ongoing concern of their neurological status, an emergent computed tomography (CT) while on ECMO and/or post ECMO magnetic resonance imaging

(MRI) could be performed. Patient outcome was assessed by the onset of any Acute Neurologic Event (ANE) during ECMO support. Patients presenting hemorrhagic or ischemic stroke and/or clinical or electrical seizure and/or brain death were considered ANE+ (20,21). The timing of ANE onset was defined as the delay between ECMO start and the first clinical and/or electrical manifestation corresponding to ANE.

Statistical analysis

Baseline characteristics were reported as median (interquartile range) or mean (standard error of the mean) and n (%) for quantitative and qualitative variables, respectively. Inter-group comparisons were performed by using the Mann–Whitney *U* test for continuous variables and Chi-square test or Fisher's test when appropriate for categorical variables.The Wilkoxon signed-rank test was used to compare values between days of ECMO. p value of less than 0.05 was considered as significant. Statistical analysis was performed using SPSS 19 software (Chicago, IL).

Results

Baseline characteristics and outcome

All the 29 screened patients were included during the study period as no patient met the exclusion criterion. These 29 patients underwent 31 ECMO runs (including 22 VA runs and 9 VV runs) as 2 patients were converted from VA to VV ECMO. At least one neuroimaging procedure was performed in 25/29 (86%) patients (HUS n=17, CT n=7, MRI n=13) and 24/29 (82.8%) children were monitored by continuous aEEG, completed by discontinuous conventional EEG if necessary. Twelve of the 29 patients (41.4%) were considered ANE+. Baseline characteristics of the whole population and according to the ANE+/ANE- status are described in table 1 and the case analysis summary of ANE+ patients is presented in table 2.

The 4 patients without neuroimaging presented no clinical or electrical neurological complication and were considered ANE- as the 5 patients without any EEG monitoring.

Autoregulation monitoring

Among the whole cohort, the median cerebral autoregulation monitoring time was 79.4 hours (44.8-115.2) corresponding to 65 % (43.4-89.8) of ECMO run duration. Absolute monitoring time and monitoring time related to the ECMO length were not different comparing ANE- and ANE+ patients (82hours (49.4-205) vs 66.1hours (43.6-111.6),p =0.53 and 51.9% (81.2-206) vs 73.3% (61-96.6), p=0.18). COx measurement was available in all the 29 monitored patients and MAPopt, LLA and ULA were available 90.8% (84.3-93.3) of monitoring time. As shown in supplemental Digital Content- table 1. CA metrics were not different comparing VA an VV ECMO runs.The evolution of Cox and of the percentage of time spent with a MAP below LLA and above ULA over ECMO run in the whole cohort are shown in figure 2. The results of CA metrics in the whole cohort and according to the ANE-/ANE+ status are presented in figure 3 and their evolution over time according to the neurological outcome in figure 4.

Discussion

We report an exploratory study focusing on CA monitoring in ECMO children. The first important result is that continuous CA monitoring at the bedside using routine monitoring devices is feasible. COx was available in all monitored patients and MAPopt, LLA and ULA were obtained in 90.8% of the monitored time using a Multi-Window approach. We report that the first 24 hours of ECMO represent the most critical period regarding CA. Children who developed ANE had higher COx and spent significantly more time above the autoregulatory threshold of COx>0.3 during ECMO run. MAP was below LLA and above ULA over longer time in ANE+ compared to ANE- patients, especially within the initial period after ECMO start.

In our cohort, the incidence of ANE was 34.5%. As a comparison, Hervey- Jumper *et al* reported an incidence of overall stroke of 13.1% among 31 335 ECMO patients in the US *(22)*.

This difference is largely due to the sensitivity of our outcome measure that includes clinical, electrophysiological and radiological neurological evaluations. In a recent study, among 70 children treated by ECMO and continuously monitored by EEG, 23% presented electroencephalographic seizures, close to what we have seen in our patients *(23)*. ANE has been previously used to compare critically ill adults and children of various ages and appears relevant for evaluating early overall neurological impairment *(20,21,24)*. This incidence may also be explained by the young age at cannulation (median age 84 days, 27.6% of neonates) and a high rate of patient cannulated after cardiac surgery (31%) which are well known risk factors for neurological complication under ECMO *(22)*.

Another controversial point is the choice of 0.3 as the COx cut-off as various cut-offs of COx and other CA indexes are used in the literature *(4)*. However, all the statistical analyses presented in this report were also performed with the cut-offs of 0.2 and 0.4 with comparable results (data not shown).

CA metrics were not different during VA or VV runs, with the limitation that only 9 VV ECMO runs were studied. This could be surprising as patients cannulated in VA ECMO are hemodynamically unstable and one can imagine that direct arterial perfusion by a non-pulsatile flow may have severe impact on CA. However, patients in VV ECMO also present risk factors of cerebral hemodynamic disruption like PCO2 and PO2 variations or sepsis and animal models have also shown impairment of CA during VV ECMO *(25)*.

In agreement with previous studies *(23,26)* our data suggest that mostly ANE occur within the first 24 hours after ECMO start. Our study adds that this period also represents the most critical time with regards with CA disorders. Interstingly, recent studies have reported the independant relationship between a large decrease of PCO2 immediately after ECMO start and the risk of cerebral damage *(27,28)*. In this context, all the data are consistent to conclude that this period requires particular attention in clinical practice and in further studies.

The triggers of CA deterioration are very challenging to investigate individually at the bedside. In particular, the specific impact of ECMO itself suggested by animal studies *(11,12)* is impossible to analyze with such studies. Indeed, before ECMO start, all these patients experienced severe

medical condition (cardiac arrest, associated TBI, septic shock, cardio pulmonary bypass, perinatal anoxo ischemia, etc) which are all well known risk factors of CA impairment *(4,6–10)*. Furthermore, as most ANE occur promptly after ECMO start, during the most critical period with regards of CA, their causal relationship remains unclear. Indeed, the timing of ANE is too imprecise to compare CA before and after its onset.

In such critically ill patients, neurological outcome is multifactorial and the primary cerebral insult caused by the underlying disease may have a very strong impact. However, the limitation of secondary injuries appears crucial and the control of CA regardless of its trigger represents an interesting candidate. In this context, like in other conditions, the MAP level, may be a key target. The association between low blood pressures and poor neurological outcome that we have shown, appears intuitive. Interstingly, our data also suggest a strong association between the time above ULA and the risk of ANE which is an unusual result comparing with CA studies in other conditions. As some studies have shown critical increase of MAP after ECMO onset, this appears as an underestimated potential secondary controllable factor *(29,30)*. In our study, the mean MAP within the first 24 hours was significantly higher among ANE+ patients. This result is interesting but needs to be considered with much caution as, even this was not statistically significant, the patients of the ANE+ group were slightly older. The impact of other candidates like PO2 and PCO2 variations, ECMO settings or sedative agents on CA need to be investigated. Subsequently, the following steps will be to investigate the ability of clinicians to improve CA at the bedside and, next, to improve outcome using CA-oriented therapy.

Limitations

First, the main limitation of this exploratory study is the small size of the cohort including different patients, ECMO modes and types of cannulation. Our preliminary results will need to be confirmed in larger cohorts and further study will need to focus on specific medical conditions and age groups. Secondly, CA monitoring was performed only within about two third of ECMO time, due to connection delay. Even this appears representative and clinically useful, this may be easily optimized by a better training of the teams to CA monitoring initiation. Furthermore,

this study reports only results issued from left rSO2, justified as all patients were monitored by almost left NIRS but only 19/29 had bilateral monitoring. However, Papademetriou *et al* have shown some differences regarding oxygenation between the two cerebral hemispheres among infants treated by ECMO *(31)*. Third, we report a univariate analysis of the association between CA metrics and neurological outcome as the small size of the cohort is a limitation for adjusting for suspected confounding factors. Finally, here we explore only the effect of MAP on CA, neglecting CPP. However, ICP may be raised is some of these patients (for example after cardiac arrest) and the investigation of ICP by non-invasive methods may be a key point to understand better CA disorders *(32,33)*.

Conclusion

Our study confirms the feasibility of monitoring cerebral autoregulation in paediatric patients supported by ECMO using routine clinical practice monitoring devices. The first 24 hours seem to be the most critical period with regards to dysautoregulation and an association was found between the CA deterioration and the incidence of ANE. Further studies are needed to understand better the underlying mechanisms of CA impairment under ECMO in order to imagine autoregulation-oriented MAP management in these patients.

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Figures

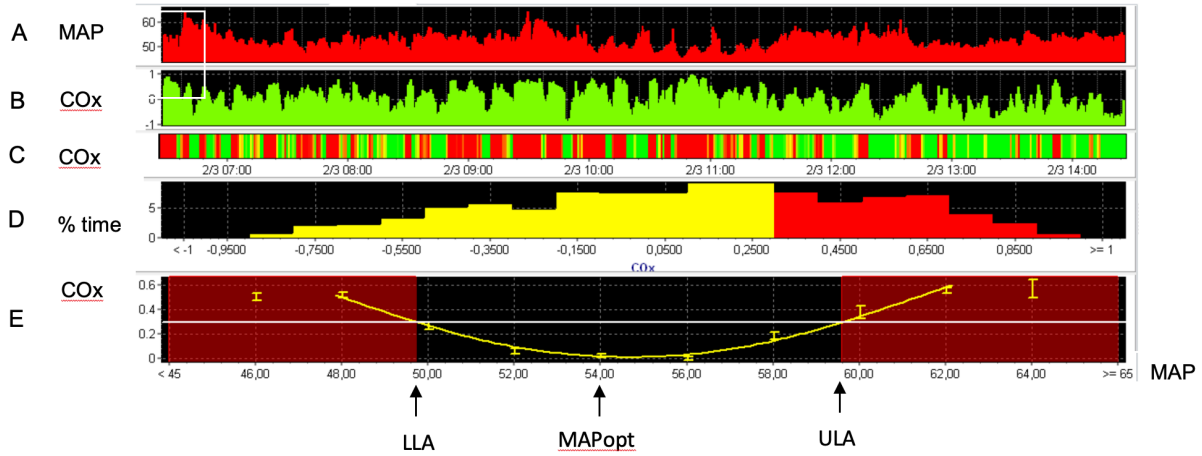


Figure 1. Screenshot of a 8 hour epoch of autoregulation monitoring in a one year old patient under ECMO. Chart A, evolution of MAP expressed in mmHg over time. Chart B, evolution of left COx over time. Chart C, risk chart whereby a negative COx is denoted by a green color, a COX between 0 and 0.3 by orange color and a Cox >0.3 (considered as critical) by red color. Chart D, percentage of time passed in each division of 0.1 of COx. The right part of the chart colored in red corresponds to the percentage of time passed in "critical zone" (COx>0.3). Chart E, COx values averaged (represented as mean and standard error) into bins of MAP spanning 2 mmHg. The horizontal white line represents the COx value of 0.3. U shape curve is fitted. As mentioned in the chart, the nadir of this curve (around 55 mmHg) represents the MAPopt for this period and the intersection between the U shape curve and the horizontal white line gives the LLA (around 49 mmHg) and the ULA (about 59 mmHg).
MAP, Mean Arterial Pressure; COx, Cerebral Oxygenation index; MAPopt, optimal MAP; LLA, lower limit of autoregulation; ULA, upper limit of autoregulation.

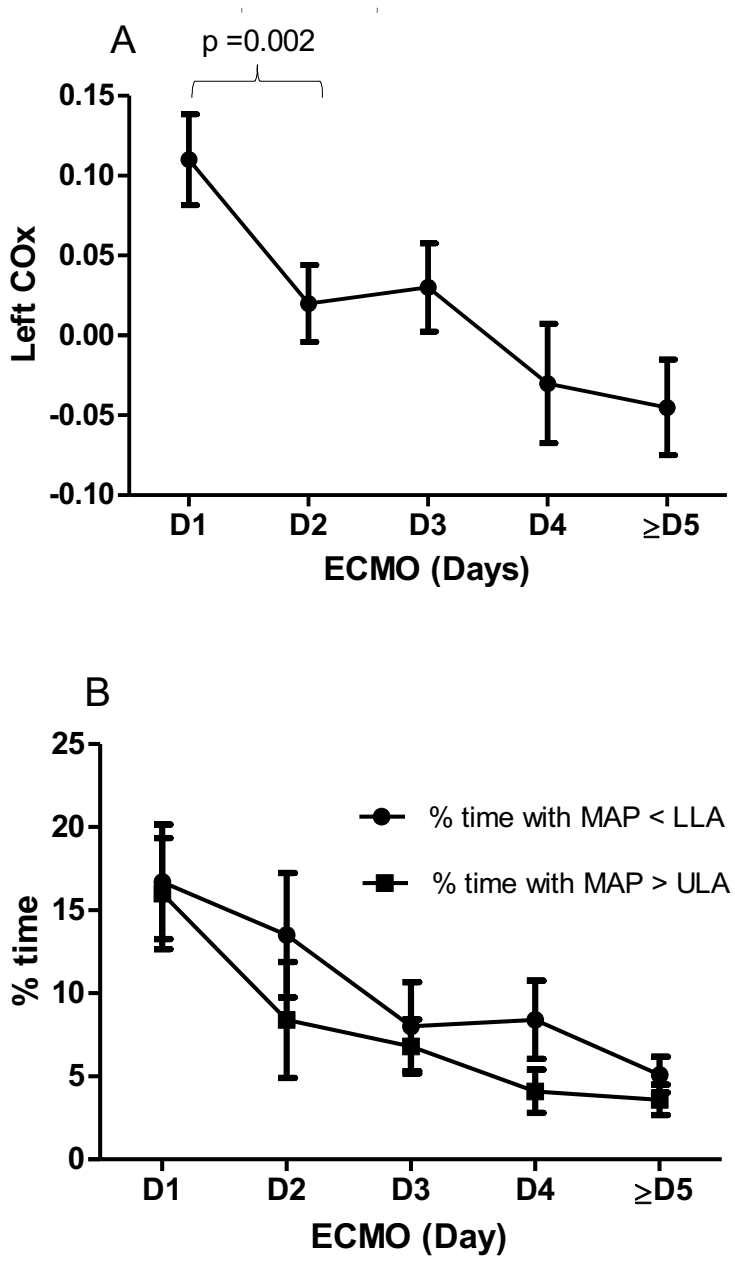


Figure 2. Evolution of cerebral autoreguilation metrics overtime after ECMO start in the whole cohort. Values represent mean values +/- SEM. The Wilcoxon signed-rank test was used to compare the values two by two. * $p<0.05$, considered as significant **A.** Evolution of Cox **B.** Evolution of the percentage of time spent with MAP below LLA and above ULA respectively.

COx, Cerebral Oxygenation index; MAP, Mean Arterial Pressure; LLA, lower limit of autoregulation; ULA, upper limit of autoregulation.

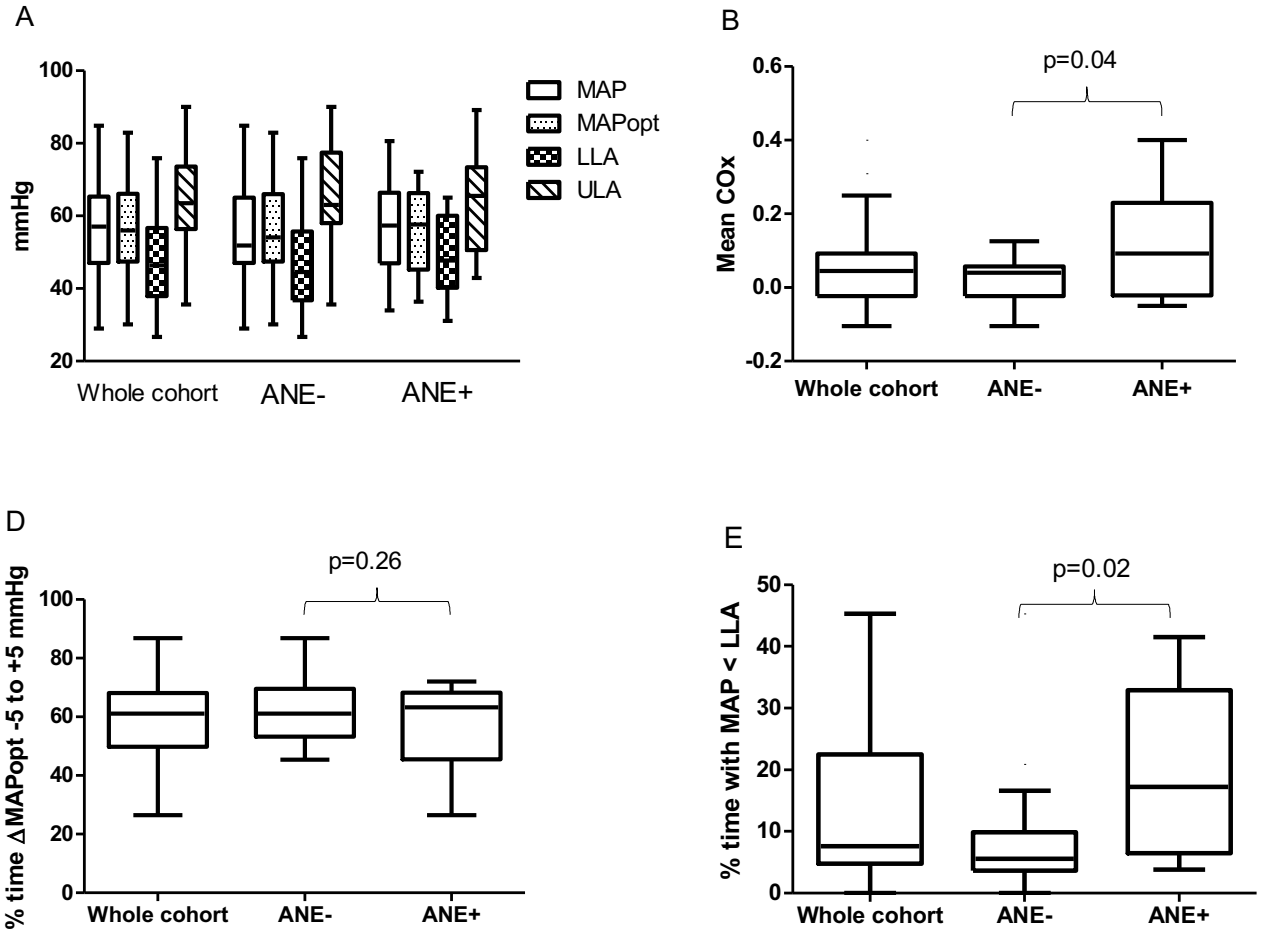


Figure 3. Autoregulation metrics in the whole cohort and according to neurological outcome during the whole ECMO run. **A**. mean MAP, mean MAPopt, mean LLA and mean ULA **B.** Mean Cox **C**. Percentage of time with Cox> 0.3 **D.** Percentage of time with MAP – MAPopt between -5 and +5 mmHg **E**. Percentage of time with MAP < LLA. **F**. Percentage of time with MAP >ULA.

Data are shown in box-and-whisker plots, indicating the median, interquartile range, and range. The Mann–Whitney test was used to compare the 2 groups of infants.

COx, Cerebral Oxygenation index; MAP, Mean Arterial Pressure; ΔMAPopt = median MAP-MAPopt; LLA, lower limit of autoregulation; ULA, upper limit of autoregulation.

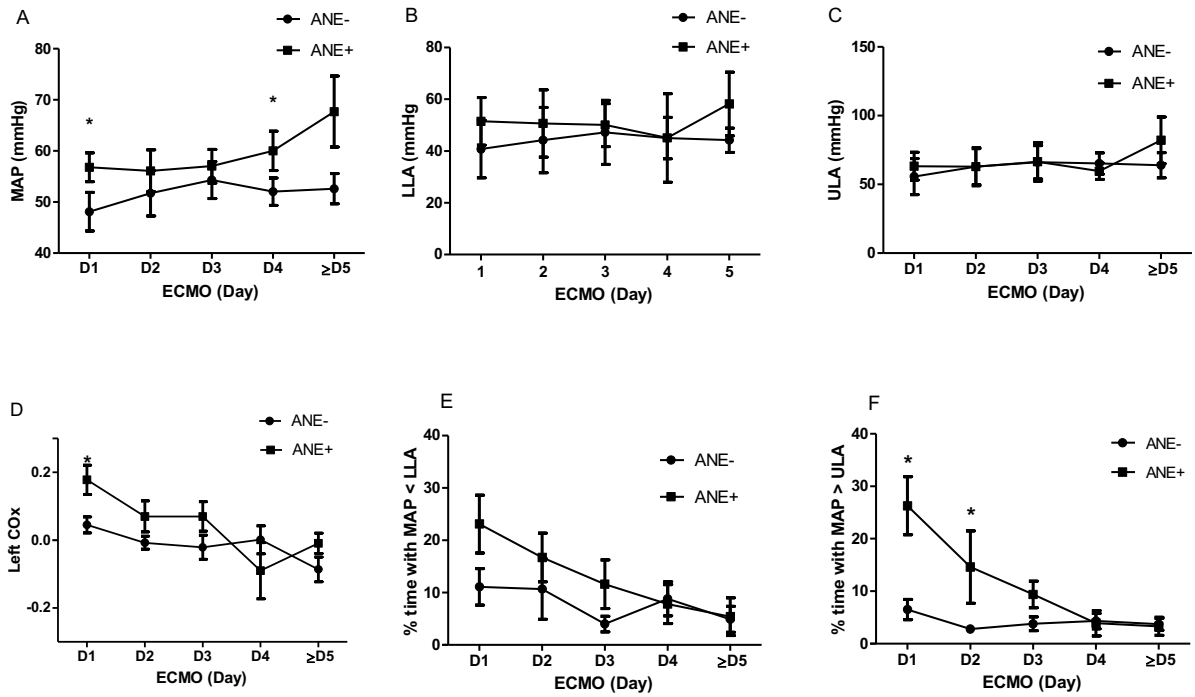
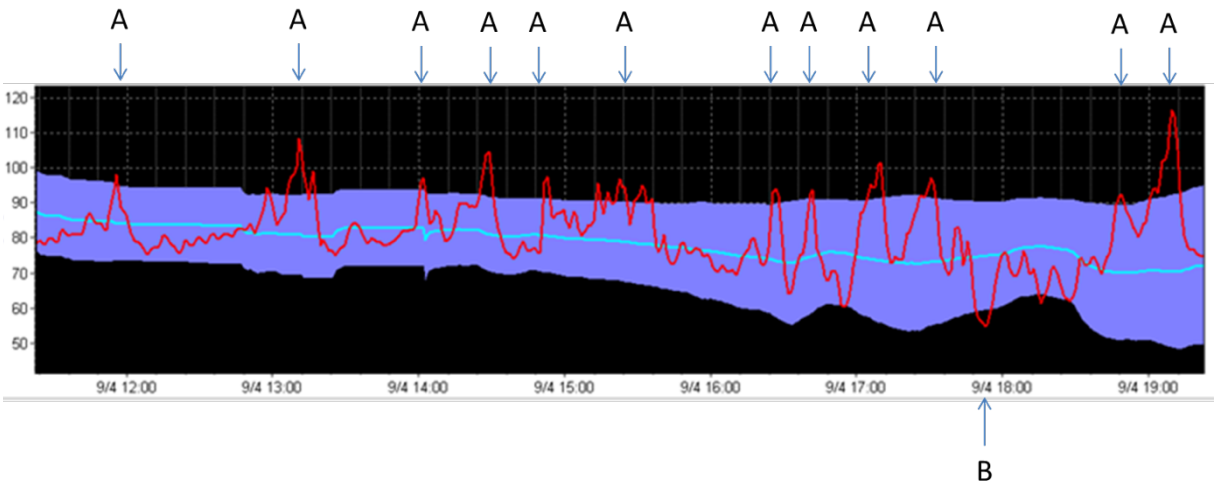


Figure 4. Evolution of cerebral autoreguilation metrics overtime after ECMO start according to neurological outcome. Values represent mean values +/- SEM for each group. The Mann–Whitney test was used to compare the 2 groups. * $p<0.05$, considered as significant. **A.** Evolution of MAP **B.** Evolution of LLA **C.** Evolution of ULA **D.** evolution of Cox **E.** Evolution of the percentage of time spent with MAP below LLA. **F.** Evolution of the percentage of time spent with MAP above ULA.

COx, Cerebral Oxygenation index; MAP, Mean Arterial Pressure; LLA, lower limit of autoregulation; ULA, upper limit of autoregulation.



Supplemental Digital Content-Figure 1. Screenshot of a 8 hour epoch of autoregulation monitoring in a patient under ECMO. Red line represents measured MAP, blue line represents MAPopt and the blue zone corresponds to the area between ULA and LLA. Periods with MAP>ULA (A) and with MAP < LLA (B) are noticed in the figure.

MAP, Mean Arterial Pressure; MAPopt, optimal MAP; LLA, lower limit of autoregulation; ULA, upper limit of autoregulation.

Tables

Table 1. Characteristics of the patients in the whole cohort and according to ANE+/ANE- status

Characteristic	Whole cohort	ANE - (n=17)	ANE + (n=12)	p value
Age (months)	2.8 (0.4-42.5)	2.3 (0.06-6.7)	31.2 (1.8-68.8)	0.18
Weight (kg)	4.8 (3.2-15)	4.1 (3.2-6.1)	13.5 (4.8-19)	0.09
Neonates (<28 days)	8 (27.6)	6 (35.3)	2 (16.7)	0.25
Male	18 (62.1)	10 (58.8)	8 (66.6)	0.48
Chromosomic anomaly	5 (17.2)	4 (23.5)	1 (8.3)	0.29
Indication				0.36
Haemodynamic	18 (62.1)	10 (58.8)	8 (66.6)	
Respiratory	10 (34.5)	7 (41.2)	3 (25)	
ECPR	1 (3.4)	0 (0)	1 (8.3)	
Cannulation by mobile unit	5 (17.2)	2 (11.8)	3 (25)	0.33
Post cardiotomy ECMO				
Number of patients	9 (31)	7 (41.2)	2 (16.7)	0.22
Time of CPB (min)	210 (90.5-285)	239 (130-300)	81 (66-)	0.1
Oxygenation parameters for respiratory ECMO				
Oxygenation index	30.7 (9-39)	26.2 (5.2-36.1)	38.9 (32.5-43.4)	0.13
PaO2/FiO2	57 (49-325.8)	57 (51-211.8)	48.8 (33.8-)	0.31
Cardiac arrest before or during cannulation				
Number of patients	7 (24.1)	2 (11.8)	5 (41.6)	0.08
Total time until ROSC	11.5 (3.2-33.7)	21 (7-28)	10 (2.7-31.2)	0.65
pH before cannulation	7.15 (7.05-7.34)	7.27 (7.15-7.43)	7.05 (6.95-7.18)	**0.001**
Lactate before cannulation (mmol/l)	5.2 (2.2-9.5)	3.2 (1.4-5.4)	9.5 (5.6-14)	**0.004**
ECMO VA[a]	22 (75.9)	12 (70.6)	10 (83.3)	0.37
First cannulation site[a]				0.09
VA (n= 22)				
Central	10 (34.5)	8 (47.1)	2 (16.7)	
Leg	2 (6.9)	1 (5.9)	1 (8.3)	
Neck	10	3 (17.6)	7 (58.3)	
VV (n=7)				
Internal jugular vein[b]	6 (20.7)	4 (23.5)	2 (16.7)	
Femoral/ jugular veins	1 (3.4)	1 (5.9)	0 (0)	
ECMO duration (hours)	81 (48.5-160)	94 (49.5-460)	61.5 (45-94)	0.16
Outcome				
Lenght of mechanical ventilation (days)	10.5 (5.5-17.7)	12.5 (5.5-19.5)	9.5 (7.5-14.7)	0.25
PICU LOS	17 (9.5-30)	21 (9.5-50.5)	12.5 (8.5-18.7)	0.12
Hospital LOS (days)	37 (14-68)	45 (18.5-75)	23 (8.7-51.7)	0.17

Alive H24 ECMO discharge	19 (65.5)	12(70.5)	7 (58.3)	0.38
Alive at hospital discharge	14 (48.3)	8 (47.1)	6 (50)	0.58

Data are expressed as median (interquartile ranges) or n (% of the number of patients of the column). p<0.05 was considered significant. No correction for multiple comparison was applied.
ECPR, Extra-corporeal CardioPulmonary Resuscitation; CPB, CardioPulmonary Bypass; ROSC, Return Of Spontaneous Circulation;PICU, Pediatric Intensive Care Unit; LOS, Length Of Stay; VA, veno arterial; VV, veno venous
[a] Here is reported the first site of cannulation. Cannulation was further converted to VV (Jugular vein/Femoral vein) in 2 patients.
[b]Dual lumen cannula through right internal jugular vein was used in 2 patients.

Table 2. Case analysis summary for patients who met the criteria of ANE.

Case	Age	Primary Diagnosis	Cardiac arrest prior to ECMO	ECMO mode	Cannulation site	Main imaging findings	Seizures	Brain death	Timing of ANE after ECMO start[a]	Outcome at hospital discharge
1	4 y	Myocarditis	**Yes**	VA	Neck	Right watershed cerebral infarct and left mild cortical ischemia	Clinical and electrical	No	D1	Alive
2	9 y	Sicle cell disease, ARDS	**No**	VV	Neck	Right frontal and parietal hemorrhage	No	No	NA	Alive
3	0 d	Meconium aspiration,HIE	**No**	VA	Neck	Bilateral ischemic and hemorrhagic lesions of the white cerebral matter, left frontal hemorrhage	Electrical	No	D4	Alive
4	6 d	CDH	**No**	VA	Neck	No	Electrical	No	D1	Alive
5	14 y	Septic shock	**No**	VA	Leg	Left ischemic and hemorrhagic lesions of the cerebellum	No	No	NA	Alive
6	4 y	Myocarditis	**Yes**	VA	Neck	Right deep Sylvian ischemic stroke	No	No	D1	Dead
7	2 mo	AVSD, Post operative	**No**	VA	Chest	No	No	Yes	D3	Dead

		LCOS								
8	2 mo	TOF ,post operative septic shock	**Yes**	VA	Chest	No	Clinical and electrical	No	D1	Dead
9	6 y	Drowning	**Yes**	VV	Neck	NA	Clinical and electrical	No	D1	Dead
10	3 y	Septic shock	**No**	VA	Neck	Right watershed cerebral infarct	No	No	D1	Alive
11	2 mo	Pertussis	**No**	VA	Neck	NA	No	Yes	D3	Dead
12	2 y	Cardiogenic shock	**Yes**		Neck	No	Electrical	Yes	D1	Dead

[a]Timing of ANE after ECMO start corresponds to the date of the first clinical and/or electrical manifestations of ANE after ECMO start. VA, venoarterial; VV, venovenous; ARDS, Acute Respiratory Distress Syndrome; HIE, Hypoxic_Ischemic Encephalopathy; CDH, Congenital Diaphragmatic Hernia ; AVSD, Atrio Ventricular Septal Defect; LCOS, Low Cardiac Output Syndrom; TOF,Tetralogy of Fallot

Supplemental Digital Content-table 1. Autoregulation parameters during ECMO run according to the type of cannulation.

Variable	VA runs (n=22)	VV runs (n=9)	p value
Age (months)	2.26 (0.3-25.6)	8.1 (0.5-99.7)	0.39
Time of monitoring (hours)	67.7 (23.6-93)	113.8 (85.7-354.6)	**0.009**
Time of monitoring / ECMO duration (%)	67.6 (41.5-90.7)	64.3 (41.3-97.2)	1
Mean COx	0.04 (-0.01-0.12)	0.03 (-0.04-0.06)	0.65
% time with COx> 0.3	24.2 (21.5-34.2)	20.4 (14.4-30.9)	0.149
COx (AU) > 0.3 /hour x 100	4.6 (3.5-6.3)	3.84 (2.3-5.1)	0.32
% time MAPopt, LLA and ULA available	90.9 (81.2-93.4)	90.7 (81.1 -93.3)	0.31
Mean MAP (mmHg)	52.6 (48.8-60.5)	61.3 (44.8-78.1)	0.32
Mean MAPopt	54.1 (47.9-62.5)	63.3 (46-71.7)	0.28
Mean LLA	45.3 (37.6-55.1)	51.9 (37.6-64.2)	0.32
Mean ULA	63 (56.7-69.8)	72.1 (55.3-87.9)	0.21
% time ΔMAPopt -5 to +5 mmHg	62.5 (50.7-66.2)	59 (49.2-63.8)	0.62
% time ΔMAPopt < - 5 mmHg	22.3 (9.4-26.4)	23.6 (13.6-30.2)	0.59
% time ΔMAPopt > 5 mmHg	15.2 (9.6-22.7)	17.4 (8.5-25.8)	0.65
% time MAP < LLA	7.9 (4.9-24)	6.95 (3.3-9.2)	0.44
% time MAP > ULA	5.7 (3.1-13.6)	7.16 (3.4 -14.4)	0.76

% time MAP < LLA or MAP > ULA	12.6 (9.9-40.5)	12.5 (9.3-21.2)	0.68

Data are expressed as median (interquartile ranges). $p<0.05$ was considered significant. No correction for multiple comparison was applied.

COx, Cerebral Oxygenation index; AU, Area Under; MAP,Mean Arterial Pressure; LLA,Lower Limit of Autoregulation; ULA, Upper Limit of Autoregulation; ΔMAPopt = median MAP-MAPopt