Canonical Correlation Analysis in the Study of Cerebral and Peripheral Haemodynamics Interrelations with Systemic Variables in Neonates Supported on ECMO.

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Abstract Neonates supported on extracorporeal membrane oxygenation (ECMO) are at high risk of brain injury due to haemodynamic instability. In order to monitor cerebral and peripheral (muscle) haemodynamic and oxygenation changes in this population we used a dual-channel near-infrared spectroscopy (NIRS) system. In addition, to assess interrelations between NIRS and systemic variables, collected simultaneously, canonical correlation analysis (CCA) was employed. CCA can quantify the relationship between set of variables and assess levels of dependency. In 4 out of 5 patients, systemic variables were found to be less inter-related with cerebral rather than peripheral NIRS measurements. Moreover, our results demonstrated some inter-patient variability in the interrelation between the systemic and the cerebral/peripheral haemodynamics variables, which may be indicative of physiological differences in the mechanisms that regulate heamodynamics of the brain and the muscle among the population.

1 Introduction

Extracorporeal membrane oxygenation (ECMO) is a life support system for patients with intractable cardio-respiratory failure. Neonates supported on ECMO often suffer from periods of haemodynamic instability, hypoxia and/or hypercapnia. In addition, the ECMO procedure itself may cause physiological changes due to ligation of the major neck vessels, heparinitazion, and hemodilution, which can cause alterations in cerebral blood flow and potentially disrupt autoregulation [1]. Consequently, ECMO patients have increased risk for brain injury with reported abnormal neuroimaging ranging from 28% to 52% depending in the imaging technique used [2].

Several studies have described changes in the cerebral haemodynamics before, during and after ECMO procedure. Liem et al [1] reported that mean arterial blood pressure (MABP), arterial oxygen saturation (SaO_2) and partial pressures of oxygen and CO_2 measured transcutaneously were some of the variables that better explained changes in total haemoglobin (HbT) measured by NIRS. Ejike et al. [3] reported that the regional cerebral oxygenation presented a negative correlation with arterial partial pressure of CO_2 (pCO_2) and no significant correlation with changes in ECMO flow. Papademetriou et al [4] used dual-channel NIRS system during ECMO flow changes and reported the presence of low frequency oscillations (<0.1 Hz) in peripheral oxyhaemoglobin (HbO_2), which are not present in cerebral HbO_2, demonstrating differences between cerebral and peripheral haemodynamics in this patient group.

Several studies have investigated the relationship between spontaneous changes in MABP and cerebral NIRS signals as assessment of brain autoregulation [5-7]. Brady et al [6] investigated correlation between NIRS and MABP in paediatric patients undergoing cardiac surgery with cardiopulmonary bypass for correction of congenital heart defects. They found an association between hypotension during cardiopulmonary bypass and impairment of autoregulation. We have also previously [7] studied the relation between MABP and haemoglobin difference ($HbD=HbO_2$-HHb, oxy minus reduced haemoglobin) and tissue oxygenation index ($TOI=HbO_2/HbT$) by means of correlation, coherence and partial coherence analysis, and its use in clinical outcome prediction; although higher values were found in the population with adverse clinical outcome, indicating stronger relation between MABP and HbD/TOI, no strong evidence was established. However, ECMO is a complex procedure and the study of the interrelation of haemodynamic variables, only, with MABP may not be sufficient.

In this study we describe the use of canonical correlation analysis (CCA) to investigate the differences between the interrelations in cerebral and peripheral NIRS measurements with the systemic variables in ECMO patients. In our analysis the systemic variables were defined as the independent dataset, while the cerebral and peripheral NIRS measurements were defined as dependent variables.

2 Methods

Canonical Correlation Analysis (CCA) is a statistical method that analyzes the interrelation between variables in multi-dimensional datasets. CCA can be seen as an extension to normal correlation analysis, in which the proximity between two multidimensional datasets, instead of vectors, is analyzed by means of canonical angles [8]. CCA determines how strongly the variables in both datasets are related. It is also possible to determine which and how many of the independent variables explain most of the variation in the dependent dataset.

Measurements from 5 subjects (ranging from 1-1825 days) on veno-arterial (VA) ECMO procedure were used in this study. A dual channel near infrared

system (NIRO 200, Hamamatsu Photonics KK) was used to measure the changes in HbO_2, HHb and TOI using spatially resolved spectroscopy. From these signals HbD and total haemoglobin changes ($HbT=HbO_2+HHb$) were calculated and used, together, with TOI for further analysis. NIRS data were collected at frequency of 6Hz. Channel 1 was placed on the forehead in order to assess cerebral NIRS changes, while channel 2 was placed on the calf to assess peripheral NIRS changes. A full set of systemic data including, MABP, central venous pressure (CVP), end-tidal carbon dioxide pressure ($EtCO_2$), heart rate (HR), respiration rate (RR), core and skin temperatures and arterial oxygen saturation (SaO_2); were continuously measured in real time at the bedside (Intellvue MP70, Philips Medical). All signals were down-sampled to 1Hz and artifacts were removed manually by means of interpolation. Figure 1 shows an example of the systemic and NIRS measurements from one neonate. Measurements were done during stepwise changes in the ECMO flow; the flow was reduced from baseline (100% ECMO flow) in steps of 10%, approximately every 10 minutes, until 70% of the baseline ECMO flow was reached, afterwards the flow was increased back to baseline following the same profile. In cases where the patients couldn't accommodate a 30% reduction in ECMO flow it was only reduced by a total of 20%. The interrelations between the set of peripheral and cerebral NIRS changes with the systemic variables were studied using two different approaches. The first approach used the complete measurement period and the ECMO flow when available as a parameter in the analysis. In the second approach, the signals were segmented in epochs of constant ECMO flow and the methods were applied separately to each epoch. In addition, in order to normalize the results to be comparable among the patients, we estimated the ratio between the percentage of variance in the peripheral NIRS explained by the systemic variables and the percentage of variance of the cerebral NIRS explained by the systemic variables. We call this index the peripheral to cerebral haemodynamic ratio (PCHR). PCHR can be used to quantify the differences in the interrelations between both, cerebral and peripheral, circulation mechanisms versus systemic variations. PCHR values lower than 1 indicates that variations in the systemic variables are more likely to be reflected in the brain than in the muscle.

3 Results

Table 1 shows PCHR for different ECMO flows and for the full measurement period. Results for the full measured period show that only patient 4 presented a PCHR>1, indicating that the variations in the systemic variables were more likely to be reflected in the brain NIRS measurements rather than the peripheral in that patient; in the other patients the peripheral NIRS changes are more likely to be affected by variations in the systemic variables. In addition, patient 3, in contrast with the other patients, was the only one who presented, at every ECMO flow rate, consistently PCHR<1 and as it happened was the only patient in our group that the

clinicians were confident to reduce the flow down to 70% from baseline. Table 2 shows which systemic variables contributed more to the changes in cerebral/peripheral NIRS variables, when analyzing the completed measurement period. HR and skin temperature were the systemic variables that affected the most the cerebral and/or peripheral haemodynamic variables in the patients. MABP, CVP, Skin Temperature, SaO_2 and ECMO affected the NIRS variables in a lower extent.

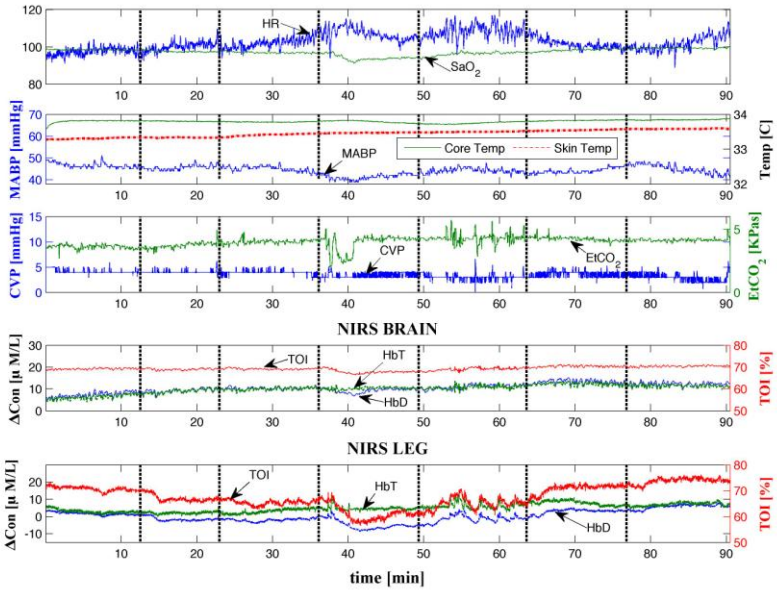


Figure 1. Systemic and haemodynamics measurements recorded from patient 3. The dashed vertical lines represent the changes in ECMO flow.

4 Discussion

PCHR<1, but close to 1, were observed in 4 out of 5 patients when analyzing the full measurement period. Earlier studies on neonates supported on ECMO indicate that autoregulation may be disrupted [1]; which can be the cause of PCHR values close to 1 as the brain haemodynamic and oxygenation changes will respond passively to systemic variations. In addition, when reducing ECMO flows is expected that the peripheral circulation would be more affected by systemic changes than the brain circulation. At baseline level (100% ECMO flow) all patients reported a PCHR<1, when reducing the flow to 90% 3 out of 5 patients reported PCHR>1, indicating that systemic changes were more reflected in the cerebral circulation than in the peripheral circulation; while patient 5 couldn't

accommodate extra reductions in the flow and was returned to baseline level. At 80% flow 2 out of 4 patients presented PCHR>1; furthermore, in this stage, 3 of the patients couldn't accommodate more reductions in the flow and were returned to baseline level. Only patient 3 was able to accommodate a reduction to 70% in the ECMO flow and was the only patient who presented consistently PCHR<1. When returning ECMO flow to baseline level, 3 out of 4 patients presented PCHR≥1. These results suggest that at low ECMO flows cerebral circulation is more vulnerable to changes in systemic variables.

Table 1. Ratio between the percentage of the variance in the cerebral haemodynamics and the peripheral haemodynamics explained by variations in the systemic variables (PCHR), for different ECMO flow percentages and the full measurements period. Spaces marked with – indicate that there was not possible to perform the analysis due to the lack of measurements.

	ECMO Flow Percentage							
	100%	**90%**	**80%**	**70%**	**80%**	**90%**	**100%**	**Full Period**
Patient 1	0.56	0.76	1.19	-	-	1.59	1.00	0.85
Patient 2	0.68	1.55	1.61	-	-	0.55	-	0.82
Patient 3	0.91	0.95	0.49	0.89	0.91	0.47	0.38	0.91
Patient 4	0.66	1.68	0.73	-	-	0.71	1.00	1.21
Patient 5	0.75	1.42	-	-	-	-	1.33	0.82

Table 2. Systemic variables that presented a correlation higher than 0.5, in absolute value, with cerebral/peripheral haemodynamic variables represented by a B/L sign, respectively. The blank spaces indicate no correlation and a – sign indicates that the parameter was not used in the analysis due to lack of measurements or distortion by artifacts.

Patient	HR	MABP	CVP	CoreT	SkinT	SaO_2	RR	$EtCO_2$	Flow
1	B	B/L	B		L				-
2	B/L	B	B	B	B/L	L	B/L	-	B/L
3	L	L		B/L	B/L	B/L	-	B	B/L
4	B/L		L	-	B/L	-			B/L
5	B/L	B	B/L		B/L	B/L			-

In the population studied HR and skin temperature were the variables that affected the most the cerebral and peripheral NIRS signals. Out of 5 patients MABP was correlated with cerebral and peripheral haemodynamic variables in 3 and 2 patients respectively. Out of 4 patients SaO_2 was correlated with cerebral and peripheral haemodynamic variables in 3 and 2 patients respectively. Out of 4 patients $EtCO_2$ was correlated with the cerebral haemodynamic variables in one patient. Furthermore, ECMO flow presented a strong correlation with cerebral and peripheral NIRS variables in all the patients with flow measurements. The lack of homogeneity in relation to the systemic variables that affect the cerebral or peripheral circulation in our study suggests differences in the clinical condition of each patient; however, due to the small patient numbers is difficult to deduct any clinical hypothesis. Interestingly enough and in contrast with these results, Tisdall

et al [9] in healthy adults found that changes in SaO_2 and $EtCO_2$ highly contribute to changes in the cerebral NIRS TOI signal. In addition, CCA pointed out that variation in the skin temperature highly affect the cerebral and peripheral NIRS changes; conversely, Harper et al [10] reported that a change in core temperature can produce changes in blood flow due to changes in blood viscosity and metabolic rate, among other reasons.

Several factors should be taken into account before interpreting the results provided by CCA. Among the limitations, the length of the signal under analysis and the presence of noise, non-linearities and nonstationarity can be cited. In order to overcome some of these problems, and compare the results between patients, normalization such as the PCHR ratio should be used; otherwise, the results should be interpreted carefully. Cerebral and peripheral haemodynamic and oxygenation changes are caused by multiple factors; several systemic variables should be analyzed in order to obtain a general idea of the underlying mechanism affecting them. CCA is a useful tool to investigate this problem as it helps to assess and quantify the interrelation between both set of variables, simultaneously.

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