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Article

Analysis of P(v-a)CO₂/C(a-v)O₂ Ratio and Other Perfusion Markers in a Population of 98 Pediatric Patients Undergoing Cardiac Surgery

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Abstract: BACKGROUND: The so-called Low Cardiac Output Syndrome (LCOS) is one of the most common complications in pediatric patients with congenital heart disease undergoing corrective surgery. LCOS requires high concentrations of inotropes to support cardiac contractility and improve cardiac output, allowing for a better systemic perfusion. To date, serum lactate concentrations and central venous oxygen saturation (ScVO₂) are the most commonly used perfusion markers, but they are not completely reliable to identify a state of global tissue hypoxia. The study aims to evaluate whether the venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio [P(v-a)CO₂/C(a-v)O₂] can be a good index to predict the development of LCOS in the aforementioned patients, so as to treat it promptly. METHODS: This study followed a population of 98 children undergoing corrective cardiac surgery from June 2018 to October 2020 at the Department of Cardiac Surgery of University Hospital Integrated Trust and their subsequent admission at the Postoperative Cardiothoracic Surgery Intensive Care Unit. During the study, central arterial and venous blood gas analysis were carried out before and after cardiopulmonary bypass (CPB) (pre-CPB and post-CPB), at admission to intensive care unit, before and after extubation and at any time of instability or modification of the patient's clinical and therapeutic conditions. RESULTS: The data analysis shows that 46.9% of the children developed a LCOS (in line with the current literature) but that there is no statistically significant association between the P(v-a)CO₂/C(a-v)O₂ ratio and LCOS onset. Despite the limits of statistical significance, however, a 31% increase in the ratio emerged from the pre-CPB phase to the post-CPB phase when LCOS is present. CONCLUSIONS: This study confirms a statistically significant association between the most used markers in adult patients (serum lactate concentration, ScVO₂ and oxygen extraction ratio-ERO₂) measured in the pre-CPB phase and the incidence of LCOS onset, especially in patients with hemodynamic instability before surgery.

Keywords: venoarterial carbon dioxide difference; congenital heart disease; cardiopulmonary bypass; postoperative care; physiologic monitoring; infant

1. Introduction

The Low Cardiac Output Syndrome (LCOS) is a clinical condition caused by a transient decrease in systemic perfusion secondary to a myocardial dysfunction. The result is an oxygen delivery (DO₂) /oxygen consumption (VO₂) uncoupling, eventually leading to metabolic acidosis. [1]

This syndrome is defined by a cardiac index (CI) lower than 2 L/min/m², in association with signs of tissue hypoperfusion (cold extremities, mottling, oliguria, high lactate levels) but with no signs of hypovolemia, requiring inotropic drugs or mechanical circulatory support, i.e. extracorporeal membrane oxygenation (ECMO). [2,3]

LCOS is most frequently observed in patients undergoing cardiopulmonary bypass (CPB) during cardiac surgery for correction of a congenital heart disease. Literature reports a 25-60% incidence of LCOS in pediatric cardiac surgery patients. [3–5]

Causes of LCOS can include myocardial ischemia due to aortic cross-clamping, residual effects of cardioplegia, CPB-induced myocardial dysfunction and inflammatory pathway activation due to the exposure of blood to foreign surfaces during CPB. [6]

Early recognition and treatment of LCOS are crucial in order to minimize perioperative related morbidity and mortality.

CI measurement can result difficult in pediatric patients through thermodilution due to both the device size and the peculiar cardiovascular pathophysiology of little patients with congenital heart disease, hence the interest to define a reliable marker of LCOS in this subgroup of patients. CI measurement can result difficult in pediatric patients through thermodilution due to both the device size and the peculiar cardiovascular pathophysiology of little patients with congenital heart disease, hence the interest to define a reliable marker of LCOS in this subgroup of patients. Another aspect that must be consider in this type of patients, which adds difficulties in CI measurement, is that the definition “pediatric heart defects” encompass a large spectrum of pathologies with different physiopathological implications. These are normally divided in two big categories considering the clinical presence of cyanosis and the characteristics of pulmonary circulation: cyanotic and acyanotic defects. Table 1 summarizes the principal defects.

Table 1. Principal cardiac malformations.. Abbreviations: AS: aortic stenosis; ASD: atrial septum defect; AVSD: atrioventricular septum defect; COA: coartation; d-TGV: transposition of great arteries; PDA patent ductus arteriosus; TAPVR: Total anomalous pulmonary venous return; TOF Tetralogy of Fallot.

Pulmonary flow	Acyanotic	Cyanotic
<i>Augmented</i>	Left to right shunt: VSD, PDA, ASD, AVSD	Commistion lesions: d-TGA, TAPVR
<i>Normal</i>	Obstructive lesions AS, PS, COA, Cardiomyopathies	-
<i>Reduced</i>	-	Pulmonary flow obstruction with septal defect: TOF, tricuspidal atresia, Ebstein malformation

A few recent studies [7,8] have identified veno-arterial carbon dioxide difference/arterial-venous oxygen difference ratio $[P(v-a)CO_2/C(a-v)O_2]$ as an index of tissue hypoxia caused by acute circulatory failure. The physiological rationale is that, according to Fick's equation, oxygen consumption (VO₂) and CO₂ production (VCO₂) are proportional to cardiac output. Under normal conditions VCO₂, VO₂ and venous to arterial CO₂ content (CvCO₂-CaCO₂) and arterial to venous O₂ content (CaO₂-CvO₂) are comparable. Hence, VCO₂ should not exceed O₂ production, and the respiratory exchange ratio should not exceed 1. The relationship appears as follows: $CO \times (CvCO_2 - CaCO_2)/CO \times (CaO_2 - CvO_2)$.

Since cardiac output is present in both the numerator and denominator the ratio is: $C(v-a)CO_2/C(a-v)O_2$. In steady state conditions it is possible to replace CO_2 concentrations with partial pressure obtaining the $P(v-a)CO_2/C(a-v)O_2$ ratio.

It has been speculated that this ratio could be used as a marker of global tissue hypoxia in adult patients undergoing cardiac surgery. The Authors demonstrated that this ratio might be used as a prognostic tool with better relevance when compared to other commonly used perfusion indexes (lactates, central venous oxygen saturation [$ScVO_2$], Oxygen Extraction Ratio [ERO_2], $P(v-a)CO_2$, anion gap, prolonged capillary refill time). A ratio higher of 1.6 mmHg/mL is considered predictive of oxygen supply dependency [7,8].

The aim of this study was to evaluate the possible use of $P(v-a)CO_2/C(a-v)O_2$ ratio as a marker of tissue hypoxia in pediatric cardiac patients undergoing cardiac surgery and/or requiring ECMO.

2. Materials and Methods

This study included pediatric patients (0-14 years of age) having undergone cardiac surgery with or without postcardiotomy mechanical support between June 2018 and October 2020 and being subsequently admitted to Cardiothoracic Surgery Intensive Care Unit at the University Hospital Integrated Trust of Verona, Italy. All subjects belonged to the REINSURE-ARDS registry, a prospective registry of patients requiring intensive care unit (ICU) admission for any form of respiratory failure (Prog 1946CESC, Prot 72485 12/11/2018, amendment 26/02/2021). Patient identification remained anonymous, all participants' legal representative provided informed consent before inclusion to the registry and for the use of their clinical and biological data.

No exclusion criteria were identified.

Cardiac surgery procedures include either full correction operations and temporary or long-term palliative solutions.

The following data were collected:

- Age and anthropometric measurements (weight and length)
- Type of congenital heart disease (both cyanotic and acyanotic) and type of surgery
- Pre- and post-surgery laboratory tests (serum creatinine and hemoglobin)
- Intraoperative data (length of CPB, need for transfusions, renal and cerebral near infrared spectroscopy [NIRS] and body temperature)
- Post operative data (hemodynamic instability, renal and cerebral near infrared spectroscopy [NIRS] and body temperature, vasopressor/inotrope infusion, need for mechanical circulation support)

Blood gas analysis both from the arterial catheter and the central venous line were collected:

At anesthesia induction (pre-CPB).

- At CPB discontinuation.
- Upon ICU admission.
- Before extubation.
- After extubation.
- Before ICU discharge.
- At any significant hemodynamic change (patient needing fluid and/or pharmacologic therapy).

At the time of blood gas collection, body temperature and both renal and cerebral NIRS values were also recorded.

Arterial and central venous blood gas samples were analyzed using a point of care gas analyzer (GEM 4000, Instrumentation Laboratory, Bedford, MA, USA)

5 markers of tissue perfusion were taken into account: lactate, $ScVO_2$, ERO_2 , $\Delta P(v-a)CO_2$ and $P(v-a)CO_2/C(a-v)O_2$ ratio.

The value of $[P(v-a)CO_2/C(a-v)O_2]$ is calculated from the O_2 -derived and CO_2 -derived variables. The calculation formulas are as follows:

$$CaO_2 = SaO_2 \times Hb \times 1.34 + PaO_2 \times 0.0031$$

$$CvO_2 = ScVO_2 \times Hb \times 1.34 + PVO_2 \times 0.0031$$

$$C(a-v)O_2 = CaO_2 - CvO_2$$

$$P(v-a)CO_2 = PvCO_2 - PaCO_2$$

$$P(v-a)CO_2/C(a-v)O_2 = (PcvCO_2 - PaCO_2)/(CaO_2 - CcVO_2)$$

The primary outcome was to assess the ability of the $P(v-a)CO_2/C(a-v)O_2$ ratio to predict tissue hypoxia in the pediatric cardiac population. Secondary outcome was to evaluate the relationship of other 5 different perfusion markers at different sampling times with the development of LCOS.

The incidence of LCOS was evaluated and defined by hemodynamic instability with the need of high dose of vasopressors/inotropes (defined as milrinone >0.25 mcg/kg/min, dopamine >3 mcg/kg/min, adrenaline >0.05 mcg/kg/min, dobutamine >5 mcg/kg/min, noradrenaline >0.1 mcg/kg/min).

Statistically significant differences were evaluated with Fisher's exact test for nominal variables.

A Wilcoxon signed-rank test (Mann-Whitney) was also used to evaluate the relationship between markers and LCOS development. A non-parametric test was chosen due to the asymmetrical distribution of variables. Main effects and interaction plot graphs were used to complete the analysis. The statistical analysis was performed with Minitab 19.

3. Results

The study included 98 pediatric patients undergoing corrective cardiac surgery for congenital heart defects.

Table 2 shows the demographic data of the population.

Table 2. Patients' Demographic Data.

Sex	Male	56,1 % (n=55)	
	Female	43,9% (n=43)	
Age (med±SD)	32,0 ±48,0 months	Male	35,9 ±51,1 months
		Female	27,0 ±34,7 months
Height (med ±SD)	82,9±35,4cm	Male	85,0±37,7cm
		Female	78,0±32,1cm
Weight (med ±SD)	12,7±13,8 kg	Male	13,9 ±14,9 kg
		Female	11,0 ±12,1 kg

Mean age, expressed in months, was 32.0 ± 48.0 SD (standard deviation).

All congenital heart defects (CHD) were included in the study. In our sample 35 patients were affected by a cyanotic heart defect and 63 patients by acyanotic heart defect (Table 3).

Table 3. Incidence of the different congenital heart defects and related incidence of Low Cardiac Output Syndrome (LCOS).

Population (n=98)	LCOS
Acyanotic, n (%): 63 (62%)	20 (31.7 %)
Cyanotic, n (%): 35 (38%)	26 (74.2%)

LCOS was detected in 46.9% cases. The incidence of LCOS was significantly higher in cyanotic heart defects compared to non-cyanotic ones (74.2 % vs 31.7%, p value <0.05).

The concentrations of 5 different perfusion markers at the different sampling times were evaluated so as their relationship with the development of LCOS, both in the whole studied population and in the two sub-groups (cyanotic and acyanotic CHD).

3.1. $P(v-a)CO_2/C(a-v)O_2$ ratio

$P(v-a)CO_2/C(a-v)O_2$ ratio have only a statistical significant effect in the whole group in the pre-CBP phase (p=0.023) (Figure 1).

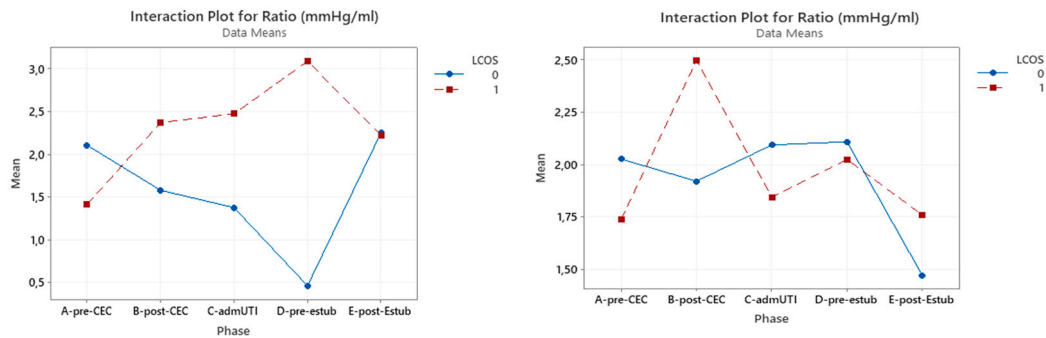


Figure 1. Interaction plot for $P(v-a)CO_2/C(a-v)O_2$ in relation to Low Cardiac Output Syndrome (LCOS) onset (0=no development of LCOS, 1=development of LCOS) in the two subgroups cyanotic (left) and acyanotic (right) at the different sampling times.. Abbreviations: A-pre-CEC: at anesthesia induction (pre-CPB), B-post-CEC: at CPB discontinuation, C-admUTI: upon intensive care unit admission, D-pre-estub: before extubation; E-post-estub: after extubation.

Nonetheless, an interaction was found between the onset of LCOS and the pre-CPB and post-CPB phases, with a 31% increase in patients who developed LCOS and a 17% decrease in patients who do not develop LCOS (Table 4).

Table 4. $P(v-a)CO_2/C(a-v)O_2$ values (mmHg/ml) at the different sampling times correlated with presence/absence of Low Cardiac Output Syndrome (LCOS). Abbreviations: LCOS (Low cardiac output syndrome), CPB (Cardiopulmonary bypass), ICU (Intensive Care Unit), SD (standard deviation), CHD (congenital heart defect).

Sampling times	LCOS	Whole population		Cyanotic CHD		Acyanotic CHD	
		Mean value (SD) mmHg/ml	P-value	Mean value (SD) mmHg/ml	P-value	Mean value (SD) mmHg/ml	P-value
Pre-CPB	Yes	1,55 (1,00)	0,023	1,41 (0,85)	0,131	1,74 (1,18)	0,286
	No	2,05 (1,05)		2,10 (1,22)		2,06 (1,02)	
Post-CPB	Yes	2,44 (2,94)	0,5	2,40 (3,79)	0,377	2,49 (1,33)	0,167
	No	1,87 (1,26)		1,58 (0,91)		1,92 (1,30)	
ICU adm.	Yes	2,21 (1,67)	0,256	2,47 (2,06)	0,160	1,84 (0,82)	0,990
	No	1,95 (1,64)		1,37 (0,94)		2,09 (1,75)	
Pre-ext.	Yes	2,61 (4,41)	0,770	3,09 (5,86)	-	2,02 (1,24)	0,958
	No	2,04 (1,53)		0,45 (-)		2,11 (1,53)	
Post-ext.	Yes	2,04 (1,74)	0,239	2,22 (1,99)	0,99	1,76 (1,32)	0,586
	No	1,52 (1,41)		2,25 (2,22)		1,47 (1,39)	

3.2. Serum Lactates

Table S-I (Supplementary Material) illustrates the correlation between serum lactate levels and LCOS development in the whole population, which was significant pre-CPB ($p = 0.048$), post-CPB ($p = 0.001$) and at ICU admission ($p = 0.026$). In the cyanotic CHD group a statistical significance was reached only pre-CPB ($p = 0.001$), while this was found only post-CPB ($p = 0.013$) in the acyanotic CHD group.

Serum lactates tend to be higher in patients with LCOS and for the cyanotic CHD group. This difference is statistically significant until ICU admission only in the entire population group.

Figure 2 shows the interaction plot of lactate level in relation to LCOS onset, subpopulation (cyanotic CHD and acyanotic CHD) and sampling time.

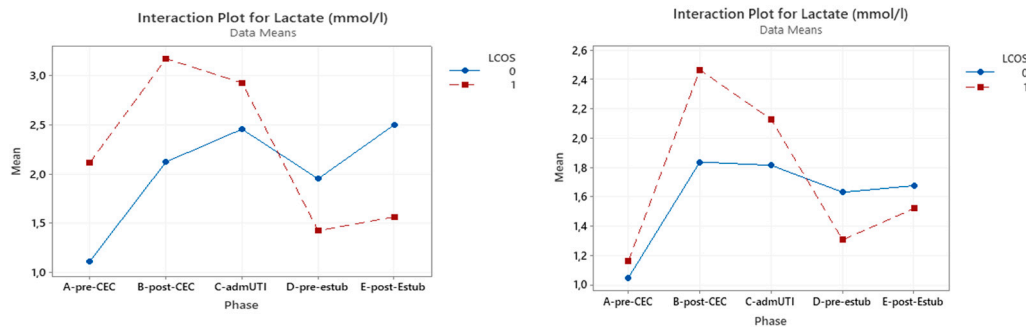


Figure 2. Interaction plot for lactate in relation to Low Cardiac Output Syndrome (LCOS) onset (0=no development of LCOS, 1=development of LCOS) in the two subgroups cyanotic (left) and acyanotic (right) at the different sampling times. Abbreviations: A-pre-CEC: at anesthesia induction (pre-CPB), B-post-CEC: at CPB discontinuation, C-admUTI: upon intensive care unit admission, D-pre-estub: before extubation; E-post-Estub: after extubation.

3.3. ScVO₂

A significant correlation was found between ScVO₂ with LCOS development pre-CPB ($p < 0.0001$) and after extubation ($p = 0.05$).

In the cyanotic group this marker did not reach statistical significance at any evaluated time, while this was reached in the acyanotic group in the pre-CPB sampling ($p = 0.002$). (Table 6)(Figure 3).

Table 6. ScVO₂ values (mmol/l) at the different sampling times correlated with presence/absence of Low Cardiac Output Syndrome (LCOS). Abbreviations: LCOS (Low cardiac output syndrome), CPB (Cardiopulmonary bypass), ICU (Intensive Care Unit), SD (standard deviation), CHD (congenital heart defect).

Samplingtimes	Whole population		Cyanotic CHD		Acyanotic CHD		
	LCOS	Mean value (SD) mmol/l	P-value	Mean value (SD) mmol/l	P-value	Mean value (SD) mmol/l	P-value
Pre-CPB	Yes	61,83 (14,73)	0,000061	58,41 (14,63)	0,792	66,28 (13,98)	0,002
	No	74,06 (14,73)		59,48 (13,99)		77,03(9,82)	
Post-CPB	Yes	67,89 (12,44)	0,197	65,86 (12,95)	0,919	70,53 (11,55)	0,652
	No	70,59 (14,39)		63,29 (22,26)		71,38 (12,57)	
ICUadm.	Yes	65,36 (15,78)	0,224	63,25 (17,63)	0,345	68,41 (12,52)	0,309
	No	69,01 (13,79)		57,04 (15,49)		71,62 (11,82)	
Pre-ext.	Yes	67,04 (15,36)	0,301	63,52 (17,62)	0,689	72,45 (9,25)	0,940
	No	70,86 (14,00)		72,20 (23,50)		70,77 (13,77)	
Post-ext.	Yes	62,17 (15,85)	0,05	57,74 (16,78)	0,848	69,18 (11,73)	0,654
	No	69,61 (12,54)		61,07 (16,67)		70,41 (12,12)	

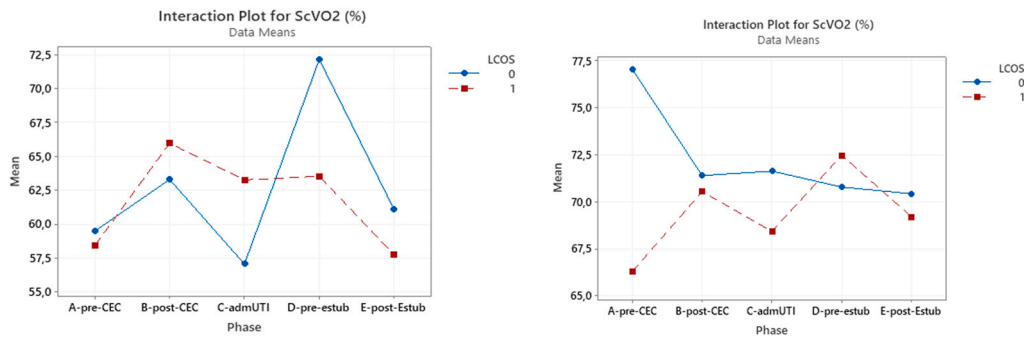


Figure 3. Interaction plot for ScVO₂ in relation to Low Cardiac Output Syndrome (LCOS) onset (0=no development of LCOS, 1=development of LCOS) in the two subgroups cyanotic (left) and acyanotic (right) at the different sampling times. Abbreviations: A-pre-CEC: at anesthesia induction (pre-CPB), B-post-CEC: at CPB discontinuation, C-admUTI: upon intensive care unit admission, D-pre-estub: before extubation; E-post-Estub: after extubation.

3.4. ERO₂

Within the whole studied population, reached statistical significance for prediction of LCOS development only pre-CPB ($p = 0.027$). This was confirmed in LCOS patients of the acyanotic group ($p = 0.013$), but ERO₂ did not have a significant impact in the cyanotic CHD group. (Table 7) (Figure 4)

Table 7. ERO₂ values (%) at the different sampling times correlated with presence/absence of Low Cardiac Output Syndrome (LCOS). Abbreviations: LCOS (Low cardiac output syndrome), CPB (Cardiopulmonary bypass), ICU (Intensive Care Unit), SD (standard deviation), CHD (congenital heart defect).

Samplingtimes	LCOS	Whole population		Cyanotic CHD		Acyanotic CHD	
		Mean value (SD)%	P-value	Mean value (SD)%	P-value	Mean value (SD)%	P-value
Pre-CPB	Yes	32,1 (14,4)	0,027	30,4 (15,4)	0,938	43,2 (12,5)	0,013
	No	27,6 (12,1)		31,4 (13,1)		26,9 (11,8)	
Post-CPB	Yes	29,3 (15,1)	0,874	25,6 (13,2)	0,542	33,8 (16,4)	0,403
	No	30,1 (14,7)		31,7 (21,2)		30,3 (13,6)	
ICUadm.	Yes	32,6 (17,2)	0,580	30,6 (17,4)	0,375	35,6 (17,0)	0,223
	No	32,3 (18,4)		36,9 (15,9)		31,5 (18,8)	
Pre-ext.	Yes	34,4 (22,7)	0,921	34,6 (23,5)	0,309	34,2 (22,5)	0,769
	No	34,2 (22,2)		18,8 (16,8)		37,7 (25,1)	
Post-ext.	Yes	37,8 (23,6)	0,549	37,4 (23,3)	0,340	38,4 (24,9)	0,902
	No	36,2 (23,0)		26,6 (9,1)		38,9 (25,7)	

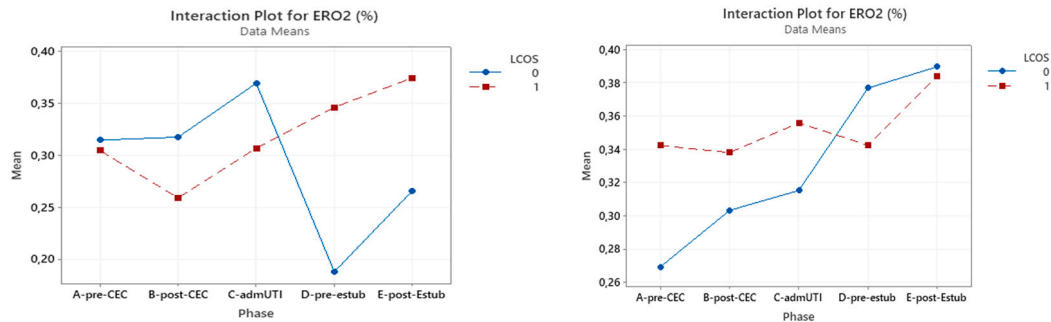


Figure 4. Interaction plot for ERO2 in relation to Low Cardiac Output Syndrome (LCOS) onset (0=no development of LCOS, 1=development of LCOS) in the two subgroups cyanotic (left) and acyanotic (right) at the different sampling times. Abbreviations: A-pre-CEC: at anesthesia induction (pre-CPB), B-post-CEC: at CPB discontinuation, C-admUTI: upon intensive care unit admission, D-pre-estub: before extubation; E-post-Estub: after extubation.

3.5. $\Delta P(v-a)CO_2$

$\Delta P(v-a)CO_2$ was significant in pre-CBP considering the whole group ($p=0.034$). In the cyanotic group only in the pre-CBP phase a statistically significance was reached ($p=0.018$), while in the acyanotic group this result was obtained in the post-CBP phase ($p=0.013$). (Table 8)(Figure 5)

Table 8. Delta $P(v-a)CO_2$ values (mmHg) at the different sampling times correlated with presence/absence of Low Cardiac Output Syndrome (LCOS). Abbreviations: LCOS (Low cardiac output syndrome), CPB (Cardiopulmonary bypass), ICU (Intensive Care Unit), SD (standard deviation), CHD (congenital heart defect).

Samplingtimes	Whole population			Cyanotic CHD		Acyanotic CHD	
	LCOS	Mean value (SD) mmHg	P-value	Mean value (SD) mmHg	P-value	Mean value (SD) mmHg	P-value
Pre-CPB	Yes	6,49(4,71)	0,034	5,39 (3,67)	0,018	7,89 (5,57)	0,734
	No	8,27 (3,92)		9,56 (4,50)		7,97 (3,71)	
Post-CPB	Yes	8,25 (5,11)	0,837	6,24 (3,94)	0,512	12,24 (6,93)	0,013
	No	8,26 (5,21)		8,00 (5,22)		7,80 (3,83)	
ICUadm.	Yes	10,29 (5,85)	0,303	11,13 (6,46)	0,650	9,22 (4,95)	0,990
	No	8,92 (5,66)		10,13 (7,81)		8,55 (4,99)	
Pre-ext.	Yes	8,43 (6,98)	0,512	8,94 (8,02)	-	7,75 (5,58)	0,646
	No	7,00 (5,05)		2,00 (-)		6,93 (5,13)	
Post-ext.	Yes	6,85 (5,86)	0,734	7,58 (6,79)	0,99	7,89 (5,57)	0,734
	No	6,96 (5,71)		6,50 (4,95)		7,97 (3,71)	

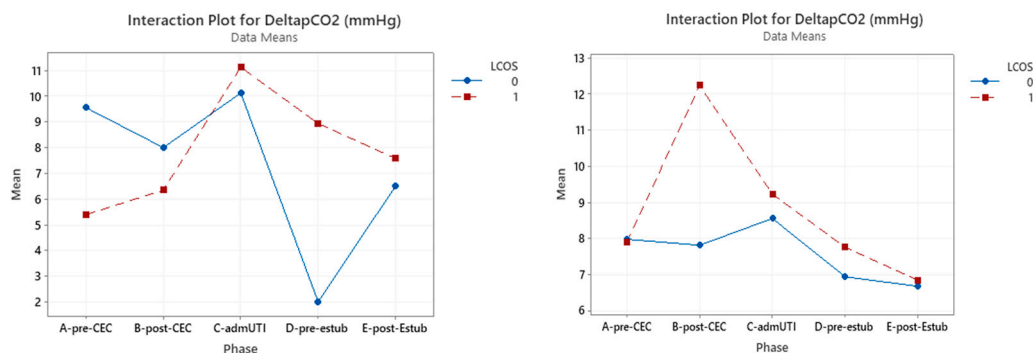


Figure 5. Interaction plot for $\Delta P(v-a)CO_2$ in relation to Low Cardiac Output Syndrome (LCOS) onset (0=no development of LCOS, 1=development of LCOS) in the two subgroups cyanotic (left) and acyanotic (right) at the different sampling times.. Abbreviations: A-pre-CEC: at anesthesia induction (pre-CPB), B-post-CEC: at CPB discontinuation, C-admUTI: upon intensive care unit admission, D-pre-estub: before extubation; E-post-Estub: after extubation.

4. Discussion

Organ perfusion monitoring is crucial in the management of acute circulatory failure and its evaluation needs to be both clinical and biological. The ideal marker of organ perfusion should be quick, not invasive and easy to measure. The aim of this study was to assess the possible role of some commonly used perfusion markers (such as serum lactate and $ScVO_2$) and some others more seldom used (ERO_2 , $\Delta P(v-a)CO_2$, ratio $\Delta P(v-a)CO_2/\Delta C(a-v)O_2$) to identify the onset of LCOS and of an anaerobic state.

LCOS early recognition and treatment are crucial in order to avoid ischemic tissue damage and multiorgan failure.

Serum lactate concentrations are frequently used to detect an anaerobic state, but their rise is often delayed and therefore inadequate. Lactate levels are often inappropriate in the cardiac surgery setting as hyperlactatemia may occur as a consequence of surgical stress, use of beta-adrenergic drugs [9] or lactate lung production [10]. Within surgical stress lactate washout is indeed reduced and production is enhanced by the anaerobic glycolysis pathway. [11] Moreover, the surgery related blood flow improvement, especially for renal and coronary perfusion, is associated with higher lactate washout with consequent increased serum levels [12][13]. Nonetheless, high and persistent lactate levels are not justified by these mechanisms.

This study shows that increased serum lactate concentrations are associated with the development of LCOS in the pre- and after-CPB and ICU admission samples. Therefore, we can define lactate as a reliable LCOS predictor, even though interaction curves might suggest an influence of CPB.

$ScVO_2$ is another commonly used marker of tissue hypoxia. This marker has been widely used in pediatric cardiac surgery for a long time, but its use is limited by residual interatrial or intraventricular shunt. We observed a significant association between LCOS and $ScVO_2$ in pre-CPB and post extubation samples in the whole population and in the pre-CPB in the acyanotic CHD. CPB seems to have a different impact on $ScVO_2$ values according to the child's cardiopathy, decreasing in the acyanotic one and increasing in the cyanotic group. This might be ascribable to an improved perfusion in the cyanotic group.

ERO_2 expresses the relationship between DO_2 and VO . When CO is significantly reduced (e.g., blood loss, tamponade, anemia or hypoxia), an increase in ERO_2 allows VO_2 to remain stable until DO_2 lowers to the critical cut-off and an anaerobic state is initiated. We found indeed that LCOS was significantly related with this marker only pre-CPB within the whole population and in the acyanotic cohort.

Recently, the $\Delta(v-a)CO_2$ has been proposed as a marker of hypoperfusion.[14] It correlates with CO in adult critically ill patients, being its increase associated with lower CO and higher morbidity.

[15] Little is known about the utility of ΔPCO_2 in the monitoring of pediatric patients after cardiac surgery. In pediatric patients a relationship between ΔPCO_2 and ScVO_2 has been demonstrated after complete reparation of cardiac defects [16]. Rhodes et al. recently studied the ability of ΔPCO_2 to predict a poor outcome associated with LCOS in children, concluding that this marker correlates with both cardiac output and oxygen delivery and it may identify patients at risk for important morbidity immediately upon admission in ICU. [17] Within our study ΔPCO_2 could predict LCOS in the whole population and in the cyanotic CHD group in the pre-CBP phase, it was significantly associated also with LCOS in the post-CBP sample in the acyanotic group. Therefore, it might be an important prognostic tool in this specific groups of patients.

$\Delta\text{P(v-a)CO}_2/\Delta\text{C(a-v)O}_2$ has been demonstrated to be more sensitive than serum lactate levels thanks to the shorter timeframe for signs of hypoperfusion, and more specific as it can detect situations leading to an increase in serum lactates not depending on hypoxia. [15] Nevertheless, it was not a reliable marker of anaerobic metabolism in our pediatric cardiac population and, therefore, this ratio could not be suggested to predict LCOS in this setting. Our findings are not aligned with the current available literature: Monnet et al. [7] and Du et al. [8] demonstrated that this ratio is a marker of anaerobic metabolism, hence apt to predict an adequate response to a DO_2 challenge. However, these studies did not evaluate the ratio as a prognostication marker for LCOS onset.

Patel et al. [18] considered $\Delta\text{P(v-a)CO}_2/\Delta\text{C(a-v)O}_2$ as a tool to predict the onset of anaerobic metabolism during CPB. Similarly, Mekontso et al [19] showed its ability to detect anaerobic metabolism in a more reliable way when compared to other indexes (SaO_2 , ScVO_2 , ERO_2 , ΔPCO_2), but none of them investigate its ability to predict and/or detect LCOS. Recently, Dubin et al. [20] found that $\Delta\text{P(v-a)CO}_2/\Delta\text{C(a-v)O}_2$ is not a reliable marker of anaerobic metabolism in the case of hemodilution. Due to their reduced circulating blood volume and to the need of pre-filling the bypass circuit, pediatric patients are potentially more exposed than adults to hemodilution.

Our results should be interpreted in the light of this last finding. Indeed, the ratio inability to adequately reflect a reduction in blood flow might be due to the fact that in a situation of hemodilution this marker is primarily influenced by hemoglobin rather than by anaerobiosis.

Despite not significant, patients with low CO during CPB presented higher ratio values and, in these patients, an increasing trend can also be observed in the following phases suggesting hypoperfusion during and after CBP. This means that the increase in ratio values during and following CPB can suggest that the patient might be poorly perfused.

Serum lactates are confirmed to be a good marker of hypoperfusion also at the end of CPB and at ICU admission, even though its trend might be amplified by CPB itself.

On the other hand, ScVO_2 is a reliable indicator of low perfusion even after extubation.

The complexity of hemodynamic monitoring in patients following cardiac surgery and its need to embrace multiple sets of parameters rather than just following a single biomarker trend has recently been studied by Hong et al [21] who successfully developed several machine learning models to predict LCOS onset after surgery. In its study he demonstrated that as many as 11 parameters (between biomarkers, echocardiography and clinical indicators) were necessary to successfully predict LCOS onset in a cohort of adults patients undergoing cardiac surgery.

Another recent study [22] demonstrated the positive correlation between a score composed by 8 items (namely ejection fraction, oliguria, fluid bolus need, capillary refill time, inotrope requirements, arterial lactates and cerebral NIRS) and the length of hospital stay, ICU length of stay, vasoactive-inotropic score, lactate mean and aortic clamp duration in a population of 54 pediatric patients following cardiac surgery.

One single marker cannot detect hemodynamic instability and the evaluation of a critical patient must include a comprehensive approach (clinical course, vital signs, hemodynamic and tissue perfusion monitoring). For instance, after cardiac surgery hyperlactatemia is not exclusively a sign of only anaerobic metabolism, and neither do adequate values of ScVO_2 show that resuscitation is being conducted adequately with absolute certainty. The ratio could be a useful parameter for physicians

to detect LCOS only if considered together with clinical, laboratory and instrumental data collected during hemodynamic alterations in a critical care setting.

Moreover, the choice of the anticoagulation strategy during CPB or ECMO support could also play a role in defining the severity of hypoperfusion, affecting the development of complications. In the pediatric population, the use of bivalirudin compared to heparin seems to be able to reduce the risk of bleeding and thrombosis. This could guarantee a better hemodynamic stability, with reduced need of resuscitation therapies and an improved microcirculatory perfusion. Recently, the use of Nafamostat Mesylate (NM), a new regional anticoagulant, has been proposed during ECMO assistance in pediatric and adult patients who had evidence of adverse events due to heparin therapy (resistance, heparin-induced thrombocytopenia, clinically uncontrolled bleeding) [24]. This serine-protease has shown pleiotropic effects like the ability, when administered before myocardial reperfusion in animal experimental models of cardiac infarction, to modulate the inflammatory response and reduce myocardial damage. The suppression of both complement-mediated response and neutrophil activation was associated with an advantage in terms of survival in ECMO patients treated with NM. Considering this evidence, it could be interesting to understand if the choice of the anticoagulation strategy could influence the onset of LCOS, identified through common markers of tissue perfusion.

This study has some limitations. First, the study was conducted on a small convenient sample of patients (even though comparable to other studies in the field) who presented a large variability for age and underlying cardiac defects.

Second, only patients who underwent open heart surgery with the use of CPB were studied. Third, practice variability with respect to sedative and catecholamine administration may represent a confounder.

Finally, even if we have taken into account the capacity of 5 markers in predicting LCOS development, this study has not evaluated the capacity of capillary refill time (CRT) in predicting the onset of organ dysfunction. Capillary refill time is defined as "time required for return of color after application of blanching pressure to a distal capillary bed". Nowadays a lot of literature evidence [23,24] suggests that a prolonged CRT (>3 seconds) could be used as a simple, rapid, reproducible and non-invasive parameter with a better ability than hemodynamic macroparameters in identifying microcirculatory hypoperfusion, predicting the severity of hemodynamic instability and the response to resuscitation therapies both in sepsis and cardiogenic shock. Even if it has been demonstrated as effective as conventional markers in adults, CRT presents some critical procedural aspects, for instance the site of measurement, the access to this site in many circumstances (for example surgery) and the position in which we have to perform it. These limitations could be even more exacerbated in the pediatric population. For these reasons and considering that we do not currently have guidelines that standardize its execution, its measurement is not a common clinical practice in ICU.

5. Conclusions

$\Delta P(v-a)CO_2/\Delta C(a-v)O_2$ is not able to predict LCOS onset in pediatric patients undergoing cardiac surgery, despite a rising trend during CPB in patients who then develop LCOS. Besides, raised serum lactate concentrations, reduced $ScVO_2$ and increased ERO_2 -measured in the pre-CPB phase- were significantly associated with LCOS onset, thus suggesting them as reliable low perfusion indexes before CPB.

We can conclude that in the evaluation of a cardiac pediatric patient a global approach is always to be preferred, taking into consideration clinical data and invasive and non-invasive monitoring. A comprehensive vision allows for a better outcome prediction compared to single values, despite their accuracy.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Table S1: illustrates the correlation between serum lactate levels and LCOS in the whole population.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Ethics committee: Comitato Etico Territoriale Area Sud-Ovest Veneto, Verona Hospital and University Trust, Italia, Italy protocol code 72485 and date of approval on 12 November 2018.

Data Availability Statement: The data presented in this study are available from the corresponding author on request.

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