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Central venous to arterial carbon dioxide difference monitoring after cardiac surgery in infants and neonates

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Abstract

Objective—Venous to arterial carbon dioxide difference ($AVCO_2$) correlates with cardiac output (CO) in critically ill adults, but its utility in pediatric patients is unclear. We sought to correlate $AVCO_2$ with other CO surrogates (arteriovenous oxygen saturation difference [AVO_2], central venous oxygen saturation [$ScVO_2$], and lactate); as well as investigate its capacity to predict poor outcomes associated with low cardiac output (LCOS) in infants after cardiac surgery with cardiopulmonary bypass (CPB).

Design—Retrospective chart review. Poor outcome was defined as any: inotrope score > 15; death, cardiac arrest, ECMO, unplanned surgical re-intervention.

Setting—Pediatric cardiovascular intensive care unit

Patients—139 infants <90d who underwent CPB, from October 2012 to May 2015.

Measurement and Main Results—296 arterial and venous blood gas pairs from admission (n=139), 6hrs (n=62), 12hrs (n=73), 24hrs (n=22) were included in analysis. For all pairs, $AVCO_2$ was moderately correlated with AVO_2 ($R^2=0.53$, $p<0.01$) and $ScVO_2$ ($R^2=-0.43$, $p<0.01$), but not lactate. On admission $AVCO_2$ was also moderately correlated with $ScVO_2$ ($R^2=0.40$, $p<0.01$)

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and AVO_2 ($R^2 = 0.55$, $p < 0.01$), but not lactate. 34/139 neonates (24.5%) had poor outcome. Median admission $AVCO_2$ was 5.9 mm Hg (3.8, 9.2). Patients with poor outcome had median admission $AVCO_2$ 8.3 mmHg (5.6, 14.9) vs. 5.4 (3.0, 8.4) in those without poor outcome. $AVCO_2$ (AUC=0.69, $p < 0.01$), serum lactate (AUC=0.64, $p = 0.02$) and $ScVO_2$ (AUC=0.74, $p < 0.01$) were predictive of poor outcome. After controlling for covariates, admission $AVCO_2$ remained significantly associated with poor outcome [OR 1.3, 95% CI: 1.1–1.45], including independent association with mortality, [OR 1.2 (95% CI 1.07–1.31)].

Conclusions— $AVCO_2$ is correlated with important surrogates of CO, and is associated with poor outcome and mortality related to LCOS after cardiac surgery in infants. Prospective validation of these findings, including confirmation that $AVCO_2$ can identify LCOS in real-time is warranted.

Keywords

Venoarterial carbon dioxide difference; congenital heart disease; cardiopulmonary bypass; postoperative care; physiologic monitoring; infant

Introduction

Venous to arterial carbon dioxide partial pressure difference ($AVCO_2$) measures the circulatory clearance of tissue carbon dioxide (CO_2) and is correlated with cardiac output (CO) in critically ill adult patients (1–5). Widening of $AVCO_2$ represents an imbalance between CO and tissue CO_2 production. $AVCO_2$ monitoring is gaining momentum as a surrogate of CO in critically ill adults; an increased $AVCO_2$ gradient is associated with decreased CO and morbidity in adult patients with shock from hemorrhage sepsis, and cardiac surgery (1–9).

Low cardiac output syndrome (LCOS) occurs frequently after cardiac surgery in infants and is a major contributor to postoperative morbidity. However there is no consensus for the diagnostic criteria of LCOS and accurate detection of early CO insufficiency may be difficult. Clinicians use metrics such as serum lactate, central venous oxygen saturations ($ScVO_2$), regional near infrared spectroscopy (NIRS), and inotrope requirements as bedside surrogates of CO, but these may be influenced by multiple patient and management factors unrelated to LCOS. Therefore, these variables may have inconsistent discrimination for diagnosis of LCOS and related outcomes. Little is known about the utility of $AVCO_2$ monitoring in the pediatric cardiovascular intensive care unit (CICU). One previous study correlated $AVCO_2$ with $ScVO_2$ after pediatric biventricular cardiac surgery, but didn't evaluate outcomes (10).

In this study we sought to determine if $AVCO_2$ is associated with LCOS after cardiac surgery in infants via correlation with traditional bedside surrogates of CO including serum lactate, $ScVO_2$, and arteriovenous oxygen saturation difference (AVO_2). As a secondary aim, we sought to identify the association between increased $AVCO_2$ and postoperative morbidity and mortality.

Materials and Methods

Patients and data collection

The study was approved and written informed consent was waived by the institutional review board of the University of Alabama at Birmingham. This is a retrospective chart review of all patients < 90 days old admitted to the pediatric cardiovascular intensive care unit (CVICU) at Children's of Alabama from October 2012 to May 2015 who underwent cardiac surgery for congenital heart disease with cardiopulmonary bypass (CPB). Patients were excluded if they did not have paired arterial and venous gases on admission (n=35) or if they required extracorporeal membrane oxygenation (ECMO) before leaving the operating room (n=5).

Demographic data collected included: weight, age at surgery, Society of Thoracic Surgeons - European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Categories (STAT), open chest and single ventricle status. We also collected hospital length of stay (HLOS), length of mechanical ventilation (MV) (time in hours until the first successful extubation of at least 48 hours), admission, 12 hour- and 24 hour- inotrope score (IS), serum creatinine level up to seven days post-surgical intervention, need for post-surgical ECMO, cardiac arrest and mortality. Modified IS was calculated as previously reported (11); milrinone was not included in calculation because of ubiquitous use at our institution.

Blood Gas Data

All paired arterial and venous blood gases in the first 24 hours from admission were collected. Arterial and venous blood gases were "paired" if they were timed within 30 minutes of each other. Measured oxygen saturation, CO₂ and arterial lactate were extracted. The following pairs were included in the analysis: admission, 6 hours, 12 hours and 24 hours. Pairs were assigned to a group if within ± 2 hours of time category. Any gases obtained outside these times were not considered in analysis. AVO₂ was calculated as the difference between the measured arterial minus the measured venous co-oximetry. AVCO₂ was calculated as the difference between the venous and arterial CO₂.

In order to remove pairs contaminated by right to left shunting due to atrial level communication (e.g. single ventricle and/or residual lesions in patients with a line in or near the right atrium), blood gases were excluded from analysis if they met the following criteria: tip of central line in the right atrium on admission chest x-ray and AVO₂ <10 % and AVCO₂ difference <2 mmHg. All blood gas analyses was performed on Radiometer ABL 90-FLEX (Radiometer America ABL90 Inc., Brea, CA, USA).

Definitions

"Poor outcome" was defined a priori as a composite of morbidities related to LCOS. The morbidities included were: IS > 15; death, cardiac arrest, and ECMO within 48 hours of admission; and any unplanned surgical re-interventions during hospital stay. *Only gas pairs obtained prior ECMO, cardiopulmonary resuscitation and surgical re-intervention were included.* Secondary outcomes analyzed were prolonged HLOS and prolonged MV (>75%

of study population for both) and acute kidney Injury (AKI) defined as doubling of baseline serum creatinine within seven days after surgery. ScVO₂ samples were taken from central venous lines.

Statistical analysis

Continuous variables not normally distributed were summarized as a median with interquartile range (IQR), with group comparison performed using the Mann Whitney test. Continuous variables with a normal distribution were summarized as means with standard deviations and compared using the unpaired Student's T-test. Categorical data were compared using Chi square or Fisher's Exact Test as indicated. Paired Samples T- student was used to compare variables across time categories. Bivariate correlations were analyzed using Pearson for parametric variables and Spearman for non-parametric variables. Receiver Operating Curves (ROC) were used to find a discrimination threshold. Multiple Logistic Regression was used to explore the relationship of all oxygen delivery variables (lactate, AVO₂, ScVO₂ and AVCO₂) with death and/or poor outcome. All variables with a p value <0.1 were included in the model. Backward Stepwise method with likelihood ratio was used. Variables with a Wald Statistic >0.1 were removed from the model. OR with 95% confidence intervals are reported. All p values <0.05 were considered statistically significant. All statistical tests were 2-tailed. SPSS® version 23 (IBM® Chicago, IL) was used for all statistical analysis.

Results

Patients

179 surgeries were performed on infants <90 days old during the study period. 139 patients met inclusion and exclusion criteria for analysis. Patient characteristics and their association with poor outcome and mortality are presented in Table 1. Poor outcome and mortality patients had univariate association with single ventricle, open chest and STAT category in the cohort. Poor outcome and mortality were also associated with longer duration of MV and higher prevalence of AKI. Poor outcome but not mortality was associated with longer HLOS (Table 1).

AVCO₂ trends and correlation with other cardiac output surrogate variables

Figure 1 shows the medians and IQR of AVCO₂, AVO₂, ScVO₂ and lactate at all four time points in the first 24 postoperative hours. Median admission AVCO₂ was 5.9 mm Hg (3.8, 9.2). AVCO₂ and AVO₂ significantly increase compared to admission levels over the first 24 hours post-admission while SCVO₂ and lactate decrease. A total of 296 arterial and venous gas pairs were identified for analysis: 139 on admission, 62 at 6 hours, 73 at 12 hours and 22 at 24 hours. Including all 296 pairs, AVCO₂ was moderately correlated with AVO₂ ($R^2=0.53$, $p<0.01$), and ScVO₂ ($R^2=-0.43$, $p<0.01$), but not correlated with lactate ($R^2=0.05$, $p=0.42$). Table 2 shows correlation between AVCO₂ and other makers of oxygen delivery at different time points. On admission, AVCO₂ showed a moderate correlation with AVO₂ but weaker correlation at 6 hours, 12 hours, and 24 hours. AVCO₂ had a negative moderate correlation with ScVO₂ at all time points. These correlations persisted in sub-analysis of single ventricle patients, Table 2. Lactate on the other hand, had weak correlation with

AVCO₂ only at 6 hours and did not significantly correlate with ScVO₂ or AVO₂ at any time points (data not shown).

AVCO₂ and Poor Outcome

34 of 139 infants (24.5%) had poor outcome: (mortality n=14, ECMO n=8, CPR n=19, unplanned surgical intervention n=12, admission IS > 15 n=7). Note, some patients had more than one outcome. Admission AVCO₂, ScVO₂ and lactate levels were significantly associated with poor outcome but not AVO₂ (Table 3). Unadjusted ROC analysis demonstrated admission AVCO₂ (AUC=0.69, p<0.01), serum lactate (AUC=0.64, p=0.02) and ScVO₂ (AUC=0.74, p<0.01) to be predictive of poor outcome but not admission AVO₂ (AUC= 0.57, p=0.25). Multiple logistic regression analysis was performed to identify factors independently associated with poor outcome on admission; single ventricle status, admission lactate levels, and weight were considered and eliminated from the model. After controlling for STAT category and open chest status, admission AVCO₂ remained significantly correlated with poor outcome (Table 4).

AVCO₂ and Mortality

Mortality in the cohort was 14 (10.1%). Admission AVCO₂, AVO₂ and ScVO₂, but not lactate had univariate association with mortality (Table 3). Multiple logistic regression analysis demonstrated only admission AVCO₂ and STAT category remained significantly associated with mortality; odds ratios 1.2 (95% CI 1.07–1.31) and 4.3 (95% CI 1.74–10.42) respectively. Single ventricle, weight, open chest, admission lactate levels, admission ScVO₂ and admission AVO₂ were considered but removed from the model.

AVCO₂ and other outcomes

Admission AVCO₂ was not associated with prolonged CVICU length of stay, prolonged MV or AKI. Patients remaining on inotropes at 24 hours showed a trend towards higher 24 hour AVCO₂ versus patients who had weaned off inotropes: (13.2 [9.9, 14.5]) vs. (8.7 [6.3, 10.4]), p=0.078.

Discussion

This study demonstrates the utility of monitoring AVCO₂ after CPB in infants. AVCO₂ correlates with other known surrogates of CO and oxygen delivery at CVICU admission, (ScVO₂ and AVO₂), and it may detect LCOS in infants after cardiac surgery. Importantly, this correlation remains in patients with single ventricle physiology who may be at highest risk for LCOS. Additionally, this is the first study to demonstrate that elevated AVCO₂ on admission is independently associated with a composite measure of poor outcome in this cohort. The use of AVCO₂ as an adjunct estimate of LCOS and for risk stratification of neonates and infants in the early postoperative period warrants further investigation.

AVCO₂ represents the adequacy of venous blood flow (*or CO*) to clear the CO₂ generated by the peripheral tissues (12). Contrary to oxygen derived variables such as ScVO₂ and AVO₂, AVCO₂ is not impacted by pulmonary venous desaturation, intracardiac shunting, anemia, insufficient inspired oxygen, etc. that may decrease oxygen delivery independent of CO (13–

14). $AVCO_2$ will not deviate if there is normal CO, as the venous and pulmonary blood flow will be sufficient to clear the excess CO_2 produced by hypoxic tissues (12). Therefore, it follows that $AVCO_2$ may have stronger correlation with impaired cardiac index compared to oxygen derived variables. Combining $ScVO_2$ with $AVCO_2$ monitoring may enable the clinician to more accurately target the management of LCOS and/or tissue hypoxia in this high risk population.

This study provides the first “normal values” of $AVCO_2$ for a heterogeneous group of infants after CPB at four time points: CVICU admission, 6, 12 and 24 hours (Figure 1). We did not identify a cutoff for “elevated” $AVCO_2$ *a priori* for this study - as this value has yet to be determined in this cohort of infants <90 days old after cardiac surgery with CPB (10). The median *admission* $AVCO_2$ in our cohort was 5.9 mmHg. It rises over next several hours - peaking at 12 – 24 hours with a median of 10.5 mmHg. It is unclear why the $AVCO_2$ continues to increase after admission; this time course may mirror the presence of LCOS that often follows CPB and cardiac surgery in infants. Prospective validation of our “normal” $AVCO_2$ values across a strata of surgical procedures and patient characteristics is necessary before they can be used as reference values. It is likely that there is a difference in “normal” $AVCO_2$ values among high and low risk cohorts as well as single ventricle versus two ventricle physiologies.

Postoperative LCOS is a well described clinical condition after cardiac surgery in neonates and infants and is likely a major contributor to morbidity and mortality. However, there is a lack of consensus on diagnostic criteria for LCOS. Clinicians often use deviations in serum lactate, $ScVO_2$, AVO_2 , and NIRS as surrogates of LCOS at the bedside. They have shown to have significant, yet imperfect and variable levels of correlations with LCOS (15–21). We offer $AVCO_2$ as another potential bedside metric to be considered for inclusion into scoring systems or diagnostic criteria to improve current definitions of LCOS. Not only does $AVCO_2$ have moderate correlation with other CO surrogates (SVO_2 and AVO_2), but the additional association of elevated $AVCO_2$ in patients with persistent inotropic support as well as its association with morbidity and mortality related to low CO, gives indirect evidence that elevated $AVCO_2$ may reflect real time LCOS.

Several adult studies have demonstrated that $AVCO_2$ is correlated with simultaneous measures of cardiac index (1–5). Additionally, studies in critically ill adults after abdominal surgery or with septic shock demonstrated that patients with an increased $AVCO_2$ gradient were more likely to have increased postoperative complications and poor outcomes, including death - even in patients who had a normal $ScVO_2$ (>70%) (6, 9, 22–23). In our cohort, increased $AVCO_2$ was associated with poor outcome even after controlling for STAT category and other covariates. Of the four variables evaluated (admission $ScVO_2$, AVO_2 , lactate, $AVCO_2$), only admission $AVCO_2$ remained significantly associated with death after adjusting for STAT category. Potential to identify a cohort of patients at high risk for LCOS and related morbidity immediately upon postoperative admission to the CVICU, independent of their surgical risk category, makes $AVCO_2$ a particularly promising monitoring tool. Unfortunately, due to the flatness of our ROC curve we were unable to identify a well performing cut-off $AVCO_2$ value that was associated with poor outcome in this cohort (figure not included). Combining $AVCO_2$ (a physiologic estimate of LCOS) with

a validated therapy-based LCOS surrogate (i.e. IS) at CVICU admission could be a next step for prospective research in this area - with the aim to create a score for accurate and early diagnosis of real-time LCOS as well as the ability to precisely predict morbidity directly related to LCOS (11).

Beyond those already discussed, our study has limitations including those inherent with any retrospective study. The study population was a cohort of infants <90 days old, and our findings may not be generalizable to other populations with cardiac disease or similar cohorts at different institutions. Although $AVCO_2$ correlates with some surrogates of LCOS, we do not compare $AVCO_2$ to concurrent echocardiograms or invasive hemodynamic cardiac index monitoring to determine the true capacity of $AVCO_2$ to directly measure/identify LCOS. Additionally, due to its retrospective nature and limitations of hourly electronic charting, we could not precisely compare $AVCO_2$ to simultaneous hemodynamic variables, NIRS, IS, or preload augmentation to support presence of LCOS. Prospective evaluation of $AVCO_2$ with real-time clinical markers and therapeutic interventions consistent with LCOS is necessary to validate the discriminative ability of $AVCO_2$ to identify LCOS. To investigate the association of $AVCO_2$ with postoperative morbidity, we chose a composite poor outcome given the relative low incidence of each complication. Though we demonstrated $AVCO_2$ association with important outcomes that are certainly associated with presence of LCOS, we concede some items of our composite poor outcomes could occur without LCOS. Our retrospective study was subject to the selection bias of drawing more laboratory samples in patients that had higher severity of illness. Utilization of only the admission blood gas pairs for the outcomes part of this analysis minimized this bias as all patients were subject to protocolized laboratory draw at this time point. Removing atrial line blood gases from our analysis limits the ability to generalize our findings to cohorts or institutions that utilize atrial lines.

Conclusions

Postoperative LCOS is an important source of morbidity after cardiac surgery with CPB in infants; however there is lack of consensus for diagnostic criteria of this clinical condition. In this study, we highlight the potential importance of monitoring $AVCO_2$ in infants with complex congenital heart disease after surgery with CPB and suggest $AVCO_2$ may be an important bedside tool to detect or confirm the presence of LCOS. $AVCO_2$ correlates with other well-studied CO and oxygen delivery variables, and an elevated $AVCO_2$ appears to be associated with morbidity and mortality. Importantly, $AVCO_2$ may identify patients at risk for important morbidity immediately upon admission to the CVICU. Prospective validation, including confirmation of ability of $AVCO_2$ to identify LCOS in real-time is warranted. Future research is needed to determine if the ability of $AVCO_2$ to independently predict clinical outcomes is reproducible and if combination with other clinical data, such as IS, could provide an early metric for severity of illness stratification as well as a target for quality improvement and clinical research initiatives.

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Figure 1.

Cardiac output surrogate variables over time, median and interquartile range

Abbreviations: AVCO₂, arteriovenous partial pressure of carbon dioxide difference (mmHg);

AVO₂, arteriovenous oxygen saturation difference (%); SVO₂, central venous oxygen

saturation (%); lactate (mmol/L)

Table 1

Cohort demographics and outcomes

Demographics	All (N=139)	Poor Outcome (N=34)	No Poor Outcome (N=105)	p value	Mortality (N=14)	No Mortality (N=125)	p value
Weight, kg	3.42 ± 0.77	3.20 ± 0.54	3.50 ± 0.82	0.06	3.24 ± 0.47	3.43 ± 0.79	0.38
Age, days	12 (6.38)	10 (6.22)	13 (6.53)	0.30	10 (6, 22.5)	12 (6, 44)	0.32
Single ventricle, n (%)	58 (41.7)	22 (37.9)	36 (62.1)	<0.01	11 (64.9)	47 (37.6)	<0.01
STAT category, n (%)				0.01			<0.01
1	11 (7.9)	0 (0)	11 (100)		0 (0)	11 (8.8)	
2	29 (20.9)	5 (17.2)	24 (82.8)		1 (7.1)	28 (22.4)	
3	19 (13.7)	2 (10.5)	17 (89.5)		0 (0)	19 (15.2)	
4	56 (40.3)	16 (28.6)	40 (71.4)		6 (42.9)	50 (40)	
5	23 (16.5)	11 (47.8)	12 (52.2)		7 (50)	16 (12.8)	
None	1 (0.7)	0 (0)	1 (100)		0 (0)	1 (0.8)	
Open chest, n (%)	33 (23.7)	17 (51.5)	16 (48.5)	<0.01	7 (50)	26 (21)	0.04
Outcomes							
Acute kidney injury, n (%)	49 (35.2)	19 (38.7)	30 (61.3)	0.01	10 (71.4)	39 (31.7)	<0.01
Hospital length of stay, days	18 (7, 30)	30 (22, 51)	12 (7, 28)	<0.01	32 (5.7, 81.2)	15.5 (7, 29)	0.11
LMV, hours	46 (21, 414)	158 (89, 331)	28 (16, 66)	<0.01	206 (94, 642)	41 (18, 95)	<0.01

Data presented as mean with standard deviation or median with interquartile ranges. LMV, length of mechanical ventilation; STAT, Society of Thoracic Surgeons - European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Categories

Table 2Correlations (R^2) between arteriovenous carbon dioxide difference and cardiac output surrogates

Post-operative time point	AVO ₂	p value	ScVO ₂	p value	Lactate	p value
Admission AVCO ₂ (n=139)	0.55	<0.01	-0.40	<0.01	0.02	0.85
6 hour AVCO ₂ (n=62)	0.46	<0.01	-0.37	<0.01	0.33	<0.01
12 hour AVCO ₂ (n=73)	0.49	<0.01	-0.33	0.01	0.13	0.27
24 hour AVCO ₂ (n=22)	0.45	0.04	-0.49	0.02	0.32	0.14
Admission AVCO ₂ , single ventricle patients (n=58)	0.68	<0.01	-0.45	<0.01	0.13	0.33

AVCO₂, arteriovenous carbon dioxide partial pressure difference; AVO₂, arteriovenous oxygen saturation difference; ScVO₂, central venous oxygen saturation

Table 3

Admission variables and outcomes

Admission Variable	Poor Outcome (N=34)	No Poor Outcome (N=105)	p value	Mortality (N=14)	No Mortality (N=125)	p value
AVCO ₂ (mmHg)	8.3 (5.6, 14.9)	5.4 (3.0, 8.4)	<0.01	7.4 (5.4, 11.9)	5.8 (3.4, 9.2)	0.04
AVO ₂ (%)	21.2 (12.8, 34.8)	18.1 (13.1, 25.7)	0.29	24.7 (15.3, 37.6)	18.1 (12.6, 25.9)	0.04
ScVO ₂ (%)	60.6 (44.1, 67.5)	71.7 (64.2, 81.2)	<0.01	54.7 (42.7, 66.3)	71 (61.5, 80.7)	<0.01
Lactate (mmol/L)	4.2 (2.0, 10.1)	2.3 (1.6, 4.2)	0.02	2 (1, 12.3)	2.6 (1.6, 5)	0.42

Data presented as median with interquartile ranges.

AVCO₂, arteriovenous carbon dioxide partial pressure difference; AVO₂, arteriovenous oxygen saturation difference; ScVO₂, central venous oxygen saturation

Table 4

Independent Associations with Poor Outcome

Variable	Odds Ratio	95% Confidence Interval
Admission AVCO ₂	1.3	1.1–1.45
STAT Category	1.3	0.72–2.41
Open Chest	3.4	1.1–10.75
Admission AVO ₂	0.9	0.86–0.99
Admission ScVO ₂	0.9	0.89–0.99

AVCO₂, arteriovenous carbon dioxide partial pressure difference; AVO₂, arteriovenous oxygen saturation difference; ScVO₂, central venous oxygen saturation; STAT, Society of Thoracic Surgeons - European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Categories