Venous-arterial CO2 difference to arterial-venous O2 content difference ratio as marker of resuscitation in pediatric septic shock

Yos Kowara, Arie Utariani, Bambang Pujo Semedi, Purwo Sri Rejeki

Abstract

***Objective*: Sepsis is still a major cause of mortality in pediatric intensive care units. During initial resuscitation, central venous oxygen saturation (ScvO2) and/or lactate level have become a standard monitoring target nowadays. Carbon dioxide (CO2) partial pressure difference between central vein and artery (Pv-aCO2) has also been recommended as an additional marker to identify persistent global hypoperfusion. Recently, the Pv-aCO2/Ca-vO2 ratio, which represents respiratory quotient, is presumed to be superior in detecting anaerobic metabolism.**

***Design*: Single center observational analytic research with cross-sectional study.**

***Setting*: Resuscitation Room at academic hospital.**

***Patients and participants*: Twenty-four pediatric patients with septic shock, aged 2 months to 12 years old.**

***Interventions*: Patients were resuscitated at the Emergency Department of Dr. Soetomo General Academic Hospital, Surabaya. Initial first hour therapy included oxygenation, antibiotic administration, fluid bolus, and catecholamine titration. Central venous catheter was inserted in all patients through subclavian or jugular veins.**

***Measurements and results*: Lactate was measured in the first and third hour after patient arrival. Arterial and central vein blood gas analysis was performed concurrently at the third hour. Patients were followed up after 48 hours to assess outcome. Pv-aCO2/Ca-vO2 ratio was more effective compared to ScvO2 and lactate clearance in predicting the 48-hour mortality rate (p 0.047). The cutoff value of the Pv-aCO2/Ca-vO2 ratio of 1.54 had the highest sensitivity and specificity to represent global hypoxia in pediatric patients with sepsis.**

***Conclusion*: Pv-aCO2/Ca-vO2 ratio is a useful marker in predicting mortality in pediatric patients with septic shock.**

Key words: Pediatric emergency medicine, septic shock, oxygen consumption, venous-arterial PCO2 difference, respiratory quotient, critical care outcomes.

Introduction

Sepsis is still a major cause of morbidity and mortality in children. The cross-sectional global study of 128 Pediatric Intensive Care Units (PICUs) in five continents by SPROUT, which took five days randomly during 2013-2014, reported that 569 out of 6925 children (8.9%) met the criteria of severe sepsis with the highest morbidity and mortality at 38% during the first year of life. As many as 67% experienced multi-organ dysfunction when diagnosed early. (1) All dysfunctions lead to regional and even cellular hypoxia in global tissue, which leads to high morbidity and mortality.

Current guidelines for hemodynamic management of severe sepsis and septic shock recommend the use of global tissue hypoxia markers as the ultimate target of resuscitation. (2) Early identification of tissue hypo perfusion and adequate resuscitation are key factors in the management of patients with shock. During the initial resuscitation period, targeting central venous oxygen saturation (ScvO2) or lactate, or a combination of both, have been widely used. (2,3) However, each of these two variables has its own limitations. The use of ScvO2 seems to provide better real-time information than

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lactate. Sepsis itself basically cause microcirculation heterogeneity, which results in capillary shunting. This is evident in the high ScvO2 value. Indeed, abnormally high ScvO2 values have been associated with increased mortality in patients with septic shock. (4) There is no consistent advantage found for lactate-based resuscitation over resuscitation guided by oxygen parameters. Thus, additional markers of inadequate perfusion must be explored, especially when the ScvO2 value is close to normal. (4)

Recently, the central venous-arterial carbon dioxide partial pressure difference (Pv-aCO2) is recommended as a complementary tool to identify patients with persistent global hypoperfusion. (5) A cutoff value of 6 mmHg reflects whether global oxygen flow is sufficient (gap <6 mmHg) or insufficient (gap ≥6 mmHg). (6) In fact, high Pv-aCO2 predicts clinical outcomes independently of oxygen-based parameters and can predict lactate variation. (7) Rhodes conducted a retrospective study of 139 infants aged less than 30 days who underwent cardiopulmonary bypass heart surgery. Patients with poor outcomes had differences in arterial and venous CO2 with a median value of 8.3 mmHg compared to 5.9 mmHg and this was in line with the values of lactate and ScvO2. (8) Besides prognostic value, the combination of arterial and venous CO2 gaps and the use of ScvO2 have been widely used to guide resuscitation of septic shock patients. (9,10)

In addition, several studies have suggested correcting the weakness of Pv-aCO2 by comparing Pv-aCO2 with differences in oxygen content from the central artery to the vein (Ca-vO2). The Pv-aCO2/Ca-vO2 ratio that represents the ratio of VCO2/VO2 (respiratory quotient) is superior to only Pv-aCO2 for detecting anaerobic metabolism. (11) Mekontso-Dessap, et al showed a Pv-aCO2/Ca-vO2 ratio >1.4 is superior to Pv-aCO2, ScvO2, or Ca-vO2 alone in predicting hyperlactatemia in critical adult patients. (12) More importantly, the variation in the Pv-aCO2/Ca-vO2 ratio is faster than the lactic acid kinetic, which makes it an interesting variable to monitor. In adult patients, Mesquida studied 35 patients with septic shock with criteria of 5.6±2.1 mmHg and a Pv-aCO2/Ca-vO2 ratio of 1.6±0.7 mmHg.dl/ml O2. Adult patients with lactate, which did not drop, have a higher ratio (1.8±0.8 vs 1.4±0.5). The cutoff ratio of 1.4 mmHg.dl/ml showed a sensitivity of 0.8 and specificity of 0.75 for predictions of lactate repair. (13) Another study in 84 adult septic patients has also shown a high ratio of Pv-aCO2/Ca-vO2 related to the poor lactate clearance after resuscitation, even more so than ScvO2. (7)

In this study, we discuss the question of whether Pv-aCO2/Ca-vO2 ratio is useful in predicting early mortality compared with another hypoxia marker such as ScvO2, lactate, DO2, a VO2 for pediatric septic patients. Tissue hypoxia itself refers to the imbalance between supply (oxygen delivery) and demand (oxygen consumption). (14) Measurements of oxygen delivery and consumption (both directly and indirectly) will determine the severity global tissue hypoxia, similar to how lactate represents this condition. There have been no in-depth studies of this marker in pediatric patients.

Material and methods

Study design and setting

We evaluate every pediatric patient admitted to the Resuscitation Room of Dr. Soetomo General Academic Hospital from February to April 2019. As many as 12 to 15 pediatric patients were admitted to the Resuscitation Room each month during the study. The Resuscitation Room only accepts code blue patients according to the Canadian triage criteria. The ethics commission of Dr. Soetomo General Academic Hospital has given approval for this study.

Participant selection criteria

Pediatric patients who met the following criteria were recruited into the resuscitation protocol: 1) Age 2 months - 12 years, 2) Suspect sepsis which was confirmed with 3 of the 8 sepsis signs (heart rate, systolic blood pressure, respiratory rate, temperature, pulse, capillary refill time, perfusion, consciousness) according to ACCCM-PALS guideline. (2) During the first hour, patients received standard protocols, the first being oxygenation either by administering supplemental oxygen or intubation with controlled ventilation if patient was likely to develop respiratory failure. Simultaneously, intravenous or intraosseous line was inserted, administration of crystalloids (according to body weight) and antibiotics. For initial screening, a complete blood and lactate examination (lactate-1) were carried out. If patient succumbed into fluid resistant shock, inotrope or vasopressor was administered to raise blood pressure. The exclusion criteria were 1) Major congenital heart abnormalities with the presence of shunting, 2) Lactate-1 value <2 mmol/l, 3) Pediatric Logistic Organ Dysfunction (PELOD) score <11 to assess the severity of 6 organ dysfunctions, 4) SpO2>92% due to Haldane effect.

Exposures and outcomes

After the first hour, patients were divided into cold or warm shock with normal or low blood pressure.

Type of shock was determined with support of echocardiography to analyze hemodynamic values. Echocardiographic examination was focused on inferior cava vein examination, heart contractility, and systemic vascular resistance conditions. We administered fluid bolus, inotrope or vasopressors based on echocardiography results combined with clinical condition. Central venous catheter was placed through a left or right internal jugular vein or subclavian vein with ultrasonography guidance. Confirmation of the catheter's tip was done by chest X-ray. During the next 2 hours, the condition was closely monitored for oxygenation and ventilation, improvement in perfusion, vital signs, level of consciousness, and urine production. If surgery was needed, such as thoracocentesis due to pulmonary empyema, or laparotomy due to intra-abdominal infection, the patients were prepared for operative procedure immediately.

Blood gas analysis from artery and central vein were measured 3 hours post resuscitation. Parameters taken into account include as acidity (pH), arterial oxygen tension (PaO2), arterial carbon dioxide tension (PaCO2), arterial saturation (SaO2), central venous oxygen tension (PvO2), central venous carbon dioxide tension (PvCO2), and central venous saturation (ScvO2). Cardiac index (CI) was measured with echocardiography 3 hours following resuscitation along with sampling of hemoglobin concentration (Hb) and lactate (lactate-3). These variables of global hypoxia were measured: lactate clearance (LC), arterial oxygen content (CaO2), oxygen delivery (DO2), arterial-venous oxygen content difference (Ca-vO2), oxygen consumption (VO2), oxygen extraction ratio (O2ER), venous-arterial carbon dioxide tension difference (Pv-aCO2). Patients were followed for 48 hours in intensive care unit.

- LC=lactate-1 - lactate-3 / lactate-1 x 100%
- CaO2=(Hb x 13.4 x SaO2) + (PaO2 x 0.0031)
- DO2=CI x CaO2
- Ca-vO2=CvO2 - CaO2
- VO2=CI x Ca-vO2
- O2ER=VO2 / DO2 x 100%
- Pv-aCO2=PvCO2 - PaCO2
- Ratio Pv-aCO2 / Ca-vO2=Pv-aCO2 / Ca-vO2

Statistical analysis

Statistical analysis was performed with SPSS statistics software version 20. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as the absolute number and proportions (%). A descriptive analysis was performed. Comparisons between 48-hour survival and non-survival were performed with binary logistic regression. Two-tailed $p<0.05$ was taken to indicate statistical significance. The ability of the Pv-aCO2/Ca-vO2 ratio for predicting mortality was calculated using a receiver operator characteristic (ROC) curve, and a cutoff value was counted to get the best sensitivity and specificity.

Results

From the 24 patients admitted to this study, 17 patients survived within 48 hours after initiation of resuscitation, while 7 patients did not. Patient demographic, early assessment and procedures undertaken were described in **Table 1**. Between these two groups, age and initial diagnosis of abdominal infection had a p value less than 0.250. These two variables then analyzed further using multivariate regression. There was no significant difference in variations of the initial diagnosis of the four organ systems and the procedures performed between the two groups. Initial clinical conditions including heart rate, systolic blood pressure, and arterial mean pressure did not differ between the two groups. The assessment of the expected sepsis variable also did not differ between the two groups. Similarly, the amount of fluid given during the first hour was not different, i.e. between 20-30 ml/kg. For initial prognostic factors, PELOD scores showed 2-4 organs failure in both groups.

Laboratory results regarding Hb, pH, and $[H^+]$ statistically showed p value <0.25. The difference in lactate clearance >10% did not correlate with the outcome of survival within 48 hours (p>0.25). For the seven oxygenation markers, Pv-aCO2 and ratio of Pv-aCO2/Ca-vO2 showed p value <0.25 between survivor and non-survivor groups. The Pv-aCO2/Ca-vO2 value in the survivor group (1.24±0.88 mmHg.dl/ml O2) was lower than non-survivor group (2.16±0.91 mmHg.dl/ml O2).

Results of the univariate test based on the 48 hour survival, generated 7 variables with p value <0.025, including age, abdominal infection, Hb, pH, $[H^+]$, Pv-aCO2, and Pv-aCO2/Ca-vO2 (**Table 2**). Therefore, these 7 variables were subjected to multivariate analysis (**Table 3**). The multivariate analysis results showed that only Pv-aCO2/Ca-vO2 value was significant in predicting the 48 hour outcome with RR 2.95 (95% CI 1.016-8.565), which means that patients with higher Pv-aCO2/Ca-vO2 ratio are 2.95 times more likely to die within 48 hour than those with lower Pv-aCO2/Ca-vO2 ratio, with the lowest deviation of 1.016 times and the highest deviation of 8.565 times.

To determine cutoff of Pv-aCO2/Ca-vO2 ratio, receiver operator characteristic (ROC) curve (**Fig-**

ure 1) was used. A cutoff value was calculated to determine the best sensitivity and specificity to predict 48 hour mortality (**Figure 2**).

Discussion

There was no significant difference in DO2 between survivor and non-survivor groups. In survivor group, DO2 was 578 ml/m2/min and in non-survivor group was 606 ml/m2/min. Value of VO2 in the two groups did not differ significantly. This showed that optimization in DO2 and VO2 during early resuscitation of pediatric septic patients did not affect the 48-hour outcome. This is in line with resuscitation studies based on DO2 and VO2 values in adults, which also did not show superiority compared to EGDT (early goal-directed therapy). The targets of DO2 resuscitation ≥600 ml/m2/min, and VO2≥170 ml/m2/min had not been shown to improve survivability. (14) In pediatric patients, the metabolic rate is higher per body surface area than adults, but this study shows similarity in the pathophysiology of sepsis in pediatric oxygen consumption. An adult study in septic patients with a lactate cutoff outcome of 2 mmol/l showed DO2 value 427-471 ml/m2/min and an VO2 value 109-127 ml/m2/min. (12) The normal value of ER in adult sepsis patients was around 25%. In pathological experiments in animals, O2ER reaches a critical ratio of 70%. (15) In this study the average O2ER was 37% in survivor group and 30% in non-survivor group, where there were no significant difference. This means that it has been proven that therapy based on DO2 balance and VO2 does not cause clinical differences in pediatric patients with mild or severe sepsis severity. In adult patients, a study of sepsis with a reference to lactate 2 mmol/l, the two groups also showed no difference in O2ER that was 27-28%. (12)

Pv-aCO2 is widely used combined with the ScvO2 value to describe tissue oxygenation. In adult sepsis patients, Pv-aCO2 ≥6 mmHg means good cellular level oxygenation function. When combined with low ScvO2 (<70%), it can be concluded that patients experience shock with circulatory failure, and immediate action is required to increase DO2. (7) In this pediatric study, the average Pv-aCO2 of survivor group was 6.1 mmHg, whereas in the non-survivor group, was 9.8 mmHg. When combined with ScvO2 values, the survivor group was 63% and non-survivor group was 70%. This is in line with the study conducted by Mallat, where central venous saturation failed to detect global hypoxia. (16) This is because responding to the ScvO2 target is not everything, various other variables also need to be considered. In the study of pediatric septic patients, it has been shown how Pv-aCO2 and ScvO2 cannot be a benchmark for the success of therapy. What Ospina wrote might be a reason that could explain. Pv-aCO2 may be normal even though hypoperfusion has occurred in very high cardiac output conditions such as septic shock. In this study, both the lactate and survivability groups had optimal DO2 values. High flow can prevent the accumulation of CO2 in the vein. In the same way, Pv-aCO2 can be high in normal perfusion due to the Haldane effect. That is why changes in CO2 must be evaluated together with changes in O2. (17)

Gustavo provides an explanation of the ratio of Cv-aCO2 to Ca-vO2 as an illustration of VCO2 compared to VO2. (18) Similarly, the Pv-aCO2 to Ca-vO2 ratio and the results in this study showed a significant difference for 48-hour survival. Even this ratio is the only hypoxic marker that is superior to ScvO2 or lactate itself. Previous studies have shown that Pv-aCO2/Ca-vO2 ratio and Cv-aCO2/Ca-vO2 ratio could be stronger predictors of ScvO2 in describing global hypoxia in adult septic patients through fluid response to increased VO2. (16) Other study showed a combination of hyperlactatemia and a high ratio of Cv-aCO2/Ca-vO2 correlates with high SOFA scores and 28-day mortality. (17) This finding described that combination of lactate as the end product of anaerobic metabolism, ScvO2 as the result of balance between DO2 against VO2, and the ratio of Pv-aCO2/Ca-vO2 as a representative of VCO2 to VO2, had its own utility to describe global hypoxic conditions in pediatric patients with sepsis. This is in line with what Monnet wrote. Cardiac output (CO) is no longer the only outcome factor in patients with septic shock. (19) The discrepancy between DO2 and VO2, between macrocirculation and microcirculation, and between oxygen utilization and carbon dioxide production explains why the results of this study, Pv-aCO2/Ca-vO2 ratio was the only global hypoxic markers that describe the outcome.

In this study the value of Pv-aCO2/Ca-vO2 ratio of 1.54 has a sensitivity of 0.714 and specificity of 0.706 in predicting global hypoxia in pediatric septic patients. Previous studies only existed in adult patients with sepsis. Mekontso-Dessap used a ratio of 1.412. Mallat used a number of 1.8 as a cutoff value to distinguish groups that responded to an increase in VO2 or not to 98 adult patients on mechanical ventilation. (16) The study conducted by Du for 86 adult patients reported a cutoff value of 1.23 at the 8th hour examination which correlated with lactate clearance. (7)

Study limitations

Several limitations should be taken into account from our study. First, this was a single center study. Second, it would be better if the range of pediatric population was focused on a specific age, especially at the age of less than 6 years according to the major population of this study. Third, this study did not show that lactate clearance had a correlation with mortality in 48 hours. However, lactate is still the standard of successful resuscitation in many protocols or guidelines. Some patients died although having a good lactate clearance because of hypoxia, severe acidosis, or uncorrectable hyperkalemia. And last, we did not calculate Cv-aCO_2/Ca-vO_2 as the standard of presenting VCO_2/VO_2, because there were too many theories about how to calculate Cv-aCO_2 in normal adult patient and yet it is very complicated and needs multistage calculation. (20,21) Some studies had shown that Pv-aCO_2/Ca-vO_2 can replace Cv-aCO_2/Ca-vO_2 if there were no Haldane effect. (22) In hypoxemic patients, carbon dioxide had a greater affinity to haemoglobin than in normal patients that can interfere the calculation of Cv-aCO_2. (23) Therefore, we added hypoxemia as an exclusion criterion for this study.

Conclusion

In this prospective cross-sectional study, we found no difference between oxygen delivery, oxygen consumption, oxygen extraction ratio, lactate clearance, and central vein oxygen saturation in the first 3 hours resuscitation with mortality 48 hours. Although it describes global hypoxia in its own way, this study showed ratio of venous-arterial CO_2 difference to arterial-venous O_2 content difference, which describes cellular respiratory quotient, was the best to represent global hypoxia that leads to early mortality in septic shock patients. The cutoff value of the Pv-aCO_2/Ca-vO_2 ratio of 1.54 had the highest sensitivity and specificity to represent global hypoxia in pediatric with sepsis.

Acknowledgment

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Table 1. Patient demographic, early assessment, and procedure

Subject characteristic	All (n=24)	Survivor 48h (n=17)	Non survivor (n=7)	p value
Gender				0.728
- Male	15 (62.5%)	11 (45.83%)	4 (16.67%)	
- Female	9 (37.5%)	6 (25%)	3 (12.5%)	
Age (months)	27±36	20±29	44±47	0.146
Initial diagnosis				
- Respiratory infection	16 (66.67%)	12 (75%)	4 (25%)	0.528
- Post arrest/near arrest	2 (8.33%)	1 (50%)	1 (50%)	0.511
- Meningo/encephalitis	10 (41.67%)	8 (80%)	2 (20%)	0.409
- Abdominal infection	12 (50%)	10 (83.3%)	2 (16.7%)	0.190
- Urinary tract infection	2 (8.33%)	0 (0%)	2 (100%)	0.999
Clinical condition				
- Heart rate (times/minute)	164±33	166±26	158±48	0.556
- Systolic blood pressure (mmHg)	85±31	85±23	86±46	0.949
- Mean arterial pressure (mmHg)	57±25	58±21	54±34	0.744
- Amount of sepsis variables (n)	5±2	5±1	5±2	0.738
- Loading volume in 1 hour (ml/kg)	27±16	29±17	23±13	0.396
- PELOD score	20±18	17±21	26±9	0.272
Procedure				
- Antibiotic	20 (83.33%)	14 (70%)	6 (30%)	0.841
- Fluid bolus	15 (62.5%)	11 (73.3%)	4 (26.7%)	0.728
- Dobutamine	2 (8.33%)	10 (76.9%)	3 (23.1%)	0.478
- Dopamine	13 (54.17%)	0 (0%)	2 (100%)	0.999
- Norepinephrine	4 (16.67%)	2 (50%)	2 (50%)	0.329
- Adrenaline	1 (4.17%)	0 (0%)	1 (100%)	1.000

Legend: PELOD=Pediatric Logistic Organ Dysfunction. Binary logistic regression; variables with p value <0.25 was analyzed using multivariate regression.

Table 2. Risk variables according to survival

Variables	All (n=24)	Survivor 48h (n=17)	Non survivor (n=7)	p value
Laboratory values				
- Hb (g/dl)	10.0±2.2	9.7±1.97	10.85±2.71	0.249
- Base excess (mmol/l)	-10.0±10.9	-8.8±10.9	-12.9±11.02	0.396
- PaO2/FiO2 ratio (mmHg)	256±116	273±94	217±159	0.285
- pH	7.27±0.15	7.30±0.14	7.20±0.15	0.165
- $[H^+]$ (nmoles/l)	57±20	53±16	66±27	0.180
- ΔpH	0.01±0.16	-0.00±0.17	0.02±0.10	0.755
- Lactate-1 (mmol/l)	3.3±3.5	2.7±2.7	4.6±4.9	0.256
- Lactate clearance (%)	37±36	40±35	30±39	0.547
Oxygenation markers				
- DO2 (ml/m2/min)	586±212	578±249	606±79	0.764
- VO2 (ml/m2/min)	199±92	203±77	189±128	0.723
- O2ER (%)	35.3±15.7	37.5±15.0	30.0±17.4	0.294
- Pv-aCO2 (mmHg)	7.2±5.5	6.1±5.1	9.8±6.0	0.141
- CaO2 (ml.O2/dl)	13.8±2.9	13.4±2.8	14.7±3.2	0.322
- ScvO2 (%)	65.2±16.1	63.2±15.2	69.9±18.5	0.360
- Pv-aCO2/Ca-vO2 (mmHg.dl/ml O2)	1.51±0.97	1.24±0.88	2.16±0.91	0.047

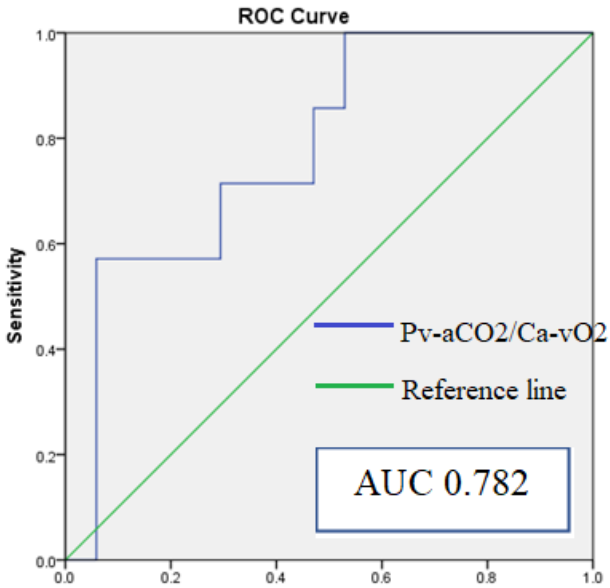
Legend: Hb=hemoglobin; PaO2=arterial oxygen tension; FiO2=concentration of oxygen; pH=acidity; DO2=oxygen delivery; VO2=oxygen consumption; O2ER=oxygen extraction ratio; Pv-aCO2=central venous-arterial carbon dioxide partial pressure difference; CaO2=arterial oxygen content; ScvO2=central venous oxygen saturation; Pv-aCO2/Ca-vO2=ratio of venous-arterial CO2 difference to arterial-venous O2 content difference. Binary logistic regression; variables with p value <0.25 was analyzed using multivariate regression.

Table 3. Multivariate analysis in predicting 48 hour survival

Variable	p value	RR	95% CI
Age	0.960	0.999	0.956-1.044
pH	0.918	0.084	0.000-…
Abdominal infection	0.758	1.602	0.080-32.149
Pv-aCO2	0.838	0.951	0.588-1.538
Hb	0.143	1.775	0.824-3.822
$[H^+]$	0.150	1.046	0.984-1.113
Pv-aCO2/Ca-vO2	0.047	2.950	1.016-8.565

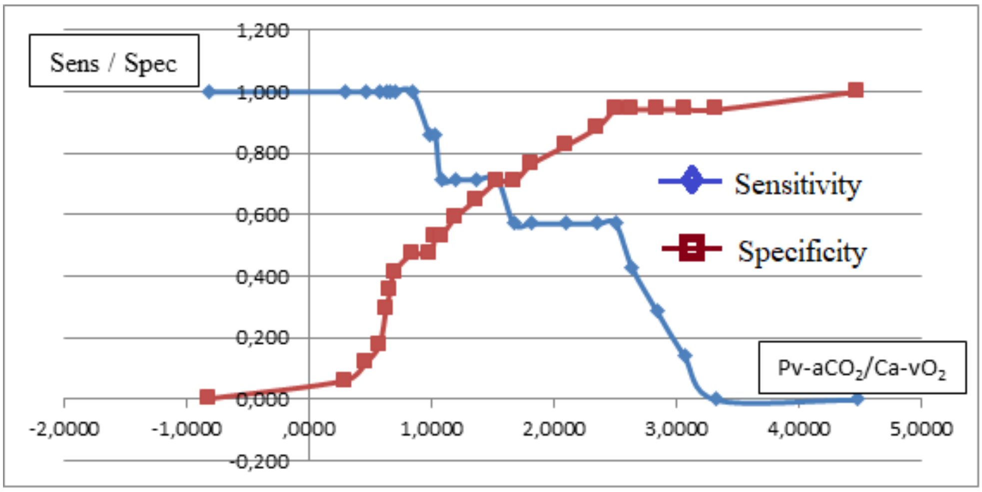
Legend: pH=acidity; Pv-aCO2=central venous-arterial carbon dioxide partial pressure difference; Hb=hemoglobin; Pv-aCO2/Ca-vO2=ratio of venous-arterial CO2 difference to arterial-venous O2 content difference; RR=relative risk; CI=confident interval. Multivariate with backward stepwise method; p value <0.05 was significant; variables list based on wasted sequence from process.

Figure 1. Receiver operating characteristic curve for prediction of mortality at 48 hours in pediatric septic shock based on the ratio of venous-arterial CO2 difference to arterial-venous O2 content difference



Legend: ROC=receiver operating characteristic; Pv-aCO2/Ca-vO2=ratio of venous-arterial CO2 difference to arterial-venous O2 content difference; AUC=area under the curve.

Figure 2. Graphic cutoff for Pv-aCO2/Ca-vO2



Legend: Pv-aCO2/Ca-vO2=ratio of venous-arterial CO2 difference to arterial-venous O2 content difference. It shows value of 1.54 with sensitivity 71.4% and specificity 70.6% to predict mortality in the first 48 hours. A Pv-aCO2/Ca-vO2 value more than 1.54 indicates higher mortality in pediatric septic shock.

References

1. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, et al. Global Epidemiology of Pediatric Severe Sepsis: The Sepsis Prevalence, Outcomes, and Therapies Study. Am J Respir Crit Care Med 2015;191:1147-57.
2. Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med 2017;45:1061-93.
3. Chong SL, Ong GY, Venkataraman A, Chan YH. The Golden Hours in Paediatric Septic Shock—Current Updates and Recommendations. Ann Acad Med Singapore 2014;43:267-74.
4. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA, et al. Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy: A Randomised Clinical Trial. JAMA 2010;303:739-46.
5. He H, Liu D, Long Y, Wang X. High central venous-to-arterial CO2 difference/arterial-central venous O2 difference ratio is associated with poor lactate clearance in septic patients after resuscitation. J Crit Care 2016;31:76-81.
6. Vallet B, Pinsky MR, Cecconi M. Resuscitation of patients with septic shock: please ‘‘mind the gap’’! Intensive Care Med 2013;39:1653-5.
7. Du W, Liu D-W, Wang X-T, Long Y, Chai W-Z, Zhou X, et al. Combining central venous-to-arterial partial pressure of carbon dioxide difference and central venous oxygen saturation to guide resuscitation in septic shock. J Crit Care 2013;28:1110.e1-e5.
8. Rhodes LA, Erwin WC, Borasino S, Cleveland DC, Alten JA. Central Venous to Arterial CO2 Difference After Cardiac Surgery in Infants and Neonates. Pediatr Crit Care Med 2017;18:228-33.
9. Vallee F, Vallet B, Mathe O, Parraguette J, Mari A, Silva S, et al. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? Intensive Care Med 2008;34:2218-25.
10. Monnet X, Julien F, Ait-Hamou N, Lequoy M, Gosset C, Jozwiak M, et al. Lactate and Venoarterial Carbon Dioxide Difference/Arterial-Venous Oxygen Difference Ratio, but Not Centrai Venous Oxygen Saturation, Predict Increase in Oxygen Consumption in Fluid Responders. Crit Care Med 2013;41:1412-20.
11. Wittayachamnankul B, Chentanakij B, Sruamsiri K, Chattipakorn N. The Role of Central Venous Oxygen Saturation, Blood Lactate and Central Venous-to-Arterial Carbon Dioxide Partial Pressure Difference as a Goal and Prognosis of Sepsis Treatment. J Crit Care 2016;36:223-9.
12. Mekontso-Dessap A, Castelain V, Anguel N, Bahloul M, Schauvliege F, Richard C, et al. Combination of venoarterial PCO2 difference with arteriovenous O2 content difference to detect anaerobic metabolism in patients. Intensive Care Med 2002;28:272-7.
13. Mesquida J, Saludes P, Gruartmoner G, Espinal C, Torrents E, Baigorri F, et al. Central venous-to-arterial carbon dioxide differences combined with arterial-to-venous oxygen content difference is associated with lactate evolution in the hemodynamic resuscitation process in early septic shock. Crit Care 2015;19:126-33.
14. Nichols D, Nielsen ND. Oxygen Delivery and Consumption: A Macrocirculatory Perspective. Crit Care Clin 2010;26:239-53.
15. Roberts JK, Disselkamp M, Yataco AC. Oxygen Delivery in Septic Shock. Ann Am Thorac Soc 2015;12:952-5.
16. Mallat J, Lemyze M, Meddour M, Pepy F, Gasan G, Barrailler S, et al. Ratios of central venous-to-arterial carbon dioxide content or tension to arteriovenous oxygen content are better markers of global anaerobic metabolism than lactate in septic shock patients. Ann Intensive Care 2016;6:10-9.
17. Ospina-Tascon GA, Umana M, Bermudez W, Bautista-Rincon DF, Hernandez G, Bruhn A, et al. Combination of arterial lactate levels and venous-arterial CO2 to arterial-venous O2 content difference ratio as markers of resuscitation in patients with septic shock. Intensive Care Med 2015;41:796-805.
18. Ospina-Tascón GA, Hernández G, Cecconi M. Understanding the venous–arterial CO2 to arterial–venous O2 content difference ratio. Intensive Care Med 2016;42:1801-4.
19. Monnet X, Teboul J-L. Cardiac output monitoring: throw it out… or keep it? Crit Care 2018;22:35-7.
20. Giovannini I, Chiarla C, Boldrini G, Castagneto M. Calculation of venoarterial CO2 concentration difference. J Appl Physiol (1985) 1993;74:959-64.

21. Douglas AR, Jones NL, Reed JW. Calculation of whole blood CO2 content. J Appl Physiol 1988;65:473-7.
22. Jakob SM, Groeneveld AB, Teboul J-L. Venous–arterial CO2 to arterial–venous O2 difference ratio as a resuscitation target in shock states? Intensive Care Med 2015;41:936-8.
23. Teboul J-L, Scheeren T. Understanding the Haldane effect. Intensive Care Med 2017;43:91-3.