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RESEARCH ARTICLE

Venous – arterial CO_2 difference in children with sepsis and its correlation with myocardial dysfunction

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ABSTRACT

Objective: This study aimed to determine the association between venous – arterial CO_2 difference (Pv-aCO_2) and clinical outcomes of interest in children with severe sepsis and septic shock.
Design: An analytical observational study of a prospective cohort was conducted.
Setting: The study was carried out from January 2015 to January 2018 in the pediatric intensive care unit of a referral hospital.
Materials and methods: Of a total of 1159 patients who were admitted to pediatric critical care, 375 had severe sepsis and septic shock, of which 67 fulfilled the inclusion criteria. Arterial and venous gases were drawn simultaneously with a transthoracic echocardiogram, Pv-aCO_2, and other measures of tissue perfusion such as arterial lactate, venous, and evolution to multiple organ failure.
Measurements and main results: Half (53.7%) of the patients were under 24 months old, with a slight predominance of male patients. The main site of infection was the lungs in 56% of the cases, with a 91.2% survival rate. Patients who died had a higher venous lactate level (interquartile range 16.2 – 33.6, $p = 0.02$). However, there was no correlation between myocardial dysfunction seen on echocardiogram and a Pv-aCO_2 greater than 6 mm Hg in children with severe sepsis and septic shock ($r = 0.13$). Pv-aCO_2 and central venous saturation had low sensitivity to detect multiple organ failure and poor correlation with the number of compromised systems ($r = 0.8$).
Conclusion: Pv-aCO_2 was not associated with myocardial dysfunction, measured by echocardiogram, in children with severe sepsis and

septic shock. It also did not correlate with the number of organs involved or mortality.

Keywords: sepsis, septic shock, myocardial dysfunction, Pv-aCO_2, children, mortality, venous saturation

INTRODUCTION

Sepsis is one of the main causes of morbidity and mortality in the pediatric population and one of the main admitting diagnoses in intensive care. It causes almost 4300 pediatric deaths per year in the United States, accounting for almost 7% of all child mortality. Recent studies have shown a global mortality of 25%. Timely intervention with adequate diagnostic tools could modify the clinical course of the disease, especially if there are clear goals and objectives.[1–4]

Almost 30% of septic children develop myocardial dysfunction.[1,5] Although some clinical signs and symptoms suggest cardiac involvement, they are not always clear, and they frequently require objective measurements to confirm the diagnosis. Invasive, minimally invasive, and noninvasive tests have been used to evaluate myocardial function directly or indirectly; all of them have benefits and limitations. However, various factors such as hypovolemia and anemia affect tissue perfusion, leading to mistaken interpretations when relating it to cardiac output. Several factors could affect central venous saturation and lead to wrong interpretations, such as incorrect catheter site, anemia, and high vasoactive support. Therefore, studies in adults have suggested that the venous – arterial CO_2 (Pv-aCO_2) difference could be a good complement when there is a suggestive clinical picture and normal or altered central venous saturation.[6–8]

Two basic mechanisms have been proposed to explain this increased arteriovenous CO_2 gradient when perfusion is compromised in low cardiac output states. The first is based on CO_2 diffusion in the peripheral and pulmonary circulation, as a function of blood flow. In low cardiac output states, transit through the capillary beds is slower. This extended blood stay produces an increased ventilation – perfusion ratio in the lungs and decreased partial pressure of CO_2 (pCO_2) in arterial blood.[3,7,9–10] The consequent hypocapnia allows greater diffusion of CO_2 toward the venous blood in peripheral capillaries, leading to hypercapnia and increasing the Pv-aCO_2 gradient as cardiac output decreases.[11–13] The second mechanism refers to events occurring on a cellular level. When blood flow decreases (ischemic hypoxia), a cellular anoxic state is produced. This increases CO_2 and lactic acid production in the Krebs cycle, secondary to anaerobic metabolism, thereby causing an increase in the Pv-aCO_2 difference.[14–15] Taking these aspects into account, we consider that it is important to determine the usefulness of the pCO_2 delta in children with severe sepsis and septic shock, as well as when analyzed in the context of critical patients with other indirect indicators of myocardial dysfunction.

MATERIALS AND METHODS

Study design

This was a prospective observational cohort study comparing the presence of myocardial dysfunction established by transthoracic echocardiogram considering it when we have an ejection fraction less than 55% and a difference in Pv-aCO_2 greater than 6 mm Hg. We chose the ejection fraction indicator because it is the simplest, fastest, and most frequently used parameter in the pediatric intensive care unit (PICU). The study was carried out in a population of patients diagnosed with septic shock during their stay in the PICU of the Fundación Cardioinfantil-IC in Bogotá, Colombia, a local and regional referral institution. It was approved by the institution's ethics and research committees, and the parents signed an informed consent prior to participation.

Study population

We included children from 1 month to 17 years 11 months old, who had severe sepsis and septic shock (as defined by the international pediatric sepsis consensus[13–14]), were admitted to the intensive care unit from January 2015 to January 2018 and underwent an echocardiogram at the request of a physician. Arterial and venous gases were simultaneously drawn along with the echocardiogram. Out of the 1159 children admitted to the PICU during this time, 375 met the inclusion criteria of having severe sepsis and septic shock. Of these, 308 had an exclusion criterion: 275 had heart disease or a history of heart disease. Additionally, 15 received a continuous steroid infusion for adrenal insufficiency, 7 had chronic pulmonary disease, and 11 had femoral access. We decided to exclude these patients because it is known that such conditions can alter the variables

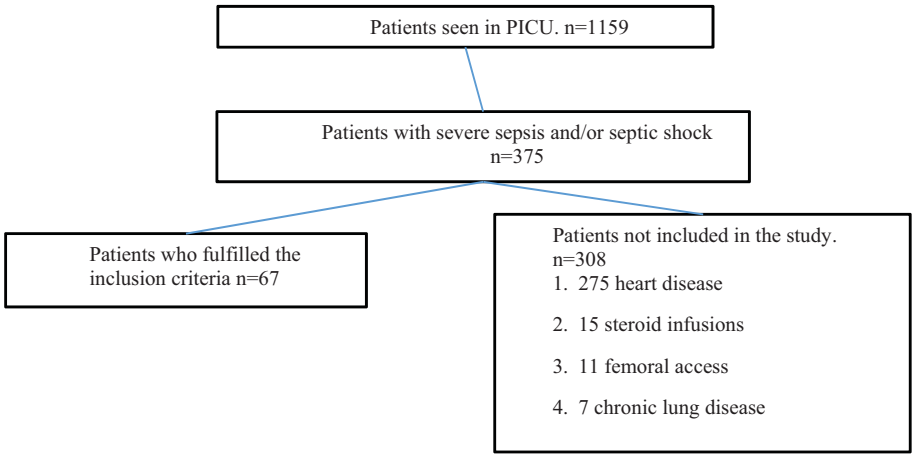

Figure 1. Study population.

of the Pv-aO2 analysis.[6 – 7] Thus, ultimately, there were 67 study participants (Figure 1). The management protocol required that patients had central venous access (jugular, subclavian, or femoral) and an arterial monitoring line. The jugular venous catheter was inserted under ultrasound guidance, using the Seldinger technique, and its position in the cavoatrial junction was confirmed by chest x-ray prior to drawing central venous gases. The arterial lines were placed with ultrasound guidance, corroborating the arterial pulse waveform morphology on the monitor and the blood gas values.

PICU, pediatric intensive care unit

Once it was confirmed that the patient fulfilled the inclusion criteria, the nursing staff (based on institutional protocol and not being study participants) drew simultaneous arterial and venous gases from the arterial line and the central line according to the institution's standardized technique, using two staff members. Arterial blood was obtained from a radial, brachial, or femoral arterial line, whereas venous blood was drawn from a central venous catheter in the internal jugular or subclavian vein. All samples were drawn in heparin tubes, leaving no space or bubbles in them. For the arterial draw, 5 mL of blood was withdrawn from the arterial line, and then 1 mL was collected in the heparin syringe. Following this, the 5 mL that was initially extracted was returned through the arterial line, thus avoiding anemia. For the venous sample, 10 mL of blood was withdrawn through the central venous catheter, then 1 mL was collected in the heparin syringe, and the original 10 mL of blood was returned to the patient. The samples were immediately sent through the pneumatic tube system, ensuring their processing in the shortest amount of time possible (under 15 minutes, in accordance with institutional standards). All blood samples were analyzed using the same blood gas machine (Siemens Rapidlab® 1265, Siemens Healthcare Diagnostics Inc., Tarrytown, New York, USA), which analyzed arterial and central venous gases. Simultaneously with the arterial and venous blood gas draws, an M-mode and two-dimensional echocardiogram was performed by the institution's pediatric cardiology team, using a MultiSync LCD 1990SX machine and standard technique. This pediatric cardiology team has more than 20 years of experience in diagnosing congenital heart disease, with our center being a local and regional referral institution for this type of pathology. The cardiologist performing the echocardiogram did not know that the patient was participating in the study nor was he or she aware of the processed gas results. Vasoactives and inotropes were used at the intensivist's discretion, blood sugar was kept below 180 mg/dL, and protective mechanical ventilation strategies were also used when the patient required ventilatory support.

Statistical analysis

The sample size was calculated using the Epidat 4.0 program for prospective cohort studies, with a 95% confidence level and a power of 80%, and a significant $p < 0.05$, for a total of 67 patients. A univariate analysis was carried out presenting the qualitative variables with absolute and relative frequencies. Quantitative variables were presented as central tendency and dispersion statistics, according to their distribution (normal or nonnormal). Following this, a

bivariate analysis was carried out according to the change in Pv-aCO_2, the echocardiograms showing myocardial dysfunction, and death, using chi-square or Fisher's test for the qualitative variables. A mean difference was applied for quantitative variables with a normal distribution, and nonparametric tests (Mann – Whitney *U*) for those with a nonnormal distribution.

RESULTS

Patient age was found to have a nonnormal distribution, and half of the patients were under 24 months (two years) old. Most of them were clustered between 10 months and four years old, with ages ranging from one month to 15 years. The ratio of male to female participants in the study was 1.2:1.

The most common site of infection was the lungs, occurring in more than half (56%) of the patients, followed by the abdomen and central nervous system in 12% of cases. Other sites of infection were present in less than 3% of the patients. Only 3% of patients had some type of polytrauma, and approximately one-third had come from surgery (Table 1).

Table 1. Distribution of absolute and relative frequencies of clinical variables in patients with severe sepsis and septic shock.

Variable	Category	n	%
Sex	Female	31	46.3
	Male	36	53.7
	Total	67	100.0
Site of infection	Lung	19	28.4
	Abdomen	4	6.0
	Genitals	1	1.5
	Not identified	1	1.5
	Bacteremia	2	3.0
	Bone	1	1.5
	CNS	4	6.0
	Urinary tract	1	1.5
	Pharynx	1	1.5
	Subtotal	34	50.7
	Lost	33	49.3
	Total	67	100.0
Postoperative	Yes	23	34.3
	No	44	65.7
	Total	67	100.0
Polytrauma	Yes	2	3.0
	No	65	97.0
	Total	67	100.0

Survival was 91.2%, with three patients dying (mortality of 8.8%). When those who died were compared with the survivors, no statistically significant differences were found in cardiac dysfunction measured by echocardiogram ($p = 1.00$), venous – arterial CO_2 differences greater than 6 ($p = 1.00$), or impaired venous saturation ($p = 1.00$). Nor were there differences found when clinical variables such as sex ($p = 0.12$), source of the infection ($p = 0.19$), and multiple organ failure ($p = 1.00$) were compared.

There were also no differences with regard to therapeutic interventions such as the administration of crystalloid and/or colloid boluses ($p = 0.77 – 1.00$), the need for hemodynamic support ($p = 1.00$), the need for mechanical ventilation ($p = 0.18$), or the use of systemic steroids ($p = 0.77$).

The analysis of quantitative variables showed that venous lactate was much higher in patients who did not survive, with a median of 4.3 (interquartile range [IQR] 1.4 – 8.2), than in those who survived (median 1.1, IQR 0.8 – 1.5). When the alterations in the Pv-aCO_2 were analyzed with respect to the presence of myocardial dysfunction on echocardiogram, no correlation was found between these two variables (Pearson's $r = 0.13$; Figure 2).

Likewise, Pv-aCO_2 was not a good detector of multiple organ failure, with low sensitivity (29%), along with other routinely used biomarkers, such as arterial (51%) and venous (53%) lactate, as well as venous oxygen saturation (40%; Figure 3).

ROC, receiver operating characteristic

A receiver operating characteristic curve is presented evaluating the sensitivity and specificity of Pv-aCO_2 with that of other indicators of tissue perfusion such as lactate and venous saturation, SvO_2 (%), central venous saturation.

Arterial and venous lactate levels showed a statistically significant association ($p = 0.007$ and 0.001, respectively), with higher values being associated with a greater number of involved systems. However, central venous oxygen saturation ($ScvO_2$; $r = 0.2$) and Pv-aCO_2 ($r = 0.08$) did not show a correlation with the number of affected systems.

DISCUSSION

One of the biggest challenges for clinicians treating patients with septic shock is to be able to determine

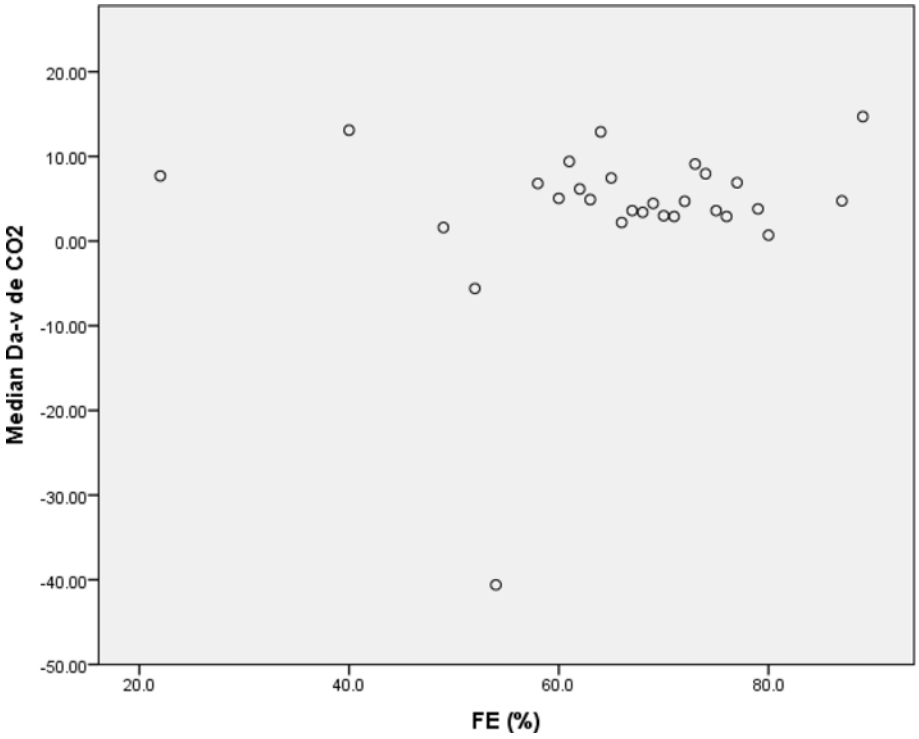

Figure 2. Correlation between ejection fraction and median venous – arterial CO_2 difference (Pv-aCO_2) in children with sepsis.

the degree and severity of the involvement of many organs that, when affected, can dramatically change the clinical course of the disease.[15–18] Microcirculation plays a fundamental role in this comprehensive assessment of patients in shock, as it is well known that some patients, in spite of achieving goals in terms of macrohemodynamics, may progress to microcirculatory dysfunction, which ultimately leads to tissue hypoxia and organ dysfunction.[16–19] Rivers et al.,[18] and Zhou et al.,[19] suggest that objective-based treatment may significantly reduce mortality in sepsis, and they linked $ScvO_2$ to the resuscitation objectives, even though, as an isolated piece of information, this decreased parameter does not determine the response to resuscitation nor the patient's severity. These findings were very important, and $ScvO_2$ has become the most used tool in adults and children to determine the compromise of myocardial function and tissue perfusion, along with arterial lactate.[17]

In our experience with a cohort of pediatric patients with severe sepsis and septic shock, in whom we simultaneously sought to determine if there was a correlation between a Pv-aCO_2 greater than six and myocardial dysfunction on echocardiogram, no correlation ($r = 0.13$) was found when adjusted for demographic data, severity, and infection site. Pv-aCO_2 and central venous saturation have a low sensitivity for detecting multiple organ failure and a poor correlation with the number of affected systems ($r = 0.8$). However, other tissue hypoperfusion markers were found, such as lactate (both arterial and venous), which showed a predictive ability for multiple organ failure. These findings are consistent with other publications in which the lactate value was related to organ dysfunction and mortality.[19] The fact that these results were reproduced in our study corroborates the usefulness of this marker and the poor association of Pv-aCO_2 in a context where other markers work.

Considering that $ScVO_2$, as an indicator of myocardial dysfunction, is indirectly and directly affected by many variables, the association of another indicator in the group in which $ScVO_2$ may be normal helps detect a greater number of patients with dysfunction.[16–18] The findings of Ospina-Tascón et al.,[7,10,16] in the adult population have shown that an increased arteriovenous pCO_2 difference (greater than 6 mm Hg) reliably reflects the presence of tissue hypoxia and a poor outcome in patients with sepsis, and a

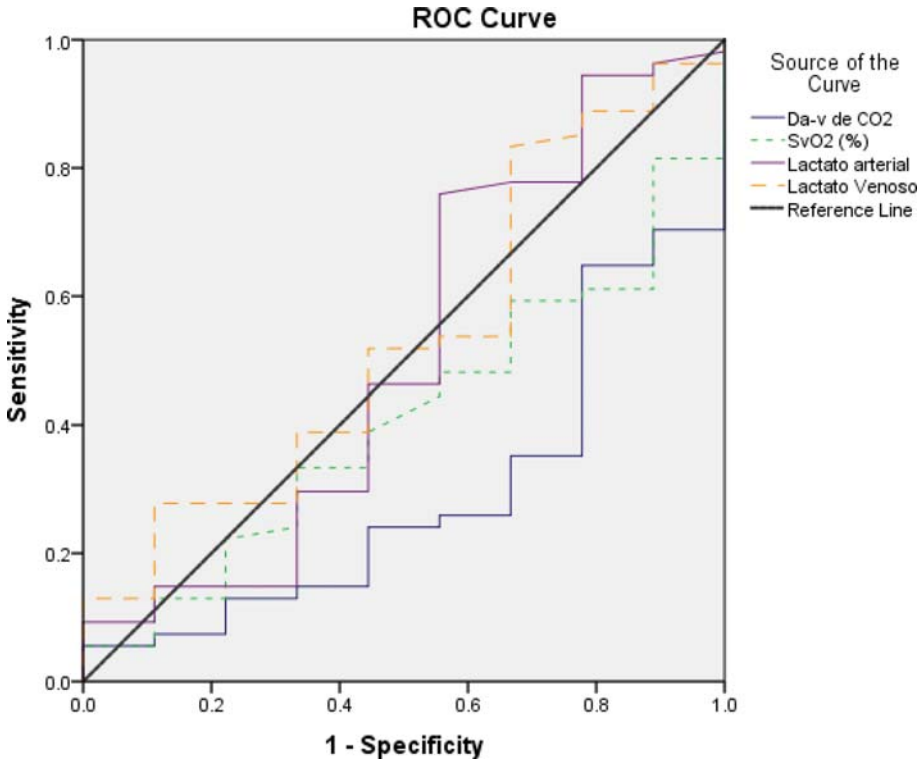

Figure 3. Sensitivity and specificity of venous – arterial CO_2 difference ($Pv\text{-}aCO_2$) for predicting multiple organ failure.

normal value has been associated with a higher rate of lactate clearance and a better cardiac index. These findings suggest that $Pv\text{-}aCO_2$ may be a good adjuvant in this group of patients to comprehensively assess the degree of microcirculation involvement and, indirectly, tissue perfusion.

Likewise, Ospina-Tascón et al., found that $Pv\text{-}aCO_2$ may be a good indicator of the intensity of fluid resuscitation in patients with sepsis, suggesting that it may be useful as an adjuvant in resuscitation goals, since there is a greater risk of mortality if it continues to be altered after 12 hours (risk ratio 2.41, confidence interval 1.42 – 4.10, $p = 0.001$). The Vallée et al., group had similar findings.[20] In an adult population of 50 patients with septic shock, they sought to evaluate the usefulness of $Pv\text{-}aCO_2$ as a complement to the $ScVO_2$ goal of fluid resuscitation. This group found that resuscitation guided by $Pv\text{-}aCO_2$ may be associated with better lactate clearance ($p < 0.05$) and suggested that this difference should be considered as an important goal in the initial resuscitation of patients with septic shock.[10] These findings are in an adult population, and experience in pediatrics is limited.

In a group of postoperative cardiovascular patients, Furqan et al., found that an increased $Pv\text{-}aCO_2$ associated with a low $ScVO_2$ could be a good predictor of a low cardiac index in this group of patients ($r = 0.47$, $p = 0.0011$), which would allow more rapid clinical decisions, fitting the specific needs of each patient. However, our study did not show that $Pv\text{-}aO_2$ was a good tool to determine tissue perfusion nor did it correlate with myocardial function. These findings may be related to the fact that some groups have found that the greatest utility of $Pv\text{-}aO_2$ is for patients with SvO_2 alteration. However, these findings are from studies in adults, and it is possible that the behavior of microcirculation in sepsis in children is different, and this partly explains our findings and the poor utility of the $Pv\text{-}aO_2$ we found.

The main limitations of our study are that, being a prospective observational study carried out at a single center, there may be selection biases. However, these were reduced by including all patients who met the inclusion criteria. Likewise, we understand that since the echocardiogram is operator-dependent, it is subject to information biases, although our center is a regional referral center for congenital heart defects, and the individuals who perform this test have extensive experience.

CONCLUSION

Pv-aCO_2 was not associated with myocardial dysfunction on echocardiogram in children with septic shock. It also was not a good predictor of progression to multiple organ failure. With current evidence, Pv-aCO_2 cannot be recommended for diagnostic evaluation in children with sepsis.

Disclosure of conflicts of interest

The authors declare that they have no conflicts of interest to disclose.

Financial disclosure

Funds for this research were provided by the researchers.

Contributor's Statements

Drs. Fernández, Gualdron, Barrera, Rodriguez, and Eraso contributed to designing and performing the study. Drs. Eraso, and Orozco participated in data collection. Drs. Fernández, Carcillo, and Pinzón supervised study development and data collection. All the authors contributed to drafting the manuscript and reviewing the final article. All the authors approved the final manuscript and agreed with all aspects of the study. None of the researchers declared conflicts of interest. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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