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RESEARCH ARTICLE

Central venous-to-arterial CO_2 difference as a biomarker of outcome in children who underwent surgery for congenital heart disease

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Abstract

Background: *In congenital heart surgery, low cardiac output syndrome (LCOS) is a major cause of morbidity in the immediate post-operative period. A decrease in cardiac output leads to an increase in tissue oxygen consumption. Several biomarkers such as venous oxygen saturation (SvO_2), arteriovenous oxygen difference ($DavO_2$), and lactate can assess tissue perfusion in the presence of LCOS. Recently, central venous to arterial CO_2 difference (ΔCO_2) has been proposed as a biomarker of tissue ischemia that could be used as a predictor of death in neonatal patients. This study aimed to analyze the relationship between ΔCO_2 and immediate post-operative outcomes in pediatric patients undergoing congenital heart surgery and its correlation with $DavO_2$, SvO_2, and lactate.* **Methods:** *We conducted a longitudinal study of patients aged 0-18 years who underwent congenital heart surgery with or without cardiopulmonary bypass at the Instituto Nacional de Pediatría, from March 2019 to March 2021.* **Results:** *Eighty-two patients were included; the median age was 17 months. About 59% had a $\Delta CO_2 \geq 6$ mmHg. Patients with $\Delta CO_2 \geq 6$ mmHg had a vasoactive-inotropic score > 5 ($p < 0.001$), $DavO_2 > 5$ mL/dL ($p = 0.048$), and lactate > 2 mmol/L ($p = 0.027$), as well as a longer hospital stay ($p = 0.043$). Patients with $\Delta CO_2 > 6$ mmHg and vasoactive-inotropic score ≥ 10 were 12.6 times more likely to die.* **Conclusion:** *ΔCO_2 is a good marker of tissue hypoperfusion and outcome in the post-operative period of congenital heart surgery.*

Keywords: *Central venous to arterial CO_2 difference. Congenital heart disease. Tissue hypoperfusion. Low cardiac output syndrome.*

Diferencia arteriovenosa de CO_2 como biomarcador de desenlace en niños operados de cardiopatías congénitas

Resumen

Introducción: *En la cirugía cardiaca de malformaciones congénitas, el síndrome de bajo gasto cardiaco (SBGC) es una de las principales causas de morbilidad en el postoperatorio inmediato. La caída del gasto cardiaco aumenta el consumo de oxígeno en los tejidos. Varios biomarcadores, como la saturación venosa de oxígeno (SvO_2), la diferencia arteriovenosa de*

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oxígeno ($DavO_2$) y el lactato han sido utilizados como indicadores hipoperfusión tisular en presencia de SBGC. Recientemente, la diferencia arteriovenosa de CO_2 (ΔCO_2) se ha propuesto como otro biomarcador de isquemia tisular que podría utilizarse como predictor de muerte en pacientes en edad neonatal. El objetivo de este estudio fue analizar la relación entre la ΔCO_2 y la evolución postoperatoria de pacientes pediátricos operados de cardiopatías congénitas y correlacionarlo con la $DavO_2$, SvO_2 y lactato. **Métodos:** *Se realizó un estudio longitudinal en pacientes de 0 a 18 años operados de corazón con empleo de bomba de circulación extracorpórea en el Instituto Nacional de Pediatría.* **Resultados:** *Se incluyeron 82 pacientes; la mediana de edad fue de 17 meses. El 59% presentó un $\Delta CO_2 > 6$ mmHg. Los pacientes con un $\Delta CO_2 > 6$ mmHg mostraron un puntaje de inotrópicos > 5 ($p < 0.001$), $DavO_2 > 5$ mL/dL ($p = 0.048$) y lactato > 2 mmol/L ($p = 0.027$), así como mayor estancia hospitalaria ($p = 0.043$). Los pacientes con $\Delta CO_2 > 6$ mmHg y un puntaje de inotrópicos ≥ 10 presentaron una probabilidad de muerte 12.6 veces mayor.* **Conclusiones:** *El ΔCO_2 en el periodo postoperatorio de una cirugía cardiaca congénita es un buen marcador de hipoperfusión tisular y de desenlace.*

Palabras clave: *Diferencia arteriovenosa de CO_2. Cardiopatías congénitas. Hipoperfusión tisular. Síndrome de bajo gasto cardiaco.*

Introduction

In recent decades, the survival of patients with congenital heart disease has improved significantly due to advances in perfusion techniques, anesthesia, cardiovascular surgery, and intensive care. However, the presence of low cardiac output syndrome (LCOS) remains one of the major determinants of post-operative morbidity[1,2].

The decrease in cardiac output results in tissue hypoperfusion with increased tissue oxygen consumption. The main causes of decreased cardiac output after using a cardiopulmonary bypass are myocardial ischemia, ischemia-reperfusion injury, and the release of inflammatory mediators when blood contacts a foreign surface. Early detection of cardiac output and targeted therapies reduce the risk of tissue hypoxia and multiorgan dysfunction[2].

Currently, the gold standard for measuring cardiac output are devices that use the thermodilution method, such as the Swan-Ganz catheter or the PICCO system. This technology also allows analysis of the contour of the invasive arterial pressure waveform. However, these devices are invasive and rarely available in intensive care units (ICUs) in low- and middle-income countries. For these reasons, several biomarkers have been used to assess tissue perfusion, such as central venous saturation, lactate, arteriovenous oxygen difference, and, more recently, arteriovenous CO_2 difference[1,3]. In recent studies, the latter has been found to be associated with a higher risk of mortality and multiorgan dysfunction when it is > 6 mmHg in critically ill patients, either adults or children[4,5].

Venous oxygen saturation (SvO_2) reflects the balance between tissue oxygen delivery (DO_2) and consumption (VO_2). As oxygen availability decreases, cellular oxygen extraction increases to maintain energy production regardless of DO_2. However, there is a "critical point" of oxygen delivery beyond which energy cannot be produced by cellular ATP formation, and VO_2 becomes dependent on DO_2, causing lactic acidosis[5,6].

As oxygen extraction increases, venous saturation gradually decreases. Although the most common cause of decreased SvO_2 is tissue hypoxia secondary to inadequate perfusion, other conditions, such as poor oxygenation or oxygen transport failure, can also affect SvO_2[6-8]. Other biomarkers, such as arterial lactate, are useful in the immediate post-operative period to assess the state of tissue perfusion. Arterial lactate is more useful when its behavior is analyzed over time. However, its disadvantage is that it can be elevated in other conditions, such as alkalosis and hyperglycemia, in addition to being a late marker of tissue hypoperfusion[9].

Several studies have reported the utility of arteriovenous CO_2 difference (ΔCO_2) as a biomarker of tissue ischemia. Its main advantage is that it can be modified in the presence of tissue hypoperfusion, even when venous saturation and lactate remain normal[6-8]. Tissue CO_2 elimination capacity is a function of cardiac output and tissue blood flow. According to the Fick equation, oxygen consumption (VO_2) equals the product of cardiac output and arteriovenous O_2 content difference (CaO_2-CvO_2). Similarly, CO_2 consumption (VCO_2) is the product of cardiac output and the difference in arteriovenous CO_2 content[10].

Decreased tissue blood flow (ischemic hypoxia) is associated with venous hypercapnia due to cellular anoxia resulting in increased CO_2 production[11]. The increase in arterial CO_2 depends on gas exchange and, because it is very efficient at the alveolar level, it is not significantly affected by decreased pulmonary flow. Hence, an increase in the CO_2 difference is indicative of tissue hypoperfusion. Under physiological conditions, with adequate venous

and systemic flow, the difference between arterial and venous CO_2 should not exceed 6 mmHg[12].

In adult patients, arteriovenous oxygen difference may be a good adjunct to hemodynamic assessment even when venous saturation is normal[4,5].

This study aimed to analyze the relationship between ΔCO_2 and post-operative evolution in pediatric patients undergoing surgery for congenital heart disease with an extracorporeal circulation pump and its correlation with $DavO_2$, SvO_2, and lactate.

Methods

Design

We conducted a longitudinal study in the cardiovascular intensive care unit (UCICV, for its Spanish acronym) of the INP. Patients from the neonatal stage to 18 years of age who underwent cardiovascular surgery for congenital malformations with an extracorporeal circulation pump between March 01, 2019, and February 28, 2021, were included in the study. Patients in whom sampling could not be completed were excluded from the study.

Data collection

Demographic variables included in the study were age, sex, weight, and cardiologic diagnosis. Surgical variables were surgery performed and surgical complexity according to RACH-1 and extended Aristotle scales[13,14], extracorporeal circulation time, and aortic clamping time. Finally, the biochemical variables in the UCICV were arteriovenous oxygen difference ($DavO_2 = CaO_2$-CvO_2)[15], oxygen extraction index ($IEO_2 = DavO_2/CaO_2 \times 100$)[15], ΔCO_2 (venous CO_2-arterial CO_2), central venous saturation, and arterial lactate. For the calculation of arteriovenous difference and ΔCO_2, arterial and venous blood gases were obtained from the central venous catheter. All measurements were collected on four moments: on admission to the UCICV, 6, 12, and 24 h later. The inotropic score was also calculated for each of these moments using the Wernosky formula[16].

The outcome variables recorded were the presence of LCOS, multiple organ failure (dysfunction of two or more organs)[17], time on mechanical ventilation, days of hospitalization, and mortality in the UCICV. LCOS was diagnosed based on clinical assessment of the following variables: tachycardia, capillary refill time > 2 s, weak pulses, marmoreal skin, urine output < 1 mL/kg/h, venous saturation < 60%, lactate > 3 mmol/L, and need for inotropic support.

Analysis

Data were collected in Excel format (Microsoft Office 2022) and then exported to STATA 17.0 (StataCorp) for statistical analysis. Qualitative variables were presented as frequencies and proportions, while quantitative variables were presented as medians and interquartile ranges. The statistical tests used to identify associations were χ^2 and Wilcoxon for qualitative and quantitative variables, respectively. In addition, Pearson correlation was used for continuous variables, specifically the relationship between ΔCO_2 and the other tissue hypoperfusion variables. Finally, logistic regression was used to estimate the odds ratio (OR) of the combined hypoperfusion variables. In all cases, $p < 0.05$ was considered statistically significant.

Results

Eighty-two patients were included in the study: 61% were male. The median age was 17 months. Fifty-nine percent of patients had $\Delta CO_2 \geq 6$ mmHg. Patients with risk adjustment in congenital heart surgery system surgical complexity ≥ 3 had $\Delta CO_2 \geq 6$ mmHg. The median cardiopulmonary bypass (CPB) time was 120 min, with no significant difference between patients with $\Delta CO_2 > 6$ mmHg or patients with $\Delta CO_2 < 6$ mmHg (Table 1).

As shown in table 2, inotropic score ≥ 5 ($p < 0.001$), lactate ≥ 2 mmol/L ($p = 0.027$), and $DavO_2 > 5$ ($p = 0.048$) were significantly associated with $\Delta CO_2 \geq 6$ mmHg. Patients with a higher ΔCO_2 showed a longer UCICV stay ($p = 0.043$) and a higher frequency of multiorgan dysfunction ($p = 0.073$) but not a longer mechanical ventilation time ($p = 0.627$) (Table 2). Patients in whom ΔCO_2 persisted above 6 mmHg at 12 h after admission to the UCICV also had higher IEO ($p = 0.057$) and persisted with higher inotropic values ($p = 0.085$).

A stronger correlation was found between ΔCO_2 and tissue hypoperfusion variables such as lactate ($r = 0.59$, $p < 0.001$) and $DavO_2$ ($r = 0.28$, $p = 0.009$) at 12 h after admission (Table 3). Similarly, when analyzing the total number of samples collected (n = 326), a statistically significant direct correlation was observed between ΔCO_2 and arterial lactate ($p < 0.001$), $DavO_2$ ($p < 0.009$), and inotropic score ($p < 0.001$). In contrast, an inverse correlation, also statistically significant, was found between ΔCO_2 and venous oxygen saturation ($r = 0.32$, $p < 0.001$) (Table 4).

When the combined analysis between tissue hypoperfusion variables was performed, patients with $\Delta CO_2 > 6$ mmHg and lactate > 2 mmol/L at the time of ICU admission were 9.7 times more likely to develop

Table 1. Demographic characteristics of patients who underwent cardiovascular surgery for congenital malformations

Variables	Total	$\Delta CO_2 < 6$ mmHg	$\Delta CO_2 \geq 6$ mmHg	p-value
Patients	100% (82)	41% (34)	59% (48)	-
Male	61% (50)	59% (20)	63% (30)	0.737
Age (months)	17 (3-51)	12 (3-49)	19 (6-60)	0.496
Age < 1 year	41% (34)	47% (16)	38% (18)	0.387
Univentricular physiology	23% (19)	24% (8)	23% (11)	0.948
RACHS ≥ 3	57% (47)	50% (17)	63% (30)	0.260
Aristotle ≥ 3	46% (38)	41% (14)	50% (24)	0.430
ECT (minutes)	120 (79-171)	115 (79-176)	121 (81-171)	0.865
Aortic clamping (minutes)	82 (37-111)	82 (33-124)	83 (38-110)	0.984

ECT: extracorporeal circulation time; RACHS: risk adjustment in congenital heart surgery system.

Table 2. Tissue perfusion variables on admission to the UCICV and outcome variables

Variables	Total (n = 82)	$\Delta CO_2 < 6$ mmHg on admission (n = 34)	$\Delta CO_2 \geq 6$ mmHg on admission (n = 48)	p-value
Lactate ≥ 2 (mmol/L)	74% (61)	62% (21)	83% (40)	0.027
Venous saturation ≤ 60	39% (32)	35% (12)	42% (20)	0.560
$DavO_2 > 5$	51% (42)	38% (13)	60% (29)	0.048
$IEO_2 > 25$	79% (65)	71% (24)	85% (41)	0.166
Inotropic score ≥ 5	55% (45)	29% (10)	73% (35)	< 0.001
UCICV stay	10 (6-21)	7.5 (4-19)	13 (7-27.5)	0.043
Mechanical ventilation time	144 (82.5-504)	120 (72-480)	144 (96-528)	0.627
Extubation on the ward	37% (30)	44% (15)	31% (15)	0.233
Acute kidney injury	28% (23)	26% (9)	29% (14)	0.789
Multiple organ failure	11% (9)	3% (1)	17% (8)	0.073
Low cardiac output syndrome	51% (62)	56% (19)	67% (32)	0.321
Ischemia	5% (4)	3% (1)	6% (3)	0.638
Arrhythmias	29% (24)	24% (8)	33% (16)	0.336
Bleeding	13% (11)	9% (3)	17% (8)	0.348
Infection	40% (33)	29% (10)	48% (23)	0.092
Arrest	6% (5)	3% (1)	8% (4)	0.397
Death in UCICV	4.8% (4)	0% (0)	8.3% (4)	0.138
Hospital death	6.1% (5)	3% (1)	8.3% (4)	0.397

$DavO_2$: arteriovenous oxygen difference; IEO_2: oxygen extraction index; UCICV: cardiovascular intensive care unit.

multiorgan dysfunction. Similarly, patients with ΔCO_2 > 6 mmHg and an inotropic score ≥ 10 were 12.6 times more likely to die (Table 5).

There were four deaths, all of them in the group of patients with ΔCO_2 > 6 mmHg at UCICV admission (Table 2 and Figure 1).

Table 3. Correlation 12 h after admission between lactate, $DavO_2$, inotropic score, and venous saturation with ΔCO_2

At 12 h (n = 81)	ΔCO_2 (r)	p-value
Lactate	0.59	< 0.001
$DavO_2$	0.28	0.009
Inotropic score	0.52	< 0.001
Venous saturation	–0.28	0.009

$DavO_2$: arteriovenous oxygen difference.

Table 4. Correlation among, lactate, $DavO_2$, inotropic score, and venous oxygen saturation of collected samples

Total (n = 326)	ΔCO_2 (r)	p-value
Lactate	0.25	< 0.001
$DavO_2$	0.22	< 0.001
Inotropic score	0.36	< 0.001
Venous saturation	-0.32	< 0.001

$DavO_2$: arteriovenous oxygen difference.

Discussion

Although the determination of ΔCO_2 is relatively easy to perform in the ICU, few studies have analyzed its relevance as a biomarker of tissue hypoperfusion in post-operative pediatric patient with congenital heart disease. Most studies have been performed in patients with sepsis. Ospina-Tascón et al.[18] found that patients with septic shock who continued to have ΔCO_2 > 6 mmHg at 6 h after initiating fluid and vasoactive support had higher SOFA severity scale scores and higher mortality (p > 0.0001). Lactate clearance was slower in this group of patients (p < 0.001). However, in this study, the correlation between cardiac index measured by thermodilution and ΔCO_2 was weak (r = 0.25, p < 0.01). In pediatric patients with severe sepsis, Fernández-Sarmiento et al. also found no correlation between ejection fraction measured by transthoracic echocardiography and ΔCO_2 (r = 0.13)[11]. In contrast, in a group of adult cardiovascular surgery patients, Takami and Masumoto found a moderate correlation between cardiac index and ΔCO_2 (r = 0.35, p < 0.001) and between venous saturation and ΔCO_2 (r = 0.35, p < 0.001)[10].

Furqan et al. found that ΔCO_2 > 6 mmHg was also associated with low venous saturation in pediatric patients undergoing surgery for congenital heart disease. Both studies concluded that ΔCO_2 could be used as a good predictor of cardiac index in patients undergoing CPB surgery (r = 0.47, p = 0.0011)[19], observations that are consistent with our findings showing that 67% of patients with ΔCO_2 > 6 mmHg had LCOS.

Venous saturation is a surrogate for cardiac output and can be used as a biomarker of tissue hypoperfusion to guide treatment goals in the septic shock patient. However, an adequate correlation between ΔCO_2 and SvO_2 has not been demonstrated in these patients. In a study conducted by Mallat et al. in adults with septic shock, patients in whom ΔCO_2 persisted > 6 mmHg, even when venous saturation was optimized to above 70%, continued to have lactate > 2 mmol/L, allowing identification of those patients in whom perfusion was still suboptimal[6]. These findings could be explained by the fact that ΔCO_2 is a biomarker of ischemic hypoxia and is not affected by changes in oxygen availability or blood hemoglobin levels, as is the case with venous saturation. Interestingly, in our group of patients, the correlation found between ΔCO_2 and venous saturation was adequate (r = –0.32, p < 0.001), similar to that described by Furqan et al. (OR = 0.340)[19]. In this group of patients, ΔCO_2 could be used with venous saturation to assess systemic perfusion.

Among other markers of tissue hypoperfusion, our study found that patients with ΔCO_2 > 6 mmHg had lactate > 2 mmol/L and arteriovenous oxygen differences > 5 on admission (p = 0.027, p = 0.048), findings similar to those described by Rhodes et al. in pediatric patients undergoing cardiovascular surgery. These authors found a good correlation between ΔCO_2 and $DavO_2$ (r = 0.55, p < 0.01)[1], suggesting that ΔCO_2 can be used in conjunction with $DavO_2$ as a biomarker of tissue ischemia during the hemodynamic assessment of patients with suspected low cardiac output. However, these authors found no correlation between ΔCO_2 and lactate (r = 0.02, p = 0.85), in contrast to our study, where patients with ΔCO_2 > 6 mmHg had higher lactate (p = 0.027). With these findings, we suggest that ΔCO_2 can be used as a tool for early detection of tissue hypoperfusion.

Regarding ventilatory support, we found that patients with ΔCO_2 > 6 mmHg did not have longer mechanical ventilation time (p = 0.627) or longer hospital stay (p = 0.49), results similar to a study by Akamasu et al. in 114 pediatric patients who underwent extracorporeal circulation pump surgery for congenital heart disease. There were no differences between patients with ΔCO_2 under or over 6 mmHg on admission (p = 0.80)[20]. In contrast, we found an association between ΔCO_2 > 6 mmHg and a longer stay in the cardiovascular ICU (p = 0.043).

Table 5. Combined analysis between tissue hypoperfusion variables, complications, and outcomes

Combined variables	Risk factor	Proportion	p-value	OR	95% CI
$\Delta CO_2 \geq 6$ + Lactate ≥ 2	Infection	54% versus 27%	0.013	3.2	1.2-7.9
	Multiple organ failure	20% versus 2%	0.029	9.7	1.15-81
$\Delta CO_2 \geq 6$ + score ≥ 10	Death in ICU	17% versus 2%	0.033	12.6	1.2-129
$\Delta CO_2 \geq 6$ + $DavO_2 \geq 5$	Infection	60% versus 29%	0.01	3.7	1.4-9.5

CI: confidence interval; $DavO_2$: arteriovenous oxygen difference; ICU: intensive care unit; OR: odds ratio.

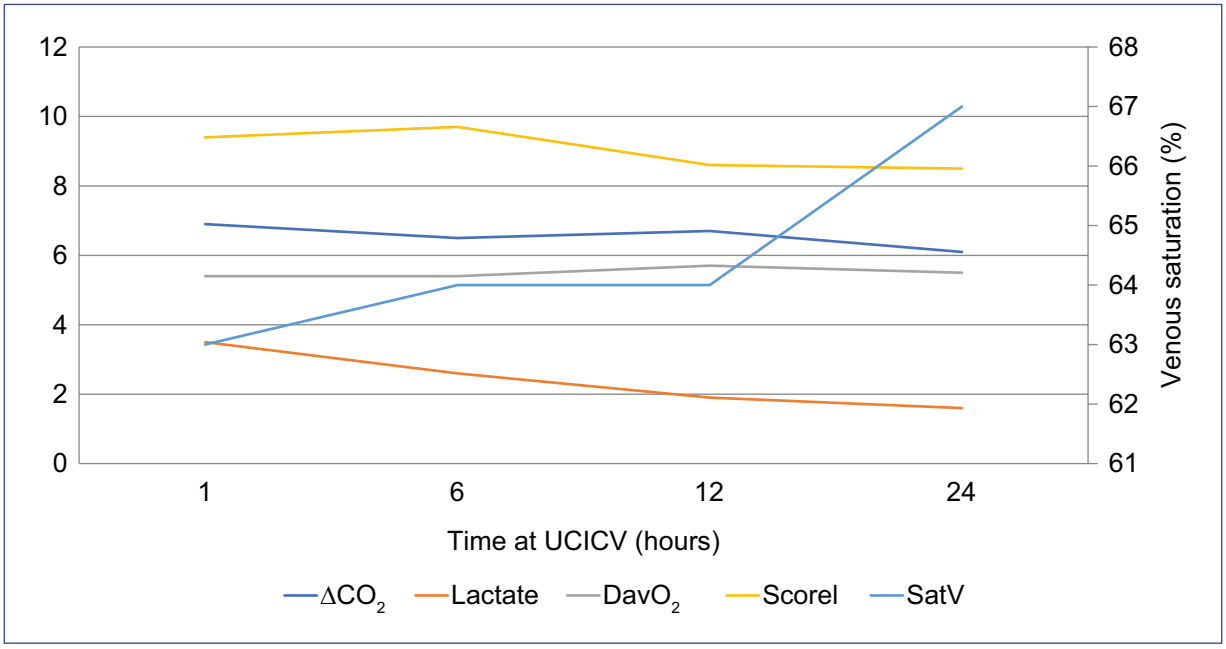

Figure 1. Behavior of tissue hypoperfusion variables and inotropic score. $DavO_2$: arteriovenous oxygen difference; SatV: venous saturation; Scorel: inotropic score.

Several studies have analyzed whether there is an association between ΔCO_2 > 6 mmHg and patient outcome. In the study by Rhodes et al.[1], patients who had an inotropic score > 15 on admission, at least one cardiorespiratory arrest event, an unplanned surgical reintervention, or the need for extracorporeal membrane support had ΔCO_2 > 6 mmHg (mean 8.3 mmHg). In the same study, those who did not have any of these events had a mean ΔCO_2 of 5.6 mmHg. Insom et al. also found that ΔCO_2 > 6 mmHg was associated with a higher inotropic score (r = 0.21, p = 0.02)[21].

Logistic regression analysis determined that ΔCO_2 > 6 mmHg at admission was independently associated with higher mortality OR 1.3 (95% CI [confidence interval], 1.07-1.31), similar to Mukai et al. in patients undergoing on-pump cardiac surgery (area under the curve 0.804, 95% CI, 0.688-0.921)[22]. In our study, patients with admission ΔCO_2 > 6 mmHg had higher inotropic scores (p < 0.001) and a higher incidence of multiorgan failure: eight patients from the ΔCO_2 > 6 mmHg group compared to only one patient from the ΔCO_2 < 6 mmHg group.

Patients with ΔCO_2 > 6 mmHg and inotropic score ≥ 10 were 12.6 times more likely to die. Unfortunately, four patients died, all from the ΔCO_2 > 6 mmHg group.

ΔCO_2 is a useful marker of tissue hypoperfusion. Patients with ΔCO_2 > 6 mmHg on admission have higher lactate, $DavO_2$, and inotropic values. Early monitoring of ΔCO_2 is a useful biomarker to identify patients at increased risk of post-operative morbidity and mortality, especially when accompanied by a high inotropic score.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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