



ORIGINAL ARTICLE

Lack of correlation between central venous minus arterial PCO₂ to arterial minus central venous O₂ content ratio and respiratory quotient in patients with septic shock: A prospective observational study



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Received 25 March 2024; accepted 28 May 2024

KEYWORDS

Carbon dioxide production;
Oxygen consumption;
Anaerobic metabolism;
Respiratory quotient

Abstract

Objective: Central venous-arterial PCO₂ to arterial-central venous O₂ content ratio (P_{cv-a}CO₂/C_{a-cv}O₂) is commonly used as a surrogate for respiratory quotient (RQ) and tissue oxygenation. Although P_{cv-a}CO₂/C_{a-cv}O₂ might be associated with hyperlactatemia and outcome, neither the interchangeability with RQ nor the correlation with conclusive variables of anaerobic metabolism has never been demonstrated in septic shock. Our goal was to compare P_{cv-a}CO₂/C_{a-cv}O₂ and RQ in patients with septic shock.

Design: Prospective, observational study.

Setting: Two adult ICUs.

Patients: Forty-seven patients with septic shock on mechanical ventilation with stable respiratory settings and vasopressor dose after initial resuscitation.

Interventions: None.

Main variables of interest: We measured arterial and central venous gases, Hb, and O₂Hb. P_{cv-a}CO₂/C_{a-cv}O₂ and the ratio of central venous-arterial CO₂ content to arterial-central venous O₂ content (C_{cv-a}CO₂/C_{a-cv}O₂) were calculated. RQ was determined by indirect calorimetry.

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Results: $P_{cv-a}CO_2/C_{a-cv}O_2$ and $C_{cv-a}CO_2/C_{a-cv}O_2$ were not correlated with RQ ($R^2 = 0.01$, $P = 0.50$ and $R^2 = 0.01$, $P = 0.58$, respectively), showing large bias and wide 95 % limits of agreement with RQ (1.09, -1.10–3.27 and 0.42, -1.53–2.37). A multiple linear regression model showed Hb, and central venous PCO_2 and O_2Hb , but not RQ, as $P_{cv-a}CO_2/C_{a-cv}O_2$ determinants ($R^2 = 0.36$, $P = 0.0007$).

Conclusions: In patients with septic shock, $P_{cv-a}CO_2/C_{a-cv}O_2$ did not correlate with RQ and was mainly determined by factors that modify the dissociation of CO_2 from Hb. $P_{cv-a}CO_2/C_{a-cv}O_2$ seems to be a poor surrogate for RQ; therefore, its values should be interpreted with caution.

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PALABRAS CLAVE

Producción de dióxido de carbono;
Consumo de oxígeno;
Metabolismo anaeróbico;
Cociente respiratorio

Falta de correlación entre la relación PCO_2 venosa central-arterial/contenido arterial-venoso central de O_2 y cociente respiratorio en pacientes con shock séptico: Estudio prospectivo observacional

Resumen

Objetivo: La relación entre la PCO_2 venosa central-arterial y el contenido arterial-venoso central de O_2 ($P_{vc-a}CO_2/C_{a-vc}O_2$) se emplea comúnmente como sustituto del cociente respiratorio (CR). Aunque la $P_{vc-a}CO_2/C_{a-vc}O_2$ puede asociarse a hiperlactacidemia y mayor mortalidad, la intercambiabilidad con CR y la correlación con variables definidas de metabolismo anaeróbico no se han demostrado en el shock séptico. Nuestro objetivo fue comparar $P_{vc-a}CO_2/C_{a-vc}O_2$ y CR en pacientes con shock séptico.

Diseño: Estudio observacional y prospectivo.

Ámbito: Dos UCIs de adultos.

Pacientes: Cuarenta y siete pacientes con shock séptico, ventilados mecánicamente, y con condiciones respiratorias y dosis de vasopresores estables, luego de la resucitación inicial.

Intervenciones: Ninguna.

Variables de interés principales: Se midieron gases arteriales y venosos centrales, Hb y O_2Hb . Se calcularon $P_{vc-a}CO_2/C_{a-vc}O_2$ y la relación entre contenido venoso central-arterial de CO_2 y el contenido arterial-venoso central de O_2 ($C_{vc-a}CO_2/C_{a-vc}O_2$). El CR se determinó por calorimetría indirecta.

Resultados: $P_{vc-a}CO_2/C_{a-vc}O_2$ y $C_{vc-a}CO_2/C_{a-vc}O_2$ no correlacionaron con CR ($R^2 = 0.01$, $P = 0.50$ and $R^2 = 0.01$, $P = 0.58$, respectivamente) y tuvieron amplios sesgos y límites de concordancia del 95 % (1.09, -1.10–3.27 y 0.42, -1.53–2.37). El modelo de regresión lineal múltiple encontró Hb, PCO_2 venosa central y O_2Hb , pero no CR, como determinantes de $P_{vc-a}CO_2/C_{a-vc}O_2$ ($R^2 = 0.36$, $P = 0.0007$).

Conclusiones: In pacientes con shock séptico, $P_{vc-a}CO_2/C_{a-vc}O_2$ no tuvo correlación con CR y estuvo determinada principalmente por factores que modifican la disociación de CO_2 desde la Hb. $P_{vc-a}CO_2/C_{a-vc}O_2$ parece ser un pobre sustituto de CR y sus valores deben interpretarse con precaución.

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Introduction

The normalization of tissue perfusion and oxygenation is the final goal of septic shock resuscitation. Unfortunately, there is no gold standard for evaluation of tissue oxygenation. The presence of hyperlactatemia or alterations in peripheral perfusion does not necessarily indicate tissue hypoxia. In experimental models of oxygen supply dependence, the abrupt increase in respiratory quotient (RQ)—the ratio of CO_2 production (VCO_2) to O_2 consumption (VO_2)—indicates the beginning of anaerobic metabolism.^{1–4} The RQ rises

because the drop in VO_2 exceeds the reduction in VCO_2 . Although VCO_2 and VO_2 decrease as a reflection of oxidative metabolism derangement, the lower reduction in the former is explained by the surge in anaerobic VCO_2 due to bicarbonate buffering of anaerobically generated protons.

The measurement of RQ requires a metabolic cart, which is not usually available in the ICU. Thus, the ratio of mixed venous minus arterial PCO_2 to arterial minus mixed venous O_2 content ($P_{mv-a}CO_2/C_{a-mv}O_2$) was proposed as a surrogate for RQ. In an observational study, values of $P_{mv-a}CO_2/C_{a-mv}O_2$ higher than 1.4 were associated with hyperlactatemia

and worse outcome.⁵ Thereafter, other studies used the ratio of venous minus arterial PCO₂ to arterial minus central venous O₂ content ($P_{cv-a}CO_2/C_{a-cv}O_2$) to assess global oxygenation.⁶⁻⁹ To improve the ability of $P_{cv-a}CO_2/C_{a-cv}O_2$ and $P_{mv-a}CO_2/C_{a-mv}O_2$ to reflect RQ, calculated CO₂ content difference has been used instead of PCO₂ difference in the computation of the ratios.^{6,10} $P_{cv-a}CO_2/C_{a-cv}O_2$ is thus recommended for the assessment of tissue oxygenation.^{11,12} Even though $P_{cv-a}CO_2/C_{a-cv}O_2$ might be associated with hyperlactatemia and outcome, neither the interchangeability with RQ nor the correlation with conclusive variables of anaerobic metabolism has never been demonstrated in septic shock. Besides, basic research suggested that $P_{mv-a}CO_2/C_{a-mv}O_2$ is more dependent on factors than modify the dissociation of CO₂ from Hb than on the actual RQ and that it can increase in presence of preserved tissue oxygenation.¹³ In addition, experimental studies failed to show a good correlation between $P_{mv-a}CO_2/C_{a-mv}O_2$ and RQ.^{13,14}

Our goal was to compare $P_{cv-a}CO_2/C_{a-cv}O_2$ and RQ in patients with septic shock. Our hypothesis was that $P_{cv-a}CO_2/C_{a-cv}O_2$ is a poor surrogate for RQ. A secondary goal was to assess $P_{cv-a}CO_2/C_{a-cv}O_2$ determinants.

Patients and methods

This study was approved by the Institutional Review Board (Comité de Revisión Institucional del Hospital Británico) on September 17, 2021 (CRIHB#865, project title: Comparison of $P_{cv-a}CO_2/C_{a-cv}O_2$ and respiratory quotient in patients with septic shock). The study was conducted in accordance with the Declaration of Helsinki of 1975. Informed consent was obtained from the patient's next of kin. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for reporting cohort studies. The completed checklist is included in the Appendix.

We studied patients older than 18 years recruited from two surgical/medical ICUs, from June 2020 to March 2023. Septic shock diagnosis was based on the presence of a source of infection, arterial hypotension refractory to fluid administration and so requiring vasopressors, and blood lactate levels higher than 2.0 mmol/L.¹⁵ All patients were intubated and mechanically ventilated on controlled mode, and received infusions of midazolam or propofol and fentanyl. The Richmond Agitation-Sedation Scale was -5 for all patients.¹⁶ Patients were included after initial resuscitation, when respiratory settings and vasopressor dose remained stable over 1 h. Patients with FiO₂ ≥ 0.60, PEEP > 10 cm H₂O, tidal volume < 300 mL, renal replacement therapy, or airway leaks, were excluded from the study since indirect calorimetry measurements might be unreliable in such conditions.

Demographic and clinical data were registered. We measured VO₂, VCO₂, and RQ by indirect calorimetry (MedGraphics CPX Ultima, Medical Graphics Corporation, St. Paul, MN, and Mindray Metabolic Module, Mindray Medical International, Shenzhen, China). We used the mean of a 5-minute period of measurements when variations were less than 5%.¹⁷ During this period of time, arterial and central venous samples were simultaneously obtained for the determination of pH, PCO₂, PO₂, Hb, and O₂Hb (Cobas b 221,

Roche Diagnostics GmbH, Mannheim, Germany). We calculated $P_{cv-a}CO_2/C_{a-cv}O_2$ by standard formulae and the ratio central venous minus arterial CO₂ content to arterial minus central venous O₂ content ($C_{cv-a}CO_2/C_{a-cv}O_2$) by the Douglas' algorithm.¹⁸ P50, the PO₂ at which Hb is 50 % saturated, was also calculated. A complete depiction of the formulae is shown in the Appendix.

Analysis of the data

We estimated that 47 patients were required to demonstrate a moderate correlation between $P_{cv-a}CO_2/C_{a-cv}O_2$ and RQ ($r = 0.40$), with a significance level of 0.05 and power of 80 %. Shapiro-Wilk test and quantile-quantile plots of the differences were used to test data normality. Correlation and agreement between $P_{cv-a}CO_2/C_{a-cv}O_2$ and $P_{cv-a}CO_2/C_{a-cv}O_2$ with RQ were assessed with simple linear regression and Bland and Altman analysis. To identify independent determinants of $P_{cv-a}CO_2/C_{a-cv}O_2$, variables showing a P -value < 0.20 in the simple linear regression and those physiologically plausible were entered into multiple linear regression analysis and a model was constructed. Differences between survivors and nonsurvivors patients were assessed by unpaired t -test, Mann-Whitney U -test, or Chi-square test. Patients were also compared according to arbitrary cutoffs of $P_{cv-a}CO_2/C_{a-cv}O_2$ and RQ (1.4 and 1.0, respectively). Data are shown as mean ± standard deviation, median [IQR], or n (%). A P -value < 0.05 was considered as statistically significant.

Results

From 341 screened patients with septic shock, 47 of them were included. The time between the onset of shock and the measurements was 1 [1-3] days. Most of the patients were not studied because indirect calorimetry measurements were not available at the screening time. The flowchart of the study is shown in the Appendix (Figure A1).

Table 1 shows the main epidemiological and clinical characteristics that did not differ between survivors and nonsurvivors. Neither there were differences according to the cutoffs of $P_{cv-a}CO_2/C_{a-cv}O_2$ and RQ (Tables A1 and A2). Nonsurvivors showed lower pH and higher lactate levels than survivors. Survivors and nonsurvivors had high mean values of $P_{cv-a}CO_2/C_{a-cv}O_2$ and $C_{cv-a}CO_2/C_{a-cv}O_2$, which were not different between groups. Values of RQ were in the normal range and not different between groups (Table 2). Patients with $P_{cv-a}CO_2/C_{a-cv}O_2 < 1.4$ had lower arterial and central venous bicarbonate, and lower central venous PCO₂ than patients with $P_{cv-a}CO_2/C_{a-cv}O_2 > 1.4$ (Table A3) Patients with RQ < 1.0 showed higher VO₂ and central venous PO₂ than patients with RQ > 1.0 (Table A4). Arterial lactate was not different among these subgroups (Tables A3 and A4).

$P_{cv-a}CO_2/C_{a-cv}O_2$ and $C_{cv-a}CO_2/C_{a-cv}O_2$ showed weak correlations and wide 95 % limits of agreement with RQ (Fig. 1). Similar correlations were obtained considering the different metabolic carts used in each hospital ($R^2 = 0.00$, $P = 0.71$ and $R^2 = 0.00$, $P = 0.81$ for MedGraphics CPX Ultima, and $R^2 = 0.05$, $P = 0.57$ and $R^2 = 0.03$, $P = 0.64$ for Mindray Metabolic Module).

Table 1 Clinical and epidemiologic characteristics of the patients.

Variable	All	Survivors (n = 29)	Nonsurvivors (n = 18)	P-value
Age, years	67 ± 13	65 ± 15	71 ± 7	0.15
Gender male, n (%)	22 (47)	15 (52)	7 (39)	0.55
SOFA score	7 ± 4	6 ± 4	8 ± 4	0.07
APACHE II score	18 ± 9	17 ± 9	21 ± 9	0.10
ICU mortality, %	38			
Source of sepsis, n (%)				
Intraabdominal	16 (34)	9 (31)	7 (39)	0.58
Respiratory	19 (40)	14 (48)	5 (28)	0.16
Urinary	6 (13)	4 (14)	2 (11)	0.79
Intravascular	4 (8)	2 (7)	2 (11)	0.97
Soft tissue	2 (4)	0 (0)	2 (11)	0.66
Norepinephrine (µg/kg/min)	0.12 [0.02–0.30]	0.09 (0.01–0.20)	0.2 (0.09–0.50)	0.07
Mean arterial pressure (mmHg)	74 ± 10	76 ± 10	71 ± 10	0.14
Heart rate (beats/min)	87 ± 18	87 ± 16	88 ± 21	0.91
Temperature (°C)	36.7 ± 0.7	37 ± 1	36 ± 1	0.17

Abbreviations: SOFA, Sepsis-related Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation. Data are expressed as mean ± standard deviation, median [IQR], or n (%).

Table 2 Values of arterial and central venous gases, co-oximetry, CO₂-derived variables, and expired gases analysis.

Variable	All	Survivors (n = 29)	Nonsurvivors (n = 18)	P-value
Arterial lactate on admission (mmol/L)	3.32 ± 2.04	3.02 ± 1.79	3.80 ± 2.35	0.18
Arterial lactate on measurement (mmol/L)	2.61 ± 2.40	1.84 ± 1.02	3.74 ± 3.3	0.04
Hemoglobin (g/L)	9.5 ± 2.2	9.90 ± 2.2	8.95 ± 2.07	0.11
Arterial pH	7.36 ± 0.08	7.38 ± 0.07	7.33 ± 0.09	0.04
Arterial PCO ₂ (mmHg)	40 ± 7	40 ± 8	39 ± 7	0.77
Arterial PO ₂ (mmHg)	92 ± 23	93 ± 19	90 ± 28	0.15
Arterial HCO ₃ ⁻ (mmol/L)	22 ± 6	23 ± 5	21 ± 6	0.29
Arterial base excess (mmol/L)	-3 ± 6	-1 ± 5	-4 ± 6	0.11
Arterial O ₂ Hb (%)	96 ± 2	97 ± 1	95 ± 2	0.02
Central venous pH	7.33 ± 0.08	7.35 ± 0.07	7.29 ± 0.08	0.02
Central venous PCO ₂ (mmHg)	46 ± 8	46 ± 8	46 ± 8	0.89
Central venous PO ₂ (mmHg)	42 ± 7	42 ± 6	40 ± 9	0.28
Central venous HCO ₃ ⁻ (mmol/L)	23 ± 6	24 ± 5	22 ± 6	0.25
Central venous base excess (mmol/L)	-2 ± 6	0 ± 5	-3 ± 6	0.12
Central venous O ₂ Hb (%)	71 ± 9	73 ± 8	68 ± 8	0.09
P50 (mmHg)	25 ± 3	25 ± 2	26 ± 4	0.09
P _{cv-a} CO ₂ /C _{a-cv} O ₂	2.05 ± 1.07	1.96 ± 0.90	2.18 ± 1.32	0.85
C _{cv-a} CO ₂ /C _{a-cv} O ₂	1.38 ± 0.95	1.38 ± 1.09	1.38 ± 0.72	0.98
O ₂ consumption (mL/min/m ²)	136 ± 47	141 ± 39	126 ± 59	0.20
CO ₂ production (mL/min/m ²)	124 ± 36	129 ± 27	116 ± 46	0.12
Respiratory quotient	0.96 ± 0.21	0.94 ± 0.14	0.99 ± 0.29	0.53

Abbreviations: P_{cv-a}CO₂/C_{a-cv}O₂, central venous-arterial PCO₂ to arterial-central venous O₂ content ratio; P_{cv-a}CO₂/C_{a-cv}O₂, central venous-arterial PCO₂ to arterial-central venous O₂ content ratio.

The multiple linear regression model showed hemoglobin, central venous PCO₂, and central venous O₂Hb as P_{cv-a}CO₂/C_{a-cv}O₂ determinants (R² = 0.36, P = 0.0007) (Table 3).

Discussion

Our main finding was the absence of a significant correlation between of P_{cv-a}CO₂/C_{a-cv}O₂ and RQ. In addition,

P_{cv-a}CO₂/C_{a-cv}O₂ was independently determined by factors that modify the dissociation of CO₂ from Hb.

Since RQ has sudden increases during experimental models of oxygen supply dependency,¹⁻⁴ a surrogate—P_{cv-a}CO₂/C_{a-cv}O₂—has been used as a tool to assess the adequacy of tissue oxygenation. Thus, observational studies found some relationship of P_{cv-a}CO₂/C_{a-cv}O₂ to hyperlactatemia and outcome.⁵⁻⁹ Nevertheless, the agreement between P_{cv-a}CO₂/C_{a-cv}O₂ and RQ, and its ability to reflect tissue hypoxia have never been shown. In addition,

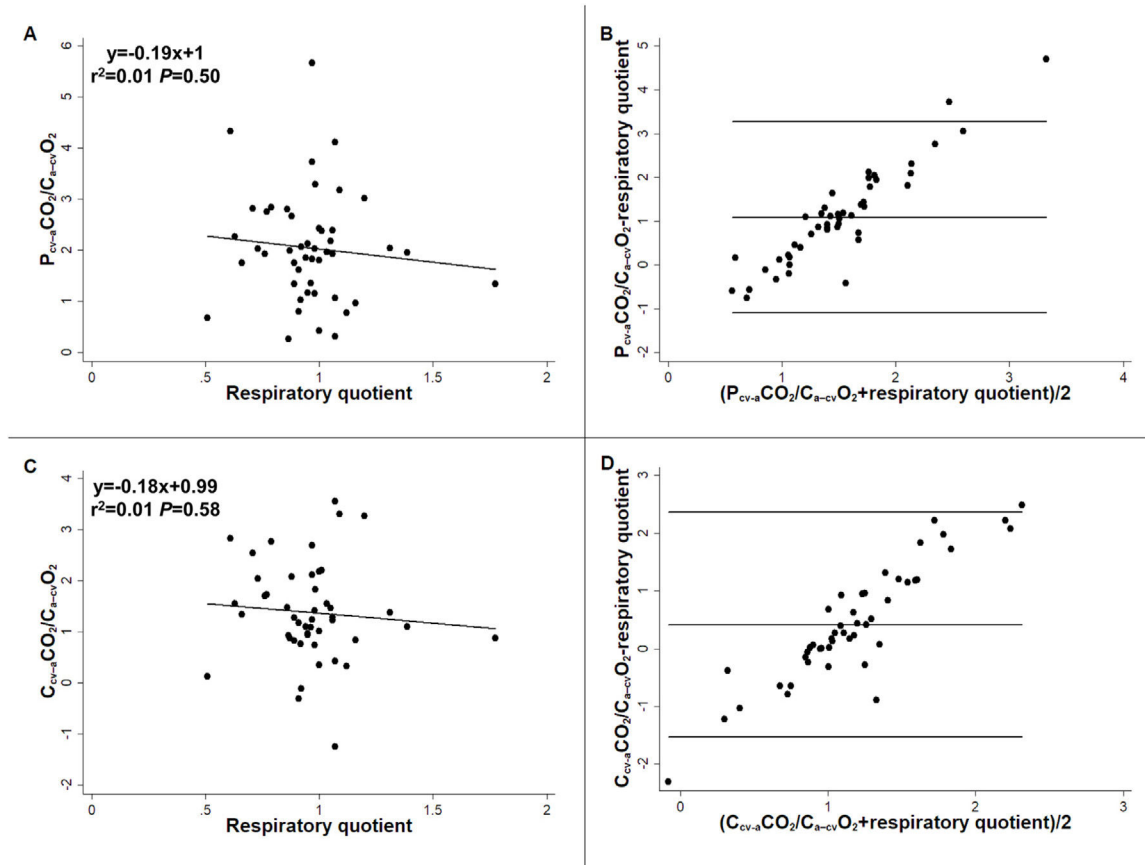


Figure 1 Correlation and agreement of central venous minus arterial PCO_2 to arterial minus central venous O_2 content and central venous minus arterial CO_2 content to arterial minus central venous O_2 content ratio with respiratory quotient. Panel A: Correlation between central venous minus arterial PCO_2 to arterial minus central venous O_2 content ratio ($\text{P}_{\text{cv-a}}\text{CO}_2/\text{C}_{\text{a-cv}}\text{O}_2$) and respiratory quotient. Panel B: Bland and Altman analysis between $\text{P}_{\text{cv-a}}\text{CO}_2/\text{C}_{\text{a-cv}}\text{O}_2$ and respiratory quotient. Panel C: Correlation between central venous minus arterial CO_2 content to arterial minus central venous O_2 content ratio ($\text{C}_{\text{cv-a}}\text{CO}_2/\text{C}_{\text{a-cv}}\text{O}_2$) and respiratory quotient. Panel D: Bland and Altman analysis between $\text{C}_{\text{cv-a}}\text{CO}_2/\text{C}_{\text{a-cv}}\text{O}_2$ and respiratory quotient.

a randomized controlled trials failed to show usefulness of $\text{P}_{\text{cv-a}}\text{CO}_2/\text{C}_{\text{a-cv}}\text{O}_2$ as a goal for resuscitation.¹⁹ Despite lack of clear evidence, some reviews have recommended its utilization and incorporated it in algorithms for the assessment and treatment of shock states.^{11,12} As recently shown in a systematic review and meta-analysis, high values of $\text{P}_{\text{cv-a}}\text{CO}_2/\text{C}_{\text{a-cv}}\text{O}_2$ have an association with mortality.²⁰ The ability to predict outcome, however, is similar or probably lower than that of lactate. Moreover, its prognostic value might be related to some of its determinants—*anemia and metabolic acidosis*—and not to the ability to reflect anaerobic metabolism.

The rationale for the use of $\text{P}_{\text{cv-a}}\text{CO}_2/\text{C}_{\text{a-cv}}\text{O}_2$ in the assessment of tissue oxygenation in patients with septic shock is based on the behavior of RQ in animal models of anaerobic metabolism.¹⁻⁴ Yet, no clinical study has comprehensively addressed this issue.²¹ On the other hand, experimental studies showed that $\text{P}_{\text{mv-a}}\text{CO}_2/\text{C}_{\text{a-mv}}\text{O}_2$ might not reflect the changes in the RQ and the adequacy of tissue oxygenation. During stepwise reductions in oxygen transport (DO_2), $\text{P}_{\text{mv-a}}\text{CO}_2/\text{C}_{\text{a-mv}}\text{O}_2$ was almost five times higher in anemic than in ischemic hypoxia despite comparable degrees of anaerobic metabolism.¹³ Moreover, $\text{P}_{\text{mv-a}}\text{CO}_2/\text{C}_{\text{a-mv}}\text{O}_2$ increased

even before the beginning of the oxygen supply dependence and the rise of RQ. Similar results were reported in hypoxic hypoxia.²² In experimental hemorrhagic shock, blood transfusion was associated with restoration of oxidative metabolism, as shown by the normalization of oxygen transport, VO_2 , and RQ. Despite this, $\text{P}_{\text{mv-a}}\text{CO}_2/\text{C}_{\text{a-mv}}\text{O}_2$ remained elevated.¹⁴

In our series of patients with septic shock, there was no correlation between $\text{P}_{\text{cv-a}}\text{CO}_2/\text{C}_{\text{a-cv}}\text{O}_2$ and RQ. Moreover, high $\text{P}_{\text{cv-a}}\text{CO}_2/\text{C}_{\text{a-cv}}\text{O}_2$ values coexisted with normal values of RQ. These findings might be explained by the fact that $\text{P}_{\text{cv-a}}\text{CO}_2/\text{C}_{\text{a-cv}}\text{O}_2$ is more dependent on Hb levels, Haldane effect, metabolic acidosis, and the position in the CO_2Hb dissociation, than on the actual RQ.¹³ In the present study, we also showed that $\text{P}_{\text{cv-a}}\text{CO}_2/\text{C}_{\text{a-cv}}\text{O}_2$ depends on some factors that modify dissociation of CO_2 from Hb, such as Haldane effect and Hb levels. In contrast, we found that base excess or lactate did not behave as determinants $\text{P}_{\text{cv-a}}\text{CO}_2/\text{C}_{\text{a-cv}}\text{O}_2$.

Unlike animal studies that show poor but significant correlations,^{13,14} we found an almost null regression coefficient between $\text{P}_{\text{cv-a}}\text{CO}_2/\text{C}_{\text{a-cv}}\text{O}_2$ and RQ. Differences might be related to different facts. In animal studies, mixed venous instead of central venous samples were used for the calcu-

Table 3 Multiple linear regression model for central venous-arterial PCO₂ to arterial minus central venous O₂ content ratio (P_{cv-a}CO₂/C_{a-cv}O₂).

P _{v-a} CO ₂ /C _{a-v} O ₂	Coefficient	Standard error	t-ratio	P-value	[95% Confidence Interval]
Hemoglobin (g/100 mL)	−0.14	0.06	−2.25	0.03	−0.27 to −0.01
Central venous O ₂ Hb (%)	0.03	0.01	2.07	0.04	0.01–0.06
Central venous PCO ₂ (mmHg)	0.07	0.02	3.86	<0.001	0.04–0.11

lation of the ratio. An observational study in patients with septic shock showed the lack of interchangeability between both determinations, with unacceptable wide 95% limits of agreement of 1.48.²³ The main explanation, however, might be that in the experimental studies there was a wide range of variation in the RQ, which increased during the severe reductions in DO₂. On the contrary, RQ remained in the normal physiologic range in the present study. Thus, RQ is a main determinant of P_{cv-a}CO₂/C_{a-cv}O₂ only in real anaerobic conditions.

We found high values of P_{cv-a}CO₂/C_{a-cv}O₂ and C_{v-a}CO₂/C_{a-cv}O₂ (2.05 ± 1.07 and 1.38 ± 0.95, respectively) that could be considered indicative of anaerobic metabolism.^{1,4} Even though our patients were critically ill, the respiratory and the hemodynamic status and the norepinephrine requirement had been unchanged over the last hour. Moreover, the RQ stayed at normal range (0.96 ± 0.21). Consequently, their condition did not evoke a state of oxygen supply dependence, which is characterized by a rapid decline leading to cardiac arrest. The surge in RQ that develops in models of tissue hypoxia constitutes an extreme event associated with an impending death (*i.e.*, mean blood pressure of 27 ± 2 mmHg in hemorrhagic shock or Hb of 1.2 ± 0.1 g/dL in hemodilution).¹³ Therefore, it is unlikely that the high P_{cv-a}CO₂/C_{a-cv}O₂ and C_{v-a}CO₂/C_{a-cv}O₂ found in this study can denote global tissue hypoxia. Accordingly, arterial lactate levels did not differ between patients with P_{cv-a}CO₂/C_{a-cv}O₂ lower or higher than 1.4. In line with our results, P_{cv-a}CO₂/C_{a-cv}O₂ did not predict the decrease blood lactate after increases in cardiac output induced by volume expansion in critically ill patients.²⁴ P_{cv-a}CO₂/C_{a-cv}O₂ neither correlated with lactate-to-pyruvate ratio during the resuscitation of septic shock.²⁵

Although the incorporation of CO₂ content instead of PCO₂ difference in the calculation might improve the performance of the ratio, C_{cv-a}CO₂/C_{a-cv}O₂ also showed poor correlation with RQ. This finding is probably related to limitations of the calculation of CO₂ content: it frequently results in unacceptable errors, such as negative C_{cv-a}CO₂/C_{a-cv}O₂. Indeed, this occurred in three of our measurements suggesting that the algorithm might be misleading for this purpose (see Fig. 1 Panel C).

Our study has some limitations. We only performed a single set of measurements at a particular timepoint, which could not be representative of patients' evolution over time. In addition, many patients were not included because indirect calorimetry was unavailable. This might limit the generalizability of our findings. Finally, each center used a different metabolic cart, each of which was previously validated.^{26–28} Since the results of different devices are not interchangeable, this could be a further drawback of the

study.²⁶ In spite of this, the results were quite similar considering each device separately.

Conclusions

To our knowledge, this is the first study comparing P_{cv-a}CO₂/C_{a-cv}O₂ and C_{cv-a}CO₂/C_{a-cv}O₂ with RQ, in patients with septic shock. Neither P_{cv-a}CO₂/C_{a-cv}O₂ nor C_{cv-a}CO₂/C_{a-cv}O₂ was correlated with RQ. Our results suggest that in patients with septic shock P_{cv-a}CO₂/C_{a-cv}O₂ should be interpreted cautiously.

Conflict of interest

The authors declare that they have no competing interests.

Authors' contributions

Conception and design: FJG, MOP, and AD; acquisition of data: FJG, MN, SPC, NL, MJR, PNRB, and VSKE; statistical analysis: FJG; drafting of the manuscript: FJG and AD. All authors critically revised the article and approved the final version.

Funding

This study was supported by the grant PICT-2018-03977, Agencia Nacional de Promoción Científica y Tecnológica, Argentina, which was not involved in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.medin.2024.05.016>.

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