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ORIGINAL INVESTIGATION

Role of Pv-aCO_2 gradient and Pv-aCO_2/Ca-vO_2 ratio during cardiac surgery: a retrospective observational study

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Abstract

Introduction: Arterial lactate, mixed venous O_2 saturation, venous minus arterial CO_2 partial pressure ($P_{v\text{-}a}CO_2$) and the ratio between this gradient and the arterial minus venous oxygen content ($P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$) were proposed as markers of tissue hypoperfusion and oxygenation. The main goals were to characterize the determinants of $P_{v\text{-}a}CO_2$ and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$, and the interchangeability of the variables calculated from mixed and central venous samples.

Methods: 35 cardiac surgery patients were included. Variables were measured or calculated: after anesthesia induction (T1), end of surgery (T2), and at 6–8 hours intervals after ICU admission (T3 and T4).

Results: Macrohemodynamics was characterized by increased cardiac index and low systemic vascular resistances after surgery ($p < 0.05$). Hemoglobin, arterial-pH, lactate, and systemic O_2 metabolism showed significant changes during the study ($p < 0.05$). $P_{v\text{-}a}CO_2$ remained high and without changes, $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ was also high and decreased at T4 ($p < 0.05$). A significant correlation was observed globally and at each time interval, between $P_{v\text{-}a}CO_2$ or $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ with factors that may affect the CO_2 hemoglobin dissociation. A multilevel linear regression model with $P_{v\text{-}a}CO_2$ and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ as outcome variables showed a significant association for $P_{v\text{-}a}CO_2$ with S_vO_2, and BE ($p < 0.05$), while $P_{v\text{-}a}CO_2$/Ca-vO_2 was significantly associated with Hb, S_vO_2, and BE ($p < 0.05$) but not with cardiac output. Measurements and calculations from mixed and central venous blood were not interchangeable.

Conclusions: $P_{v\text{-}a}CO_2$ and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ could be influenced by different factors that affect the CO_2 dissociation curve, these variables should be considered with caution in cardiac surgery patients. Finally, central venous and mixed values were not interchangeable.

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Introduction

Macrohemodynamic and metabolic variables drive cardiovascular support during cardiac surgery.[1,2] As described in other critically ill conditions, arterial lactate and mixed venous oxygen saturation (S_vO_2) have been used to evaluate tissue perfusion and oxygenation.[3,4]

Parameters derived from carbon dioxide metabolisms (CO_2), such as the difference between venous and arterial CO_2 partial pressure ($P_{v\text{-}a}CO_2$) and the ratio between this gradient and the arterial minus venous oxygen content ($P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$), have been proposed as markers of hypoperfusion and anaerobic metabolism.[5–7] However, the levels of these variables during cardiac surgery remain controversial.

In critically ill patients, reductions in both CO_2 production (VCO_2) and O_2 consumption (VO_2) are noted during oxygen supply dependence conditions. However, the decrease in VCO_2 was less pronounced than in VO_2 due to the increase in VCO_2 from anaerobic metabolism. Based on the modified Fick equation, VCO_2 is calculated as the product of cardiac output (CO) times venous minus arterial CO_2 content (VCO_2 = CO x $C_{v\text{-}a}CO_2$). Assuming a stable relationship between CO_2 partial pressure (PCO_2) and CO_2 content (CCO_2), the equation could be reformulated as VCO_2 = CO x $P_{v\text{-}a}CO_2$. Thus, $P_{v\text{-}a}CO_2$ increases in low cardiac output states and during microvascular dysfunction.[8,9]

The $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ratio has been proposed as a surrogate of the respiratory quotient (RQ) to identify the onset of anaerobic metabolism. Assuming stable conditions, CCO_2 could be replaced by PCO_2 in the formula. However, this ratio is influenced by other factors, such as changes in hemoglobin (Hb), lactate concentrations, base excess (BE), S_vO_2 (Haldane effect), and body temperature. Given that CO_2-derived parameters are measured under the influence of these factors, their physiologic meaning could be misleading. Despite these limitations, $P_{v\text{-}a}CO_2$ and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ have been used in clinical practice to guide hemodynamic support and as outcome biomarkers.[5,8,9] A better understanding of the limits and sources of errors of this practice should be considered in critically ill patients.[10] Many investigations use central venous blood values ($P_{cv}CO_2$) measured from the superior vena cava as equivalent to mixed venous blood measured from the pulmonary artery (P_vCO_2). The central venous-to-arterial CO_2 difference may represent one of the alternatives to the mixed-to-arterial CO_2 difference, but whether central venous blood values could subrogate mixed venous values is still debated.[10–12]

We hypothesized that CO_2 calculated variables are dependent on physiologic alterations. Additionally, central and mixed venous blood parameters are not interchangeable.

The main goal was to assess the physiological determinants that affect $P_{v\text{-}a}CO_2$ and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ during cardiac surgery. Second, we analyzed the agreement between mixed and central venous blood values to determine whether they are interchangeable.

Methods

The present study is a secondary retrospective analysis of a previous multicenter investigation,[13] which was approved by the Institutional Bioethical Committee, and written consent was obtained from each patient. The objective in the original paper was to determine the clinical significance of the gradient SO_2 and lactate within the superior vena cava to the pulmonary artery in critical patients. Using this database, the present research focused on 35 cardiac surgeries performed in our institution.

We enrolled patients older than 18 years of age of either sex who required the insertion of a pulmonary artery catheter: LVEF <40%, combined surgery, pulmonary-hypertension and reintervention. Patients with known uncorrected valvular incompetence or intracardiac shunting were excluded. The pulmonary artery catheter monitoring (PAC-7.5 Edwards Life Sciences) was inserted in the right internal jugular vein, and a radial arterial line was placed according to standard clinical practice.

Anesthesia was induced with etomidate and fentanyl and maintained with isoflurane and fentanyl. Mechanical ventilation was established to maintain an arterial PCO_2 between 35 and 40 mmHg. CBP was achieved with a non-pulsatile flow using a membrane oxygenator at 32–33°C. The mean arterial pressure was maintained between 50 and 60 mmHg. Vasoactive and inotropic infusions were prescribed and titrated following standard practice in each patient. Before arterial and venous cannulation, 300 $mg.kg^{-1}$ sodium heparin was administered intravenously (IV) to achieve an activated coagulation time greater than or equal to 480 seconds. Sodium heparin was later neutralized with protamine sulfate in a 1:1 proportion. All patients received 500 mg methylprednisolone during CPB. Body temperature was returned to 37°C before decannulation. Parenteral analgesia, sedation, and mechanical ventilation were sustained until the patients were hemodynamically stable, awake, and ready for weaning from mechanical ventilation.

Measurements and calculations were taken at T1, after anesthesia induction and before CPB; T2, after the end of surgery; T3 and T4, at 6- to 8-hour intervals after ICU admission.

Blood samples from the arterial line, internal jugular vein (proximal port), and pulmonary artery were drawn simultaneously and in duplicate. Hb concentration, blood gases, lactate, BE, and SO_2 were measured simultaneously in each vascular compartment (ABL-700, Radiometer, Denmark).

CO was measured in triplicate by thermodilution and was indexed by body weight. Systemic vascular resistance (SVR) was calculated. The physician in charge conducted hemodynamic and anesthetic treatment according to standard practice.

Mixed venous CO_2 content was calculated according to previously described formulas.[14] The venous-arterial PCO_2 gradients were calculated from mixed and central venous blood and expressed as $P_{v\text{-}a}CO_2$, $C_{v\text{-}a}CO_2$, and $P_{cv\text{-}a}CO_2$.

Arterial and venous oxygen contents were calculated using standard formulas. The venous-arterial CO_2 partial pressure/arterial-venous O_2 content ratio was calculated from central and pulmonary venous blood and expressed as $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ for mixed and $P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$ for central venous blood, respectively.

Statistical analysis

Data are presented as the mean and standard deviation (SD), standard error (SE) or absolute numbers and percentages (%). Variables over time were analyzed by repeated-measures ANOVA followed by the Bonferroni post hoc test. Linear correlations were studied between $P_{v\text{-}a}CO_2$ and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ with hemodynamic and metabolic variables. Multilevel linear regression models with mixed effects for $P_{v\text{-}a}CO_2$ and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ as outcome variables were performed, including CI, Hb, pH, BE, and S_vO_2 at different time intervals. Statistical significance was assumed when $p \leq 0.05$.

The interchangeability between central and pulmonary blood samples was studied using Bland-Altman analysis. The utility of this approach is limited when treatments or interventions affect the variables over time. Then, change or delta values were plotted using a Cartesian X-Y 4-quadrant plot, allowing the evaluation of the direction of the change or the concordance rate. The concordance rate was defined as the percentage of values included in the right superior and left inferior quadrants of the plots. The agreement between variables was considered weak when this percentage was less than 80%. The polar plot analysis allowed a more precise evaluation of the trend and magnitude of changes between the study (central venous blood) and reference variables (mixed venous blood). From the central point, changes in the calculated pairs of values are represented as vectors with defined angles and magnitudes. The mean angular bias (q) and the standard deviation represent all measured angles from the polar reference axis (0°). In addition, radial limits of agreement were estimated as the radial sector that contains 95% of the values (2SD). A mean angular value ±5° and a radial limit of agreement ±30° were the defined limits for the polar plot analysis.[15]

Results

Table 1 presents demographics characteristics. Norepinephrine was used in 2.7% of patients during T1, 50% in T2 and T3, and 36.1% in T4 ($p < 0.05$). Dobutamine or milrinone was used in 11.1% of patients during T1, 16.6% during T2 and T3, and 19.4% during T4 (ns). Drug infusion was titrated by the physician in charge. Three patients (8.6%) died.

Hemodynamics and metabolic course

Systemic hemodynamics, O_2 metabolism and metabolic variables are summarized in Table 2. This patient exhibited a postoperative hemodynamic pattern characterized by high CI and low SVR ($p < 0.05$). The MAP was 75.1 ± 18.7 mm Hg and increased significantly to 86.7 ± 14.1 mm Hg (T4) compared to T2 ($p < 0.05$). The Hb concentration was significantly lower than baseline during T2 and T3 ($p < 0.05$). These changes were accompanied by a decrease in arterial oxygen content (C_aO_2) at the same time intervals ($p < 0.05$). Arterial pH decreased significantly during T2 and T3 ($p < 0.05$), whereas arterial lactate levels were higher than baseline throughout the study ($p < 0.05$). Although a transient trend toward lower BE values was noted in the postoperative period, these changes were not statistically significant compared to baseline. S_vO_2 and $S_{cv}O_2$ were significantly lower during T3 and T4 ($p < 0.05$). Oxygen delivery (DO_2) increased significantly during the postoperative period (T2 and T3) ($p < 0.05$), returning to basal values at T4. VO_2 increased and remained significantly higher than baseline levels after T2 ($p < 0.05$). The oxygen extraction ratio (EO_2) increased during T3 and T4 ($p < 0.05$).

Table 1 Main characteristics of cardiac surgery patients.

Age (years)	65 ± 10
BMI ($kg.m^{-2}$)	28 ± 3
LVEF (%)	47 ± 13
CPB duration (min)	124 ± 32
Aortic clamp (min)	80 ± 29
Gender	
Female	15/35
Male	20/35
Type of Surgery	
Combined	10/35
CABG on-pump	12/35
CABG off-pump	6/35
Valvular replacement	6/35
Thoracic aortic surgery	1/35
Comorbidities	
Arterial hypertension	17/35
Dyslipidemia	9/35
Smokers	11/35
Diabetes	7/35
Creatinine > 2 $mg.dL^{-1}$	1/35

Mean values ± SD, or fractions.
BMI, body mass index; CABG, coronary artery bypass grafting; CPB, cardiopulomary bypass.

CO_2-derived measurements

CO_2-derived measurements are shown in Table 2. The $P_{v\text{-}a}CO_2$ and $C_{v\text{-}a}CO_2$ gradients did not exhibit significant changes compared to baseline. The $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ and $C_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ratios did not change until T4, when the values were significantly lower than baseline ($p < 0.05$).

$P_{cv\text{-}a}CO_2$ and $P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$ showed higher absolute values but similar trends during the study.

To identify the overall influence of the different physiologic variables, we performed a global correlation for both variables. Figure 1 shows the scatter plot and correlation coefficients between $P_{v\text{-}a}CO_2$ and the main hemodynamic and metabolic variables. A significant positive linear correlation was identified between $P_{v\text{-}a}CO_2$ and arterial lactate and EO_2 ($p < 0.05$). A negative linear correlation was identified between the same variable and BE, S_vO_2, Hb, pH, and DO_2 ($p < 0.05$). However, r^2 values were always low, denoting a weak coefficient of determination between these variables. Figure 2 shows the global correlation between $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ with the same variables. A significant positive linear correlation with CI and S_vO_2 ($p < 0.05$) was noted. On the other hand, a significant inverse linear correlation was found between $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ and Hb, arterial pH, BE, and EO_2 ($p < 0.05$), but all r^2 values were low.

Table 2 Hemodynamic, metabolic and CO_2derived variables at different time intervals.

	T1	T2	T3	T4
CI ($L.min^{-1}$)	2.09 ± 0.62	2.71 ± 0.68[a]	2.86 ± 0.71[a]	2.81 ± 1.18[a]
SVRI ($dyn.s/cm^{-5}$)	2670 ± 902	1872 ± 663[a]	2020 ± 648[a]	2224 ± 618[b]
MAP (mmHg)	75.1 ± 18.7	71.9 ± 13.5	79.4 ± 15.5	86.7 ± 14.1[b]
Hb ($g.L^{-1}$)	11.8 ± 2.4	10.1 ± 1.8[a]	9.9 ± 1.8[a]	10.7 ± 2.9
pH	7.40 ± 0.08	7.33 ± 0.09[a]	7.33 ± 0.08[a]	7.39 ± 0.1[b]
BE ($mmol.L^{-1}$)	-1.3 ± 3.26	-4.3 ± 3.8	-4.8 ± 4.4	-2.4 ± 3.7
P_aCO_2 (mmHg)	36.9 ± 7.2	39.8 ± 9.8	37.9 ± 5.5	36.4 ± 5
Lactate ($mmol.L^{-1}$)	1.27 ± 0.7	3.3 ± 1.4[a]	4.3 ± 3.5[a]	4.2 ± 4.9[a]
S_vO_2 (%)	77.0 ± 8.4	75.6 ± 6.5	64.6 ± 9.6[a,b]	62.1 ± 8.2[a,b]
$S_{cv}O_2$ (%)	77.3 ± 9.7	77.3 ± 7.3	67.6 ± 9.2[a,b]	65.2 ± 9.6[a,b]
C_aO_2 ($mL.dL^{-1}$)	15.8 ± 3.3	13.6 ± 2.4[a]	13.3 ± 2.4[a]	14.1 ± 4.1
C_vO_2 ($mL.dL^{-1}$)	12.3 ± 2.7	10.4 ± 2.3[a]	8.7 ± 2.3[a]	8.9 ± 3.4[a]
$C_{a\text{-}v}O_2$ ($mL.dL^{-1}$)	3.8 ± 1.5	3.2 ± 0.9	4.6 ± 1.1	5.0 ± 1.1[a,b]
$C_{cv}O_2$ ($mL.dL^{-1}$)	12.4 ± 2.9	10.7 ± 2.3[a]	9.1 ± 2.3[a]	9.5 ± 3.5[a]
$C_{a\text{-}cv}O_2$ ($mL.dL^{-1}$)	3.6 ± 1.8	2.9 ± 1.1	4.1 ± 1.2	4.6 ± 1.5[b]
DO_2 ($mL.min^{-1}.m^{-2}$)	487 ± 197	663 ± 275[a]	590 ± 279[a]	513 ± 259
VO_2 ($mL.min^{-1}.m^{-2}$)	108 ± 45	147 ± 51[a]	195 ± 81[a,b]	179 ± 89[a]
EO_2 (%)	23.3 ± 7.7	23.6 ± 6.3	34.5 ± 9.8[a,b]	36.5 ± 10[a,b]
$P_{v\text{-}a}CO_2$ (mm Hg)	7.8 ± 2.5	7.5 ± 4.3	7.9 ± 2.7	7.2 ± 2.5
$C_{v\text{-}a}CO_2$ ($mL.dL^{-1}$)	5.7 ± 0.7	4.6 ± 1.0	4.7 ± 0.4	4.5 ± 0.5
$P_{v\text{-}a}CO_2/C_{(a\text{-}v)}O_2$ ($mm\ Hg.mL^{-1}$)	2.1 ± 0.6	2.5 ± 1.3	1.8 ± 0.7	1.4 ± 0.6[a,b]
$C_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ($mL.dL^{-1}$)	1.5 ± 0.1	1.5 ± 0.3	1.1 ± 0.1	0.9 ± 0.1[a]
$P_{cv\text{-}a}CO_2$ (mmHg)	8.8 ± 3.0	8.0 ± 4.3	9.5 ± 3.3	7.5 ± 3.0
$P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$ ($mmHg.mL^{-1}$)	2.8 ± 1.7	2.8 ± 1.3	2.2 ± 0.9	1.5 ± 0.5[a,b]

CI, Cardiac Index; SVRI, Systemic Vascular Resistance Index; MAP, Mean Arterial Pressure; Hb, hemoglobin concentration; pH, arterial pH; BE, Base Excess; $PaCO_2$, arterial carbon dioxide partial pressure; Lactate, arterial lactate; S_vO_2, mixed venous hemoglobin saturation; $S_{cv}O_2$, central venous hemoglobin saturation; C_aO_2, arterial oxygen content; C_vO_2, mixed venous oxygen content; $C_{cv}O_2$, central venous oxygen content; DO_2, systemic oxygen delivery index; VO_2, systemic oxygen consumption index; EO_2, systemic oxygen extraction ratio. $P_{v\text{-}a}CO_2$, mixed venous minus arterial CO_2 partial pressure gradient; $C_{v\text{-}a}CO_2$, mixed venous minus arterial CO_2 Content; $P_{v\text{-}a}CO_2/C_{(a\text{-}v)}O_2$, mixed venous minus arterial PCO_2 /arterial minus mixed venous Oxygen content ratio; $C_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$, mixed venous minus arterial CO_2 Content / arterial minus mixed venous Oxygen content ratio; $P_{cv\text{-}a}CO_2$, central venous minus arterial CO_2 partial pressure gradient; $P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$, central venous minus arterial PCO_2/arterial minus central venous oxygen content ratio. T1, initial evaluation; after general anesthesia and before surgery; T2, after surgery and extracorporeal circulation; T3 and T4, after ICU admission at 6-8 hours intervals. Mean values ± SD.

[a] $p < 0.05$ vs T1.

[b] $p < 0.05$ vs T2.

Although the coefficients of determination remained weak, the statistical significance of the correlations varied over time. $P_{v\text{-}a}CO_2$ did not correlate with any of these variables at baseline, but it was significantly correlated with lactate (T2) ($p < 0.05$) or with Hb, lactate, S_vO_2, BE and EO2 at the T3 ($p < 0.05$) and T4 time points ($p < 0.05$). In addition, the $P_{v\text{-}a}CO_2$ /$C_{a\text{-}v}O_2$ ratio was significantly correlated with Hb, S_vO_2, BE and EO_2 at T1 ($p < 0.05$); S_vO_2 and EO_2 at T2 ($p < 0.05$); Hb, lactate and BE at T3 ($p < 0.05$); and CI, Hb and BE at the end of the study (T4) ($p < 0.05$).

Table 3 summarizes the multilevel linear regression model with mixed effects for the $P_{v\text{-}a}CO_2$ difference and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ratio as outcome parameters, including CI, Hb, arterial pH, BE, and S_vO_2 for each analysis. S_vO_2 and BE were the main significant determinants for $P_{v\text{-}a}CO_2$ (r^2 = 0.25), whereas Hb, S_vO_2, and BE were the statistical determinants for the $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ratio (r^2 = 0.33) ($p < 0.05$).

Bland-Altman, Quadrant plot and Polar plot analysis

The bias of the difference in the Bland-Altman analysis for $P_{v\text{-}a}CO_2$ and $P_{cv\text{-}a}CO_2$ was 0.59, whereas the limits of agreement were -3.7 to 4.9 mm Hg (2SD). $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ and $P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$ were also analyzed. The mean difference value was 0.38, whereas the limits of agreement ranged from -1.13 to 1.89 (2SD).

In Fig. 3, the upper panel shows the 4-quadrant and polar plot analysis that describes the trend and magnitude of changes between $\Delta P_{v\text{-}a}CO_2$ and $\Delta P_{cv\text{-}a}CO_2$ gradients. The concordance rate was 73 %, and the mean polar angle was -1.5° ± 38°. The radial limit of agreement was 76°. The $\Delta P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ and $\Delta P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$ ratios are shown in the lower panel. The concordance rate calculated from the 4-quadrant plot was 81%. The mean polar angle was 3.3° ± 34°, and the radial limit of agreement was 68°.

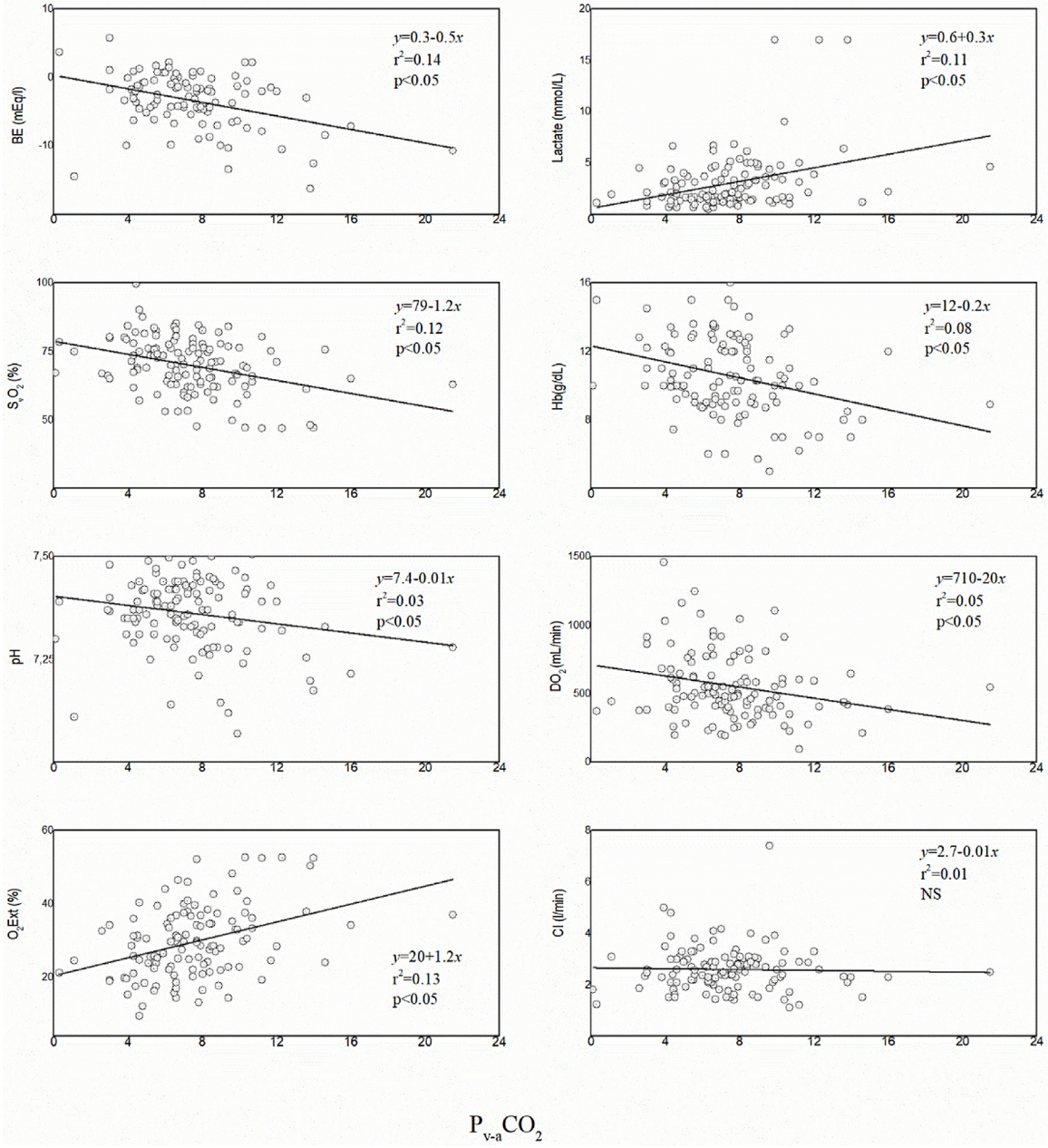

Figure 1 Correlation between mixed venous minus arterial CO_2 partial pressure ($P_{v\text{-}a}CO_2$) with hemodynamic and metabolic parameters. CI, cardiac index; Hb, hemoglobin concentration; Lactate, arterial lactate; S_vO_2, mixed venous oxygen saturation; pH, arterial pH; BE, arterial base excess; EO_2, Systemic O_2 extraction ratio; DO_2, Systemic O_2 delivery.

Discussion

First, cardiovascular and metabolic alterations at different time intervals during cardiac surgery were not followed by significant changes in the $P_{v\text{-}a}CO_2$ gradient, and the only significant difference was a decrease in the $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$ ratio at the end of the study.

Second, the $P_{v\text{-}a}CO_2$ gradient and $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$ ratio were weak but significantly associated with factors that affect the CO_2 hemoglobin dissociation curve. Furthermore, the dependence of these factors varied over time. Finally, we evidenced poor agreement between central and mixed venous calculations.

As frequently observed during cardiac surgery, patients developed a hyperdynamic pattern.[16] In this context, lactic acidosis was not related to a low cardiac output state but was more likely to be an imbalance between oxygen delivery and consumption. Persistent hyperlactatemia could also result from accelerated aerobic glycolysis under the effects of endogenous or exogenous catecholamines.[17–19]

$P_{v\text{-}a}CO_2$ and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ as hemodynamic and metabolic markers

Hemodynamic and metabolic derangements were not accompanied by significant $P_{v\text{-}a}CO_2$ gradient alterations. Our

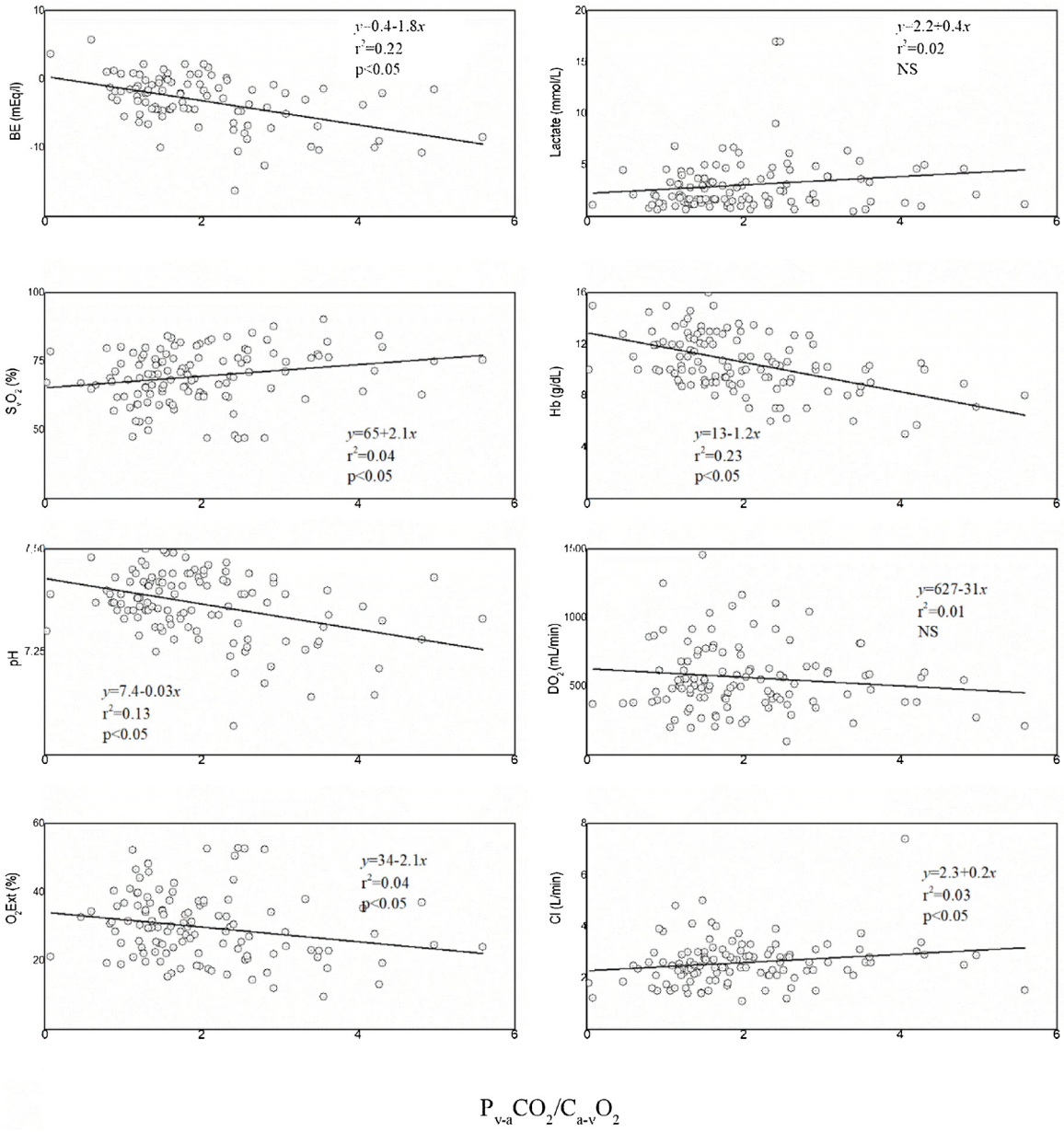

Figure 2 Correlation between mixed venous minus arterial CO_2 partial pressure/arterial minus mixed venous oxygen content ratio ($P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$). CI, cardiac index; Hb, hemoglobin concentration; Lactate, arterial lactate; S_vO_2, mixed venous oxygen saturation; pH, arterial pH; BE, arterial base excess; EO_2, Systemic O_2 extraction ratio; DO_2, Systemic O_2 delivery.

findings agree with other studies that showed a weak correlation between the $P_{v\text{-}a}CO_2$ difference and some physiologic variables (CI, pH, Hb, BE, and S_vO_2).[20,21] It has been shown that this variable was not able to detect significant changes in systemic blood flow and global O_2-derived metabolism in cardiac surgery patients.[1,22] Several confounding factors may influence the CO_2 hemoglobin dissociation curve and the relationship between PCO_2 and CCO_2 in venous blood in unstable critically ill patients.[23,24] Accordingly, the coefficients of determination between $P_{v\text{-}a}CO_2$ and Hb, pH, BE, lactate, and S_vO_2 were significant but weak, either when calculated globally or separately, at each time interval. Furthermore, the multilevel linear regression model identified BE and S_vO_2 as weak but significant determinants of the $P_{v\text{-}a}CO_2$ gradient.

The $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ratio also remained relatively stable compared to baseline until the end of the study when there was a significant reduction. Until this time, ratios were greater than the threshold described (> 1.4), indicating the onset of anaerobic metabolism. However, this issue remains controversial, and some studies failed to identify such an association after blood transfusion in hemorrhagic shock. VO_2 and the RQ were measured by analysis of normalized expired gases, but $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ remained high perhaps due to persistent hyperlactatemia.[25] The $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ratio is a composite calculation affected by many pathophysiolog-

Table 3 Multilevel linear regression model with mixed effects for $P_{v\text{-}a}CO_2$ difference and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ratio.

	Coefficient	SE	*p*-value	95% CI
$P_{v\text{-}a}CO_2$				
Constant	11.4	2.00	< 0.001	5.70 to 7.19
S_vO_2 (%)	-0.082	0.027	0.002	-0.135 to -0.029
BE (mmol.L^{-1})	-0.238	0.072	0.001	-0.381 to -0.096
r^2 = 0.25; p < 0.001				
$P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$				
Constant	0.98	0.624	0.118	-2.55 to 2.24
S_vO_2 (%)	0.046	0.007	< 0.001	0.030 to 0.061
Hb (g.L^{-1})	-0.222	0.035	< 0.001	-0.292 to -0.152
BE (mmol.L^{-1})	-0.084	0.022	< 0.001	-0.128 to 0.041
r^2 = 0.33; p < 0.001				

S_vO_2, mixed venous oxygen saturation; Hb, hemoglobin concentration; BE, base excess; SE, standard error.

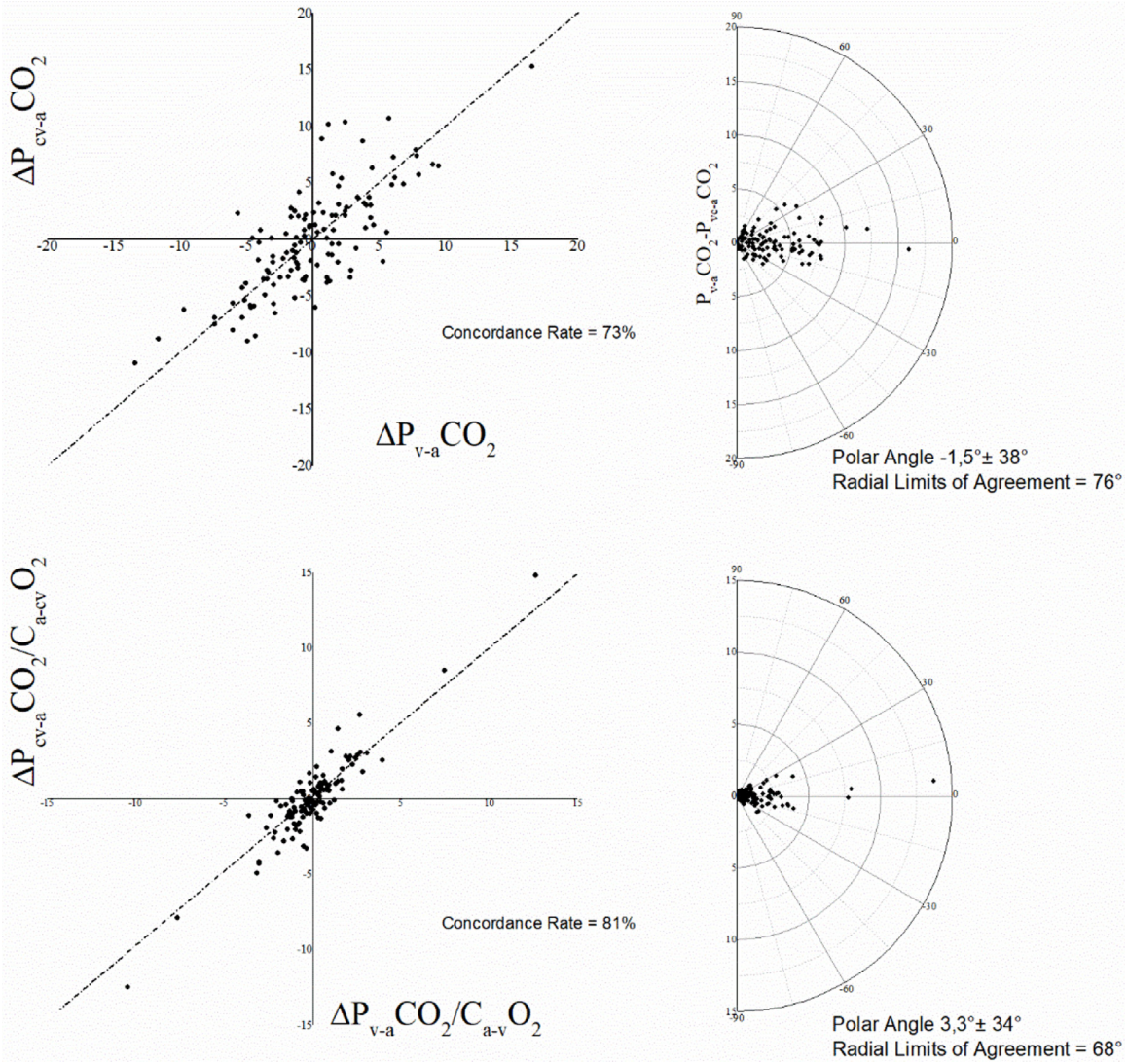

Figure 3 Upper panel: 4-quadrant plot and polar plot analysis showing concordance rate, mean polar angles, and radial limits of agreement between delta venous minus arterial CO_2 partial pressure gradients measured from mixed venous and central venous blood samples ($\Delta P_{v\text{-}a}CO_2$, $\Delta P_{cv\text{-}a}CO_2$). Lower panel: 4-quadrant plot and polar plot analysis showing concordance rate, mean polar angles, and radial limits of agreement between delta venous minus arterial CO_2 partial pressure/arterial minus venous oxygen content ratios measured from mixed venous and central venous blood samples. ($\Delta P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$, $\Delta P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$).

ical changes. The same considerations mentioned for the $P_{v\text{-}a}CO_2$ gradient could have affected the capacity of the ratio to identify tissue hypoxia. In this case, a weak but significant correlation was also found with S_vO_2, CI, Hb, arterial pH, and BE. The multilevel linear regression model revealed that Hb, S_vO_2, and BE were the main determinants affecting the ratio.[26] Transient changes in Hb concentration affected $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ independent of the occurrence of anaerobic metabolism. Hemodilution may affect the $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ gradient through changes in CO_2 dissociation from Hb. Anemic hypoxia increases oxygen extraction and may result in reductions in $C_{a\text{-}v}O_2$. Thus, one mechanism can explain the effect of Hb changes on $P_{v\text{-}a}CO_2$, whereas two mechanisms can affect the $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ratio.

S_vO_2 and BE also affect the balance between dissolved and combined CO_2. Furthermore, lactate was a significant determinant of the $P_{v\text{-}a}CO_2$ gradient and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ratio during T2 and T3 when lactic acidosis was present. The changing behavior of the correlations at different time points further reinforces the concept that both are more dependent on the variables that modify the dissociation of CO_2 from Hb compared with CI or DO_2.

During CPB, the CO_2 hemoglobin dissociation curve shifts downward in both arterial and venous blood, affecting CO_2 transport even after CPB ends.[27] A primary determinant of this change is hemodilution.[10] Restoration of blood CO_2 transport capacity does not occur immediately after hemoglobin correction. Among other factors, metabolic acidosis, changes in body temperature, and the Haldane effect could shift the CO_2 hemoglobin dissociation curve and the relationship between PCO_2 and CCO_2.[27]

During CPB, the temperature decreased to 32–33°C followed by a rewarming phase up to 37°C at the end of the procedure. Thus, by the time these patients were evaluated, body temperature was within the normal range. Hypothermia increases CO_2 solubility, and rewarming might cause the release of dissolved CO_2 from the tissues, also affecting the $P_{v\text{-}a}CO_2$ gradient.[28] Sudden changes in body temperature affect VO_2, CO_2 production, and transport, and these alterations could remain several hours after surgery.

The hyperdynamic state and vasoactive/inotropic drug infusion could be associated with the maldistribution of blood flow, and the heterogeneous circulation could slow or impair CO_2 removal from peripheral tissues.[29]

By the end of the study, sedoanalgesia and mechanical ventilation were gradually diminished, and spontaneous breathing recovered. The higher VO_2 with increased EO_2 from T3 may represent increased O_2 demands and trend with decreased S_vO_2 and increased $C_{a\text{-}v}O_2$. By this time, arterial pH and BE were within normal ranges, suggesting preserved systemic aerobic metabolism.[30]

Lack of agreement between central and mixed venous blood CO_2-derived parameters

An additional source of error should be considered when the analysis of SO_2 and the CO_2-derived variables are made from central venous blood samples.

Bland-Altman limits of agreement were large enough to make them unacceptable for clinical decisions. A Four-quadrant plot demonstrated a weak concordance rate (73%) for the central and mixed venous delta PCO_2 differences. The concordance rate for the delta PCO_2/CO_2 ratio was 81%, which is in the limit of concordance acceptance. When completing the study with the polar plot method, the radial limits of agreement were extremely high for both variables. These findings along with the initial Bland-Altman approach confirm that trends between these variables were not interchangeable. Cardiac surgery courses with sudden and significant metabolic and hemodynamic changes that may differently affect the upper part of the body, including the central nervous system, compared to the infradiaphragmatic region, mainly the splanchnic area.[11]

Limitations of the study. The retrospective characteristics of the analysis may represent a limitation. We recognized that RQ is the gold standard used to identify the onset of anaerobic metabolism, and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ is a proper surrogate, not $P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$.

Nevertheless, $P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$ is typically used for this purpose. Thus, the goal of this study was to show the poor agreement between the ratio calculated from either mixed venous or central venous samples. We agree that a proper analysis should consider the CO_2 contents instead of pressures. Although these calculations were performed, it should be emphasized that any algorithm for CO_2 content calculations has severe limitations. Douglas et al.[14] reported an excellent correlation between measured and calculated CO_2 contents. Despite this, the corresponding bias and 95% limits of agreement between the measured and calculated CO_2 contents were 0.02 and 4.66 mL/100 mL, respectively. Consequently, the measured and calculated CO_2 contents are not interchangeable. This explains for the frequent negative values of calculated $C_{v\text{-}a}CO_2$ found with the Douglas formula.

Information about body temperature was not available and precluded a more precise analysis of arterial and venous CO_2 content. Finally, the number of cases was relatively low.

Conclusions

In this population, the $P_{v\text{-}a}CO_2$ gradient and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ratio did not change significantly throughout the study and were dependent on the effects of changing physiological conditions. Many pathophysiological changes could affect the relationship between PCO_2 and CCO_2, making these measurements less sensitive to changes in systemic blood flow. Additionally, simultaneous measurements made from central and mixed venous blood showed poor agreement. Therefore, CO_2-derived variables should be cautiously used to guide hemodynamic support and to monitor tissue oxygenation during cardiac surgery.

Conflicts of interest

The authors declare no conflicts of interest.

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