Role of Pv-aCO2 gradient and Pv-aCO2/Ca-vO2 ratio during Cardiac Surgery

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Role of $P_{v-a}CO_2$ gradient and $P_{v-a}CO_2/C_{a-v}O_2$ ratio during Cardiac Surgery

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Abstract

Background. Arterial lactate, mixed venous O_2 saturation and parameters derived from CO_2 metabolism as the venous minus arterial CO_2 partial pressure ($P_{v\text{-}a}CO_2$) gradient 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 their physiologic determinants of $P_{v\text{-}a}CO_2$ difference, and the $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ratio and the interchangeability of the variables calculated from mixed and central venous samples.

Methods. We made a sub-analysis of 35 cardiac surgery patients included in a previous investigation database. Parameters were measured or calculated: after anesthesia induction (T1), end of cardiac 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 but transient changes during the study ($p<0.05$). $P_{v\text{-}a}CO_2$ remained high and without changes along the study, and $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ was also high and only decreased at T4 ($p<0.05$). A weak but significant correlation was observed both, 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. Using a similar approach, 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 mixed venous O_2 saturation (S_vO_2), and base excess (BE) ($p<0.05$), while $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ 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. Since $P_{v\text{-}a}CO_2$ 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 during the hemodynamic management of cardiac surgery patients. Finally, central venous and mixed values were not interchangeable.

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Keywords. Cardiac surgery, Tissue perfusion, Anaerobic metabolism, Carbon dioxide, Oxygen metabolism.

Background.

Macrohemodynamic and metabolic variables commonly drive cardiovascular support during cardiac surgery. (1–3) As in other critically ill conditions, arterial lactate, and mixed venous oxygen saturation (S_vO_2) have been used to evaluate tissue perfusion and oxygenation. (4–6)

Furthermore, parameters derived from carbon dioxide metabolism (CO_2), like the difference between venous minus arterial CO_2 partial pressure ($P_{v-a}CO_2$), and the ratio between this gradient and the arterial minus venous oxygen content ($P_{v-a}CO_2/C_{a-v}O_2$) have been proposed as markers of hypoperfusion and anaerobic metabolism. (7–9) However, the clinical value of these parameters during cardiac surgery remain controversial.

In critically ill patients, during oxygen supply dependence conditions, there are reductions in both CO_2 production (VCO_2) and O_2 consumption (VO_2). However, the fall in VCO_2 is less pronounced compared to VO_2 because of VCO_2 from anaerobic metabolism. From the modified Fick equation, VCO_2 could be calculated as the product between cardiac output (CO) times venous minus arterial CO_2 content ($VCO_2 = CO \times C_{v-a}CO_2$). Assuming a stable relationship between CO_2 partial pressure (PCO_2) and CO_2 content (CCO_2), the equation could be reformulated as $VCO_2 = CO \times P_{v-a}CO_2$. Thus, $P_{v-a}CO_2$ has been shown to increase in low cardiac output states but also during microvascular dysfunction. (10-12)

Although the respiratory quotient (RQ) should be calculated from the expired gas analysis, the $P_{v-a}CO_2/C_{a-v}O_2$ ratio has been proposed as a surrogate parameter to identify the onset of anaerobic metabolism. As mentioned before, assuming stable physiologic conditions, CCO_2 could be replaced by PCO_2 in the formula. However, in critically ill patients, this ratio is influenced significantly by other factors like changes in hemoglobin (Hb), lactate concentrations, base excess (BE), venous blood O_2 saturation (S_vO_2, Haldane effect), and body temperature. These parameters may suffer transient but significant alterations during cardiac surgery, reflecting changes in cellular metabolism and tissue perfusion. Since the CO_2 derived parameters are commonly measured under the influence of these factors, their physiologic meaning could be misleading. Despite these limitations, the $P_{v-a}CO_2$ gradient and the P_{v-}

$_{a}CO_2/C_{a-v}O_2$ ratio have been frequently used in the clinical practice to guide hemodynamic support and as outcome biomarkers. (7, 10-13) However, a better understanding of the limits and sources of errors of this practice should be considered in unstable critically ill patients. (14) Furthermore, 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). Whether central venous blood values could subrogate mixed venous values is still under debate. (14-17)

Our goals were to assess the physiological determinants of $P_{v-a}CO_2$ and $P_{v-a}CO_2/C_{a-v}O_2$ and the agreement between mixed and central venous blood values. We hypothesized that CO_2 calculated variables are dependent on physiologic alterations, and at the same time, central and mixed venous blood parameters are not interchangeable.

Methods.

The present study is a secondary retrospective analysis of a previous investigation performed in critically ill patients that evaluated the relationship of S_vO_2 and lactate gradients between central and mixed venous blood with clinical outcome. The study was approved by the Institutional Bioethical Committee and an informed consent was obtained from each patient. From this database, the present investigation focused on 35 cardiac surgery patients. (18)

Inclusion criteria. Adult patients elected for cardiac surgery were operated with or without extracorporeal circulation (ECC). All the patients had pulmonary artery catheter monitoring (PAC, 7.5 Edwards Life Sciences, Irvine, CA) placed before surgery, according to the usual clinical practice.

Exclusion criteria. Patients with known valvular incompetence or intracardiac shunts were excluded from the study.

The PAC was inserted via the right internal jugular vein, and at the same time, a radial arterial line, and a left internal jugular via were placed in all the patients. The hemodynamic and metabolic measurements and calculations were taken at predefined intervals: T1 - after anesthesia induction and before surgery and extracorporeal circulation; T2 - immediately after the end of surgery; T3 and T4: at 6-8 hours intervals after ICU admission.

Blood samples from the arterial line, internal jugular vein (proximal port), and pulmonary artery (distal port) were drawn simultaneously and by duplicate at each time intervals. Hb concentration, blood gases, lactate, BE, and HbO_2 saturation were measured simultaneously at each vascular compartment (ABL-700, Radiometer, Copenhagen, Denmark).

Cardiac output was measured by triplicate by thermodilution technique. The mean value was indexed by body weight to calculate cardiac index (CI). Systemic vascular resistances (SVR) were calculated using a standard formula. The physician in charge conducted hemodynamic and anesthetic treatment according to usual practice.

Anesthesia was induced with etomidate and fentanyl and maintained with isoflurane and fentanyl. Mechanical ventilation was set to keep an arterial PCO_2 between 35 to 40 mm Hg. ECC was made with a non-pulsatile flow, using the membrane oxygenator at 32-33°C temperature. Body temperature was returned to 37°C before decannulation. The mean arterial pressure was maintained between 50 to 60 mm Hg. Vasoactive and inotropic infusion were prescribed and titrated following usual practice in each patient. Before cannulation, 300 mg/kg sodium heparin was given i.v. to achieve an activated coagulation time equal to or higher than 480 s. Sodium heparin was latter neutralized with protamine sulfate in a 1:1 proportion. All the patients received 500 mg methylprednisolone during ECC. Parenteral analgesia, sedation, and mechanical ventilation were sustained until the patients were hemodynamically stable, awake, and ready for weaning from mechanical ventilation.

Calculated variables. Mixed venous CO_2 Content was calculated according to described formulas (19). 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 $P_{cv\text{-}a}CO_2$, respectively.

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 ratios respectively.

Statistical analysis

Data were presented as mean and standard deviation (SD), standard error (SE) or absolute numbers and percentages (%). Hemodynamic and metabolic parameters along the time were analyzed by repeated measures of ANOVA followed by 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 parameters. Multilevel linear regression

models with mixed effects for $P_{v-a}CO_2$ difference and $P_{v-a}CO_2/C_{a-v}O_2$ ratio as outcome variables were performed, including physiologically plausible parameters as CI, Hb, pH, BE, and S_vO_2 at the different time intervals. Statistical significances were assumed when $p \leq 0.05$.

The interchangeability between variables from central and pulmonary blood samples was studied using the Bland-Altman analysis. (20) The utility of this approach is limited when treatments or interventions affect the variables along the time. Then, the change or delta values were plot 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 lower than 80%. The analysis was complemented by conversion of the delta values to vectors in a polar plot. The polar plot analysis allowed a more precise evaluation of the trend and magnitude of the changes between the study (central venous blood) and the reference variables (mixed venous blood). From a central point, changes in the calculated pairs of values are represented as vectors with a defined angle and magnitude. The mean angular bias (θ) and the standard deviation represents all measured angles from the polar reference axis (0°). At the same time, the 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. (21,22)

Results

Table 1 shows the main characteristics of the 35 cardiac surgery patients included in this analysis. Some patients were under vasopressor and/or inotropic drugs infusion. Norepinephrine was used in 2.7% of the patients during T1, 50% in T2 and T3, and 36.1% of the cases by the end of the study period ($p<0.05$). Dobutamine or milrinone were used in 11.1% during T1, 16.6% during T2 and T3, and 19.4% during T4 periods (ns). The doses were titrated by the physician in charge according to usual clinical practice. Most of the patients succeed after the intervention and were discharged alive from the ICU. Only 3/35 (8.6%) patients died after cardiac surgery.

Systemic hemodynamic, O_2 metabolism and metabolic parameters are summarized in table 2 at the different time intervals. In brief, when compared to initial values, this patient population showed a

postoperative hemodynamic pattern characterized by high CI and low SVR ($p<0.05$). Mean arterial pressure (MAP) initial values were 75.1±18.7 mm Hg and increased significantly to 86.7±14.1 mm Hg when compared to T2 values ($p<0.05$) by the end of the study. Hb concentration was significantly lower than baseline during T2 and T3 measurements ($p<0.05$). 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 measurements ($p<0.05$), while arterial lactate was higher compared to baseline along the study ($p<0.05$). Although there was a transient trend to lower BE values 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 ICU evaluations at times T3 and T4 ($p<0.05$). Oxygen delivery (DO_2) increased significantly during the postoperative period (T2 and T3) ($p<0.05$) but returned to initial values by the end of the study. VO_2 increased and remained significantly higher than baseline after T2 ($p<0.05$). The oxygen extraction ratio (EO_2) increased during T3 and T4 evaluations ($p<0.05$).

CO_2 derived measurements and calculations are shown in table 3. The $P_{v-a}CO_2$ and $C_{v-a}CO_2$ gradients remained without significant changes compared to baseline. The $P_{v-a}CO_2/C_{a-v}O_2$ and $C_{v-a}CO_2/C_{a-v}O_2$ ratios did not change until the end of the study when values were significantly lower than baseline ($p<0.05$). Measurements taken from central venous blood $P_{cv-a}CO_2$ and $P_{cv-a}CO_2/C_{a-cv}O_2$ showed higher absolute values but a similar trend during the study.

In order to identify the overall influence of the different physiologic parameters, we made a global correlation for both variables. Figure 1 shows the scatter plot and correlation coefficients between $P_{v-a}CO_2$ and the main hemodynamic and metabolic parameters. A significant positive linear correlation was found between $P_{v-a}CO_2$ with arterial lactate and EO_2 ($p<0.05$). A negative linear correlation was found between the same variable with BE, S_vO_2, Hb, pH, and DO_2 ($p<0.05$). However, as shown in the figure, r^2 values were always low, denoting a weak coefficient of determination between these variables. Figure 2 shows the global correlation between $P_{v-a}CO_2/C_{a-v}O_2$ ratio with the same parameters. There was a significant positive linear correlation with CI and S_vO_2 ($p<0.05$). On the other hand, a significant inverse linear correlation was found between $P_{v-a}CO_2/C_{a-v}O_2$ ratio with Hb, arterial pH, BE, and EO_2 ($p<0.05$). Although statistically significant, all r^2 values were low.

The correlations between the $P_{v-a}CO_2$ gradient and the $P_{v-a}CO_2/C_{a-v}O_2$ ratio with the different physiological variables at each time interval are shown in the Supplementary Table 1. Despite the coefficients of determination remained weak, the statistical significance of the correlations varied along

the time. Thus, $P_{v-a}CO_2$ did not correlate with any of these variables at baseline, but it was significantly correlated with Lactate (T2) ($p<0.05$), and with Hb, Lactate, S_vO_2, BE and EO_2 at T3 ($p<0.05$), and T4 time points ($p<0.05$). At the same time, the $P_{v-a}CO_2$ /$C_{a-v}O_2$ ratio was significantly correlated with Hb, S_vO_2, BE and EO_2 during T1 ($p<0.05$); S_vO_2 and EO_2 during T2 ($p<0.05$); Hb, Lactate and BE at T3 ($p<0.05$); and with CI, Hb and BE by the end of the study (T4) ($p<0.05$).

Table 4 summarized the multilevel linear regression model with mixed effects, for $P_{v-a}CO_2$ difference and $P_{v-a}CO_2/C_{a-v}O_2$ 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 $P_{v-a}CO_2$ ($r^2=0.25$), while Hb, S_vO_2, and BE were the statistical determinants for the $P_{v-a}CO_2/C_{a-v}O_2$ ratio ($r^2=0.33$) ($p<0.05$).

Supplementary Table 2 showing the multiple linear regression model with mixed effects for $P_{v-a}CO_2$ gradient and $P_{v-a}CO_2/C_{a-v}O_2$ ratio as dependent variables at the different time intervals. The coefficients of determination of the models were higher than those observed in the pooled analysis but remained weak and the statistical significance of the variables were different in each time.

Bland-Altman analysis.

Figure 3, the left panel represents the Bland-Altman analysis for $P_{v-a}CO_2$ and $P_{cv-a}CO_2$ values. The bias of the difference was 0.59, while the limits of agreement were -3.7 to 4.9 mm Hg. In the right panel, the $P_{v-a}CO_2/C_{a-v}O_2$ and $P_{cv-a}CO_2/C_{a-cv}O_2$ were also analyzed following the Bland-Altman approach. The mean difference value was 0.38, while the limits of agreement ranged from -1.13 to 1.89.

Quadrant and Polar plot analysis.

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

Discussion

Three main results could be remarked from this study.

First, we were able to document the changing cardiovascular and metabolic alterations at the different time intervals during cardiac surgery. At the same time, these alterations were not followed by significant changes in the $P_{v\text{-}a}CO_2$ gradient, and the only significant change 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 values were weak but significantly associated with factors that are known to affect the CO_2 hemoglobin dissociation curve. Furthermore, the dependence of these factors varied along the time.

Finally, we documented a poor agreement between central and mixed venous calculations.

The patients developed an hyperdynamic pattern with low systemic vascular resistances, denoting vasodilation and vasoplegia, as frequently observed during cardiac surgery. (23–25) In this context, lactic acidosis was not related to a low cardiac output state but more likely to an unbalance between oxygen delivery and consumption. Despite tissue dysoxia was the most likely explanation, other mechanisms could also be possible as regional hypoperfusion, microvascular dysfunction, or cytopathic hypoxia. On the other hand, persistent hyperlactatemia could also result from accelerated aerobic glycolysis under the effects of endogenous or exogenous catecholamines. (26–28)

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

As mentioned before, the hemodynamic and metabolic derangements were not accompanied by significant $P_{v\text{-}a}CO_2$ gradient alterations. Our findings agree with other studies that showed a weak correlation between $P_{v\text{-}a}CO_2$ difference with some physiologic parameters like CI, pH, Hb, BE, S_vO_2, etc. (29,30). Moreover, it has been shown that this variable was not able to detect significant changes in systemic blood flow, and global O_2 derived metabolism following goal-directed therapy, (1) or after fluid challenges in cardiac surgery patients. (31) Several confounding factors may influence the CO_2 hemoglobin dissociation curve and then, the relationship between PCO_2 and CCO_2 in venous blood in unstable critically ill patients (32–34). Accordingly, the coefficients of determination between $P_{v\text{-}a}CO_2$ with Hb, pH, BE, Lactate, and S_vO_2 were significant but weak, either when calculated globally or by separate, 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.

At the same time, 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, the ratios were above the threshold value (>1.4) described to indicate the onset of anaerobic metabolism. However, this issue

remains controversial, and some studies failed to find such association. In an experimental investigation, after blood transfusion in hemorrhagic shock, VO_2 and the respiratory quotient measured by analysis of expired gases normalized, but $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ remained high, maybe because of persistent hyperlactatemia. (35) The $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ratio is a composite calculation affected by many pathophysiological 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, also a weak but significant correlation was found with S_vO_2, CI, Hb, arterial pH, and BE. Furthermore, the multilevel linear regression model determined that Hb, S_vO_2, and BE were the main determinants affecting the ratio. The relevance of Hb concentration on these variables has been shown in experimental and clinical conditions. (36) Accordingly, the transient changes in Hb concentration affected $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ values, independent from 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 the CO_2 dissociation from Hb. At the same time, 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 $P_{v\text{-}a}CO_2$, while two mechanisms can affect the $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ ratio.

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

During ECC, the CO_2 hemoglobin dissociation curve shifts downward both in arterial and venous blood, affecting CO_2 transport even after ECC ending (37). A primary determinant of this change is hemodilution, as shown by other studies (14). Interestingly, 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. (37)

According to the protocol, during ECC, the temperature was decreased to 32-33°C, followed by a rewarming phase up to 37°C at the end of the procedure, so by the time they 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. (38) On the other

hand, sudden changes in body temperature affect VO_2, CO_2 production, and transport, and these alterations could remain several hours after surgery (39).

As already commented, the hyperdynamic state is frequently transient, but it could be associated with changes in regional tissue perfusion. Maldistribution of blood flow and heterogeneous circulation could slow or impair CO_2 removal from peripheral tissues (40,41). Vasoactive and inotropic drugs used to support MAP and SVR may affect VO_2 and VCO_2. Thus, the exogenous sympathetic stimulus becomes another confounding factor in these patients.

By the end of the study, anesthesia, analgesia, and mechanical ventilation were gradually diminished, and spontaneous breathing recovered. (42, 43) The higher VO_2 with increased EO_2 from T3 may represent increased O_2 demands and course with decreased S_vO_2 and increase $C_{a\text{-}v}O_2$. By this time, arterial pH and BE were within normal ranges, suggesting preserved systemic aerobic metabolism.

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 S_vO_2 and the CO_2 derived variables are made from central venous blood samples. Some authors found reasonable agreement between central and mixed venous blood variables in critically ill patients (44). By the contrary, other authors do not support this clinical approach. (29)

The Bland-Altmann analysis allows the study of the agreement between two variables at the same time point. Besides this consideration, the limits of agreement were big enough to make them unacceptable for clinical decision making. Moreover, the Bland–Altman test was not designed to evaluate trends or delta changes between consecutive measurements. Thus, we applied a different analysis, including the direction and magnitude of the changes. (21,22) As defined previously, the 4-quadrant plot analysis demonstrated a weak concordance rate (73%) for the central and mixed venous delta PCO_2 difference. On the other hand, the concordance rate for the delta PCO_2/CO_2 ratio was 81%, which is in the limit of the concordance acceptance for the 4-quadrant plot analysis. 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-Altmann approach, confirm that the trends between these variables were not interchangeable. Cardiac surgery courses with sudden and significant metabolic and hemodynamic changes that may affect differently the upper part of the body, including the central nervous system, compared to the infra-diaphragmatic region, mainly the splanchnic area. (16)

Limitations of the study. The retrospective characteristics of the analysis may represent an important limitation of the study. We recognized the importance of RQ measurements directly obtained from the expired gases. The lack of this gold standard precluded to identify the onset of anaerobic metabolism. According to the Fick principle, the proper surrogate for RQ should be $P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$ and not the $P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$. Nevertheless, $P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$ is usually used for this purpose. For this reason, a 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 considered the CO_2 contents instead of pressures. Despite these calculations were performed, it should be emphasized, that any algorithm for CO_2 content calculation has severe drawbacks. Douglas et al.(19) showed an excellent correlation between measured and calculated CO_2 contents. In spite of this, the corresponding bias and 95% limits of agreement between measured and calculated CO_2 contents were 0.02 and 4.66 mL/100 mL, respectively. Consequently, measured and calculated CO_2 content are not interchangeable. This is the explanation for the frequent negative values of calculated $C_{v\text{-}a}CO_2$ found with the Douglas formula.
Information about body temperature at all time points was not available and precluded for a more precise analysis of arterial and venous CO_2 content. Finally, the number of cases was relatively low and patients were recruited from a single center, then, these results could not be extrapolated to other cardiac surgery populations.

Conclusions

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

List of abbreviations

- $P_{v-a}CO_2$: mixed venous minus arterial CO_2 partial pressure
- $P_{cv-a}CO_2$: central venous minus arterial CO_2 partial pressure
- C_aO_2: arterial oxygen content
- $C_{a-v}O_2$: arterial minus venous oxygen content
- $P_{v-a}CO_2/C_{a-v}O_2$: ratio between venous minus arterial CO_2 partial pressure gradient and the arterial minus venous oxygen content
- $C_{v-a}CO_2$: venous minus arterial CO_2 content
- VCO_2: CO_2 production
- VO_2: O_2 consumption
- CO: cardiac output
- PCO_2: CO_2 partial pressure
- CCO_2: CO_2 content
- RQ: respiratory quotient
- Hb: hemoglobin
- BE: base excess
- S_vO_2: mixed venous blood O_2 saturation
- $S_{cv}O_2$: central venous blood O_2 saturation
- $P_{cv}CO_2$: central venous CO_2 partial pressure
- P_vCO_2: mixed venous CO_2 partial pressure
- ECC: extracorporeal circulation
- PAC: pulmonary artery catheter
- CI: cardiac index
- MAP: mean arterial pressure
- SVR: systemic vascular resistances
- DO_2: systemic oxygen delivery index
- VO_2: systemic oxygen consumption index
- EO_2: systemic oxygen extraction ratio

Declarations

Ethics approval and consent to participate.

- The study was approved by the Institutional Bioethical Committee of our institution and an informed consent was obtained from each patient.

Consent for publication.

- Not applicable.

Availability of data and materials.

- All data are available and some of them are present as Supplementary Tables.

Competing interests

- The authors declare that they have no competing interests

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- Not applicable.

Authors' contributions

- All authors participated in the analysis, interpretation and writing of the paper.
- All authors read and approved the final manuscript.

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Table 1
Main characteristics of cardiac surgery patients.

Age (years)	65±10
BMI (kg/m^2)	28±3
LVEF (%)	47±13
ECC duration (min)	124±32
Aortic Clamp (min)	80±29
Gender	
Female	15/35
Male	20/35
Type of Surgery	
Combined	10/35
MR with ECC	12/35
MR without ECC	6/35
Valvular change	6/35
Thoracic aortic surgery	1/35
Comorbidities	
Arterial hypertension	17/35
Dyslipidemia	9/35
Smokers	11/35
Diabetes	7/35
CRF	1/35

Mean values ± SD, or fractions.
BMI = body mass index, MR = myocardial revascularization, ECC = extracorporeal circulation, CRF =chronic renal failure.

Table 2
Hemodynamic and metabolic parameters at different time intervals.

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

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. 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. *=$p<0.05$ vs T1; &=$p<0.05$ vs T2.

Table 3
Venous-arterial pressure and content CO_2 gradient and venous-arterial pressure and content CO_2 ratio.

	T1	T2	T3	T4
$P_{v-a}CO_2$ (mm Hg)	7.8±2.5	7.5±4.3	7.9±2.7	7.2±2.5
$C_{v-a}CO_2$ (mL/dL)	5.7±0.7	4.6±1.0	4.7±0.4	4.5±0.5
$P_{v-a}CO_2/C_{(a-v)}O_2$ (mm Hg.mL^{-1})	2.1±0.6	2.5±1.3	1.8±0.7	1.4±0.6*&
$C_{v-a}CO_2/C_{a-v}O_2$ (mL/dL)	1.5±0.1	1.5±0.3	1.1±0.1	0.9±0.1
$P_{cv-a}CO_2$ (mm Hg)	8.8±3.0	8.0±4.3	9.5±3.3	7.5±3.0
$P_{cv-a}CO_2/C_{a-cv}O_2$ (mm Hg.mL^{-1})	2.8±1.7	2.8±1.3	2.2±0.9	1.5±0.5*&

$P_{v-a}CO_2$ = mixed venous minus arterial CO_2 partial pressure gradient, $C_{v-a}CO_2$ = mixed venous minus arterial CO_2 Content; $P_{v-a}CO_2/C_{(a-v)}O_2$ = mixed venous minus arterial PCO_2 /arterial minus mixed venous Oxygen content ratio, $C_{v-a}CO_2/C_{a-v}O_2$ = mixed venous minus arterial CO_2 Content / arterial minus mixed venous Oxygen content ratio; $P_{cv-a}CO_2$ = central venous minus arterial CO_2 partial pressure gradient, $P_{cv-a}CO_2/C_{a-cv}O_2$ = 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. *=$p<0.05$ vs T1; &=$p<0.05$ vs T2.

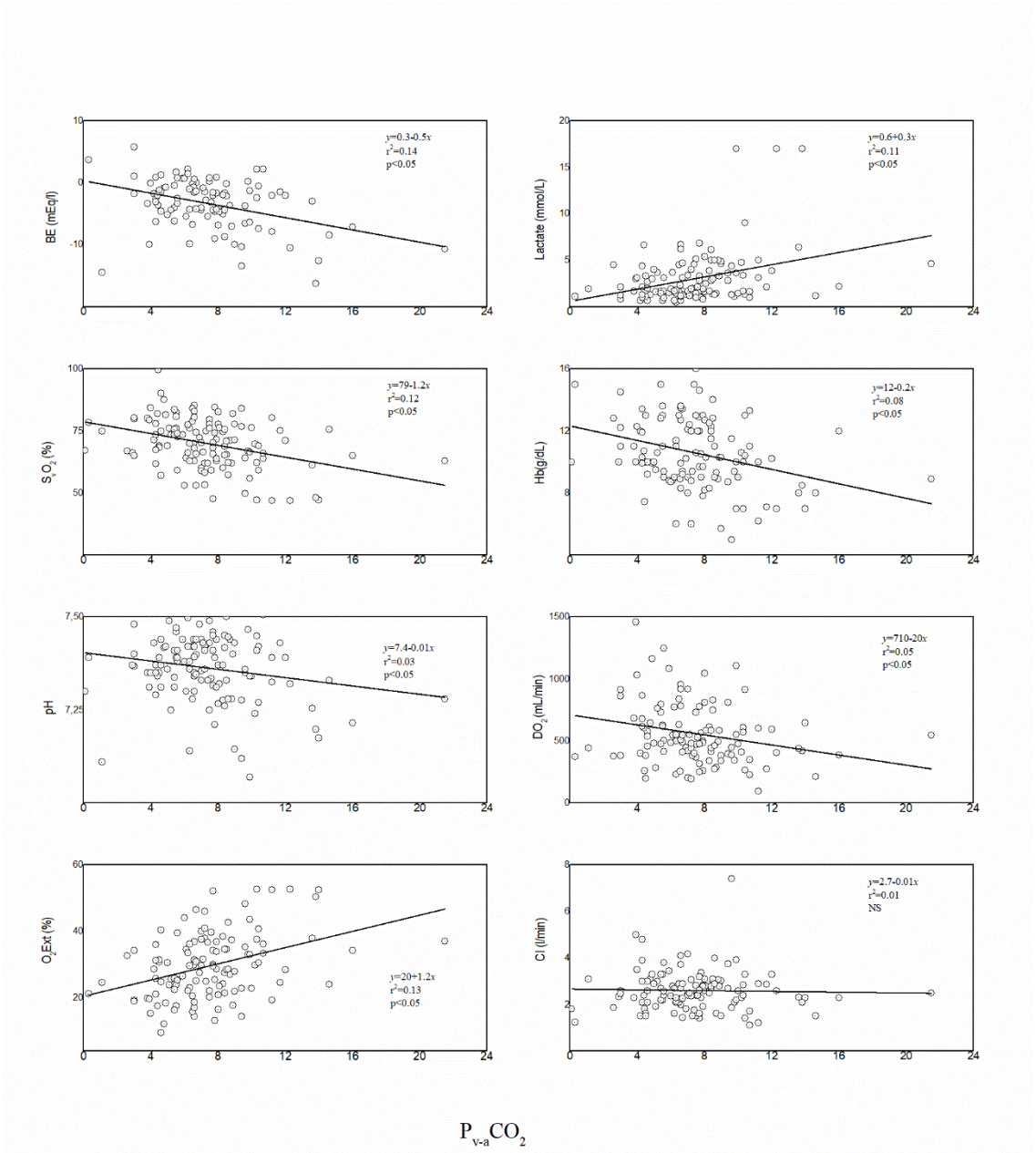

Figure 1.
Correlation between mixed venous minus arterial CO_2 partial pressure ($P_{v\text{-}a}CO_2$) with hemodynamic and metabolic parameters.

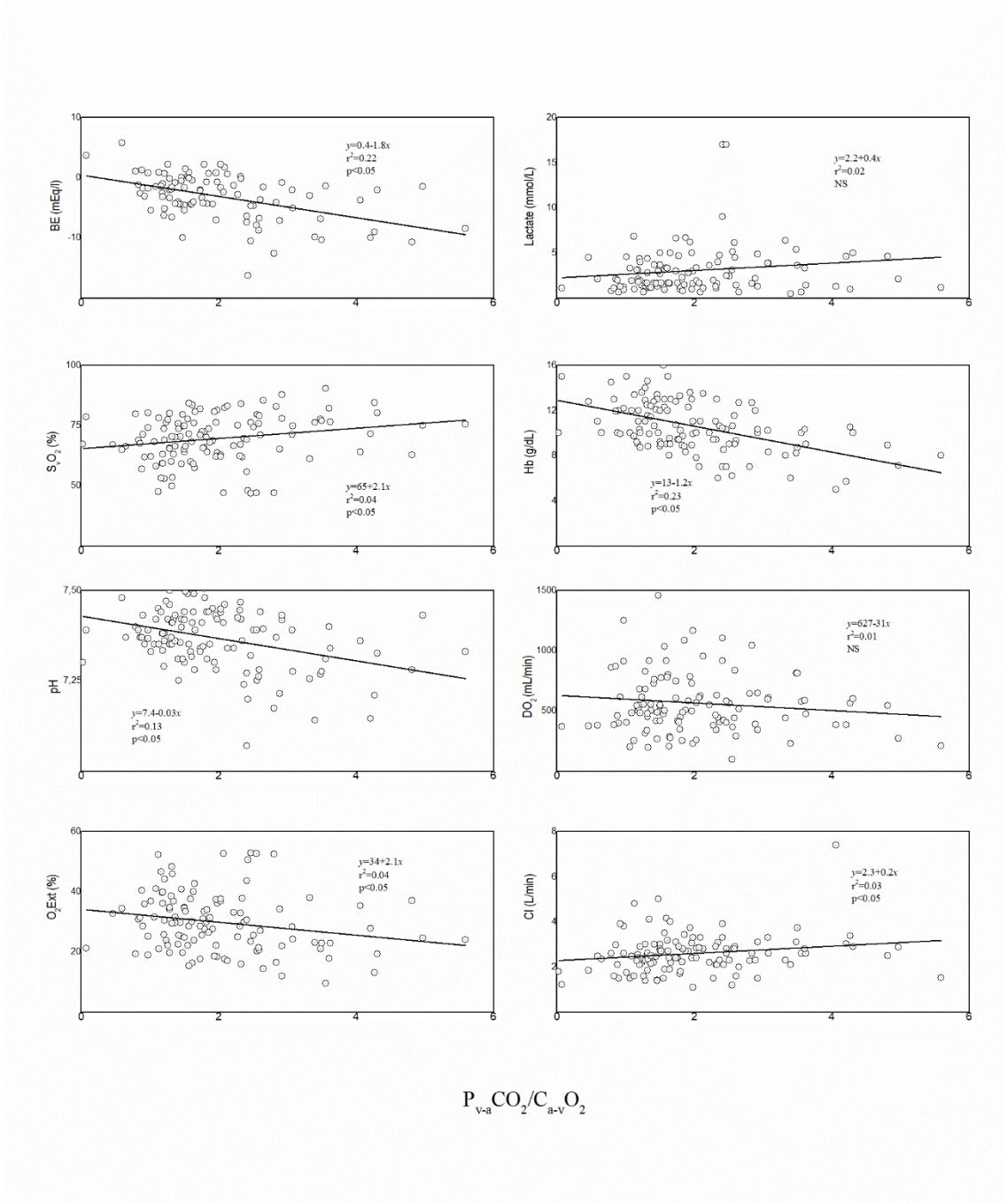

Figure 2.
Correlation between mixed venous minus arterial CO_2 partial pressure/arterial minus mixed venous oxygen content ratio ($P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$).

Supplementary Table 1

Correlation between $P_{v-a}CO_2$ and $P_{v-a}CO_2/C_{a-v}O_2$ with the different physiological variables at each time interval.

T1

$P_{v-a}CO_2$

	B	***SE***	***P***	***CI***		r^2
CI (L/min)	-0.525	0.877	0.554	-2.312	1.262	0.001
Hb (g/L)	-0.32	0.202	0.124	-0.731	0.092	0.044
Lactate (mmol/L)	0.073	0.698	0.917	-1.351	1.497	0.032
S_vO_2 (%)	-0.108	0.059	0.074	-0.227	0.011	0.068
pH	2.116	1.723	0.228	-1.394	5.625	0.015
BE (mmol/L)	-0.314	0.175	0.083	-0.673	0.045	0.077
EO_2 (%)	0.096	0.068	0.168	-0.043	0.235	0.031
DO_2 (mL/min/m^2)	-0.003	0.003	0.231	-0.009	0.002	0.015

$P_{v-a}CO_2/C_{a-v}O_2$

	B	***SE***	***p***	***CI***		r^2
CI (L/min)	0.66	0.48	0.179	-0.319	1.638	0.027
Hb (g/L)	-0.365	0.106	**0.002**	-0.581	-0.149	0.254
Lactate (mmol/L)	-0.213	0.39	0.589	-1.011	0.584	0.023
S_vO_2 (%)	0.091	0.036	**0.015**	0.019	0.164	0.149
pH	-0.657	0.992	0.513	-2.681	1.367	0.018
BE (mmol/L)	-0.287	0.092	**0.005**	-0.477	-0.097	0.25
EO_2 (%)	-0.096	0.035	**0.011**	-0.168	-0.024	0.171
DO_2 (mL/min/m^2)	-0.001	0.002	0.957	-0.003	0.003	0.033

T2

$P_{v-a}CO_2$

	B	***SE***	***p***	***CI***		r^2
CI (L/min)	-0.933	1.024	0.37	-3.025	1.159	0.006
Hb (g/L)	-0.697	0.416	0.104	-1.548	0.154	0.057
Lactate (mmol/L)	1.406	0.487	**0.007**	0.409	2.402	0.196
S_vO_2 (%)	-0.117	0.103	0.267	-0.328	0.094	0.009
pH	-0.484	3.673	0.896	-7.986	7.019	0.033
BE (mmol/L)	-0.052	0.209	0.807	-0.482	0.379	0.039
EO_2 (%)	0.184	0.099	0.074	-0.019	0.387	0.075
DO_2 (mL/min/m^2)	-0.004	0.002	0.111	-0.009	0.001	0.054

$P_{v-a}CO_2/C_{a-v}O_2$

	B	*SE*	*p*	*CI*		r^2
CI (L/min)	0.68	0.595	0.262	-0.536	1.896	0.01
Hb (g/L)	-0.27	0.255	0.298	-0.791	0.251	0.004
Lactate (mmol/L)	0.463	0.327	0.169	-0.208	1.133	0.033
S_vO_2 (%)	0.169	0.053	**0.003**	0.061	0.277	0.236
pH	2.487	2.094	0.245	-1.796	6.769	0.013
BE (mmol/L)	0.246	0.142	0.095	-0.046	0.539	0.078
EO_2 (%)	-0.156	0.056	**0.009**	-0.271	-0.042	0.19
DO_2 (mL/min/m^2)	0	0.002	0.798	-0.003	0.003	0.033

T3

$P_{v-a}CO_2$

	B	*SE*	*p*	*CI*		r^2
CI (L/min)	-0.491	0.645	0.452	-1.806	0.824	0.013
Hb (g/L)	-0.591	0.266	**0.034**	-1.133	-0.048	0.113
Lactate (mmol/L)	0.477	0.106	**0.0001**	0.261	0.694	0.384
S_vO_2 (%)	-0.108	0.047	**0.028**	-0.203	-0.012	0.118
pH	-1.325	2.715	0.629	-6.863	4.213	0.024
BE (mmol/L)	-0.394	0.103	**0.001**	-0.606	-0.183	0.345
EO_2 (%)	0.108	0.045	**0.022**	0.017	0.199	0.135
DO_2 (mL/min/m^2)	-0.002	0.002	0.164	-0.006	0.001	0.032

$P_{v-a}CO_2/C_{a-v}O_2$

	B	*SE*	*p*	*CI*		r^2
CI (L/min)	0.053	0.168	0.754	-0.289	0.395	0.029
Hb (g/L)	-0.147	0.067	**0.035**	-0.284	-0.011	0.107
Lactate (mmol/L)	0.075	0.033	**0.031**	0.007	0.143	0.117
S_vO_2 (%)	0.007	0.014	0.636	-0.022	0.035	0.025
pH	-0.591	0.702	0.406	-2.023	0.841	0.009
BE (mmol/L)	-0.089	0.031	**0.009**	-0.153	-0.024	0.213
EO_2 (%)	-0.006	0.014	0.661	-0.034	0.022	0.027
DO_2 (mL/min/m^2)	0	0	0.533	-0.001	0.001	0.02

T4

$P_{v-a}CO_2$

	B	*SE*	*p*	*CI*		r^2

CI (L/min)	0.205	0.391	0.605	-0.606	1.017	0.033
Hb (g/L)	-0.36	0.151	**0.026**	-0.674	-0.047	0.176
Lactate (mmol/L)	0.194	0.091	**0.045**	0.005	0.382	0.133
S_vO_2 (%)	-0.147	0.052	**0.01**	-0.255	-0.038	0.229
pH	-2.815	2.631	0.296	-8.27	2.64	0.006
BE (mmol/L)	-0.384	0.114	**0.003**	-0.623	-0.144	0.352
EO_2 (%)	0.138	0.052	**0.014**	0.031	0.245	0.21
DO_2 (mL/min/m^2)	-0.001	0.002	0.589	-0.005	0.003	0.031

$P_{v-a}CO_2/C_{a-v}O_2$

	B	***SE***	***p***	***CI***		***r^2***
CI (L/min)	0.368	0.108	**0.003**	0.143	0.594	0.324
Hb (g/L)	-0.169	0.044	**0.001**	-0.261	-0.078	0.384
Lactate (mmol/L)	0.034	0.034	0.325	-0.036	0.103	0.001
S_vO_2 (%)	-0.021	0.021	0.336	-0.065	0.023	0.001
pH	0.049	0.949	0.959	-1.925	2.023	0.047
BE (mmol/L)	-0.117	0.045	**0.018**	-0.212	-0.022	0.244
EO_2 (%)	0	0.021	0.413	-0.026	0.06	0.014
DO_2 (mL/min/m^2)	0	0.001	0.729	-0.002	0.001	0.042

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.

Table 4
Multilevel linear regression model with mixed effects for $P_{v-a}CO_2$ difference and $P_{v-a}CO_2/C_{a-v}O_2$ ratio

$P_{v-a}CO_2$	Coefficient	SE	p value	95% CI
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)	-0.238	0.072	0.001	-0.381 to -0.096
r^2=0.25; p<0.001				
$P_{v-a}CO_2/C_{a-v}O_2$				
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)	-0.222	0.035	<0.001	-0.292 to -0.152
BE (mmol/L)	-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.

Supplementary Table 2

Multiple linear regression model with mixed effects for $P_{v-a}CO_2$ gradient and $P_{v-a}CO_2/C_{a-v}O_2$ ratio as dependent variables at the different time intervals.

T1				
$P_{v-a}CO_2$	Coefficient	SE	p value	95% CI
Constant	15.37	4.77	0.004	5.54 to 25.17
S_vO_2 (%)	-0.113	0.062	0.079	-0.248 to -0.011
BE (mmol/L)	-0.356	0.369	0.045	-0.702 to -0.004
r^2=0.15; p=0.048				
$P_{v-a}CO_2/C_{a-v}O_2$				
Constant	-0.37	3.01	0.90	-6.59 to 5.84
S_vO_2 (%)	0.089	0.030	0.01	0.027 to 0.151
Hb (g/L)	-0.351	0.097	0.03	-0.549 to -0.153
r^2=0.40; p=0.001				

T2				
$P_{v-a}CO_2$	Coefficient	SE	p value	95% CI
Constant	8.42	3.41	0.022	1.34 to 15.50
CI (L/min)	-1.982	1.069	0.077	-4.199 to 0.236
Lactate (mmol/L)	1.453	0.563	0.017	0.276 to 2.274
r^2=0.23; p=0.021				
$P_{v-a}CO_2/C_{a-v}O_2$				
Constant	-14.07	4.94	0.009	-24.31 to -3.82
Lactate (mmol/L)	0.769	0.345	0.03	-0.052 to 1.485
S_vO_2 (%)	0.191	0.060	<0.001	0.087 to 0.304
r^2=0.30; p=0.007				

T3				
$P_{v-a}CO_2$	Coefficient	SE	p value	95% CI
Constant	12.05	3.24	0.001	5.34 to 18.36
S_vO_2 (%)	-0.089	0.046	0.06	-0.187 to 0.006
Lactate (mmol/L)	0.430	0.117	0.001	0.188 to 0.673
r^2=0.48; p<0.001				
$P_{v-a}CO_2/C_{a-v}O_2$				
Constant	1.27	0.91	0.18	-0.61 to 3.16
S_vO_2 (%)	0.037	0.014	0.01	0.007 to 0.066
Hb (g/L)	-0.214	0.071	<0.001	-0.352 to -0.067
BE (mmol/L)	-0.095	0.029	<0.001	-0.155 to 0.036
r^2=0.42; p=0.001				

T4				
$P_{v-a}CO_2$	Coefficient	SE	p value	95% CI
Constant	6.53	0.46	<0.001	5.56 to 7.49
BE (mmol/L)	-0.438	0.107	<0.001	-0.664 to -0.212
r^2=0.47; p=0.001				
$P_{v-a}CO_2/C_{a-v}O_2$				
Constant	2.03	0.52	0.001	0.92 to 3.13
CI (L/min)	0.255	0.080	<0.001	0.085 to 0.424
BE (mmol/L)	-0.065	0.031	0.05	-0.131 to 0.001
Hb (g/L)	-0.124	0.037	<0.001	-0.204 to -0.045
r^2=0.70; p<0.001				

$P_{v-a}CO_2$ = venous minus arterial CO_2 partial pressure gradient; $P_{v-a}CO_2/C_{a-v}O_2$ = venous to arterial PCO_2 gradient/arterial minus venous O_2 content ratio; SvO_2=mixed venous oxygen saturation; BE=arterial base excess; Hb= hemoglobin concentration; CI= cardiac index; Lactate=arterial lactate; r^2=coefficient of determination.

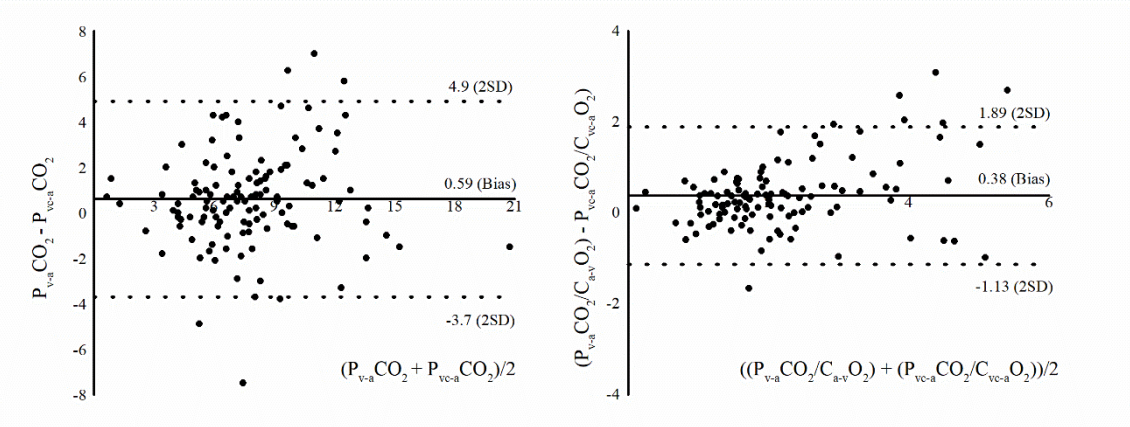

Figure 3.
Left panel: Bland-Altman analysis between mixed venous and central venous CO_2 partial pressure gradients ($P_{v\text{-}a}CO_2$, $P_{vc\text{-}a}CO_2$). Right panel: Bland-Altman analysis between mixed venous and central venous CO_2 partial pressure gradients/arterial minus venous oxygen content ratios ($P_{v\text{-}a}CO_2/C_{a\text{-}v}O_2$, $P_{cv\text{-}a}CO_2/C_{a\text{-}cv}O_2$).

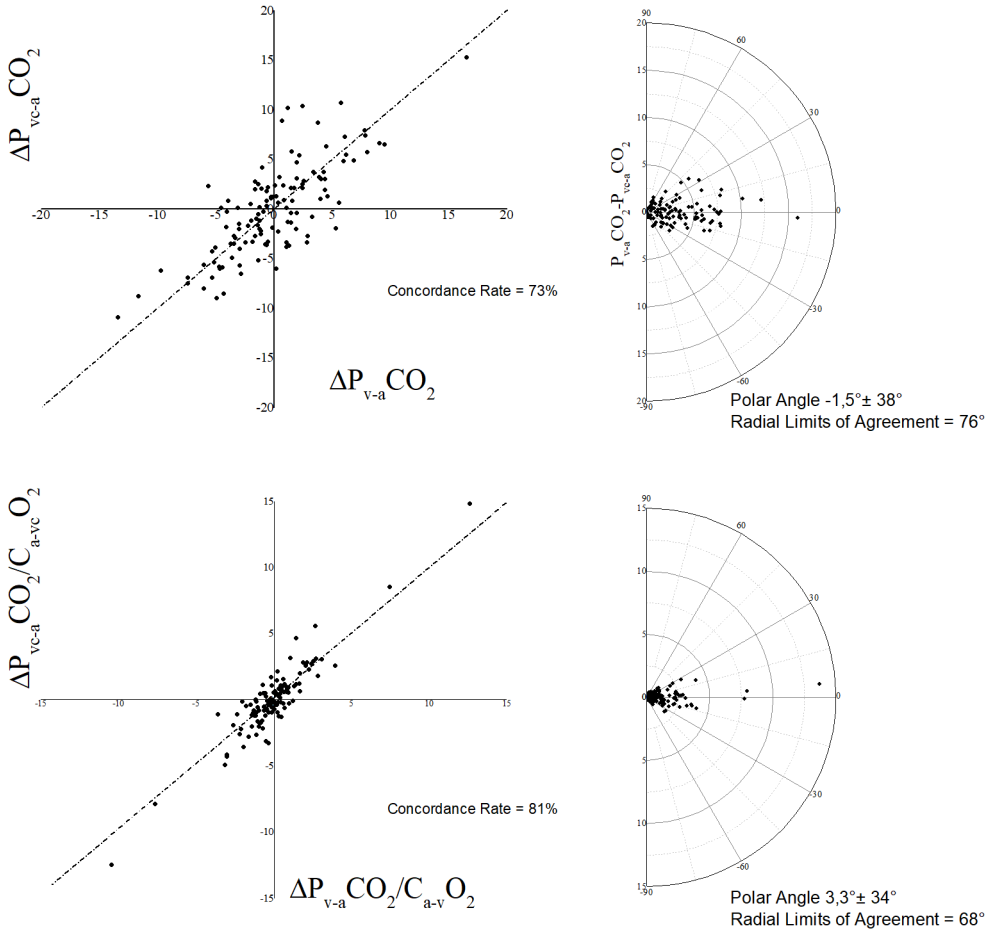

Figure 4.
Upper panel: 4-quadrant plot and polar plot analysis showing concordance rate, mean polar angles, and radial limits of agreement between delta venous minus arterial CO_2 partial pressure gradients measured from mixed venous and central venous blood samples ($\Delta P_{v\text{-}a}CO_2$, $\Delta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

Figures

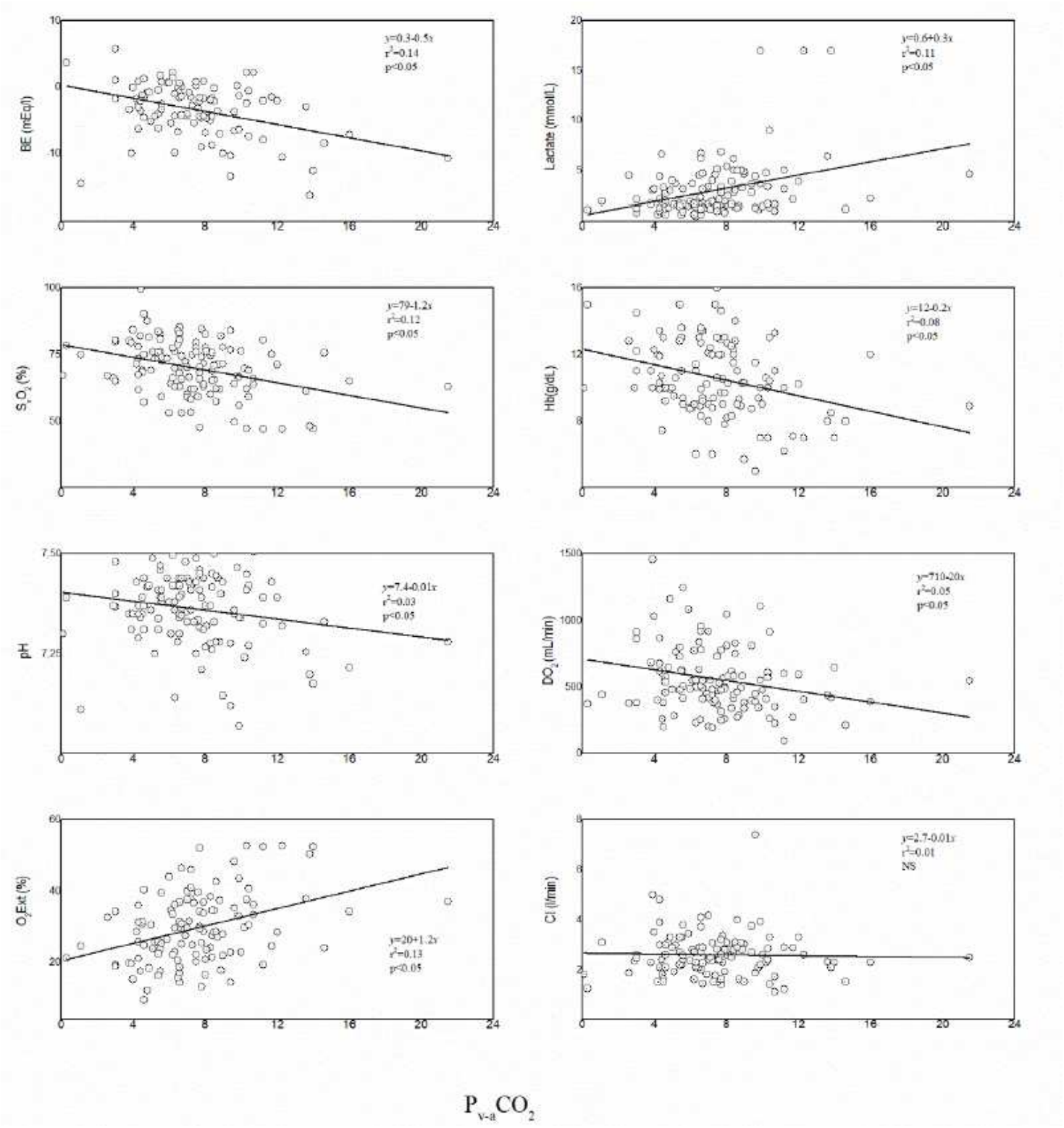

Figure 1

Correlation between mixed venous minus arterial CO2 partial pressure (Pv-aCO2) with hemodynamic and metabolic parameters.

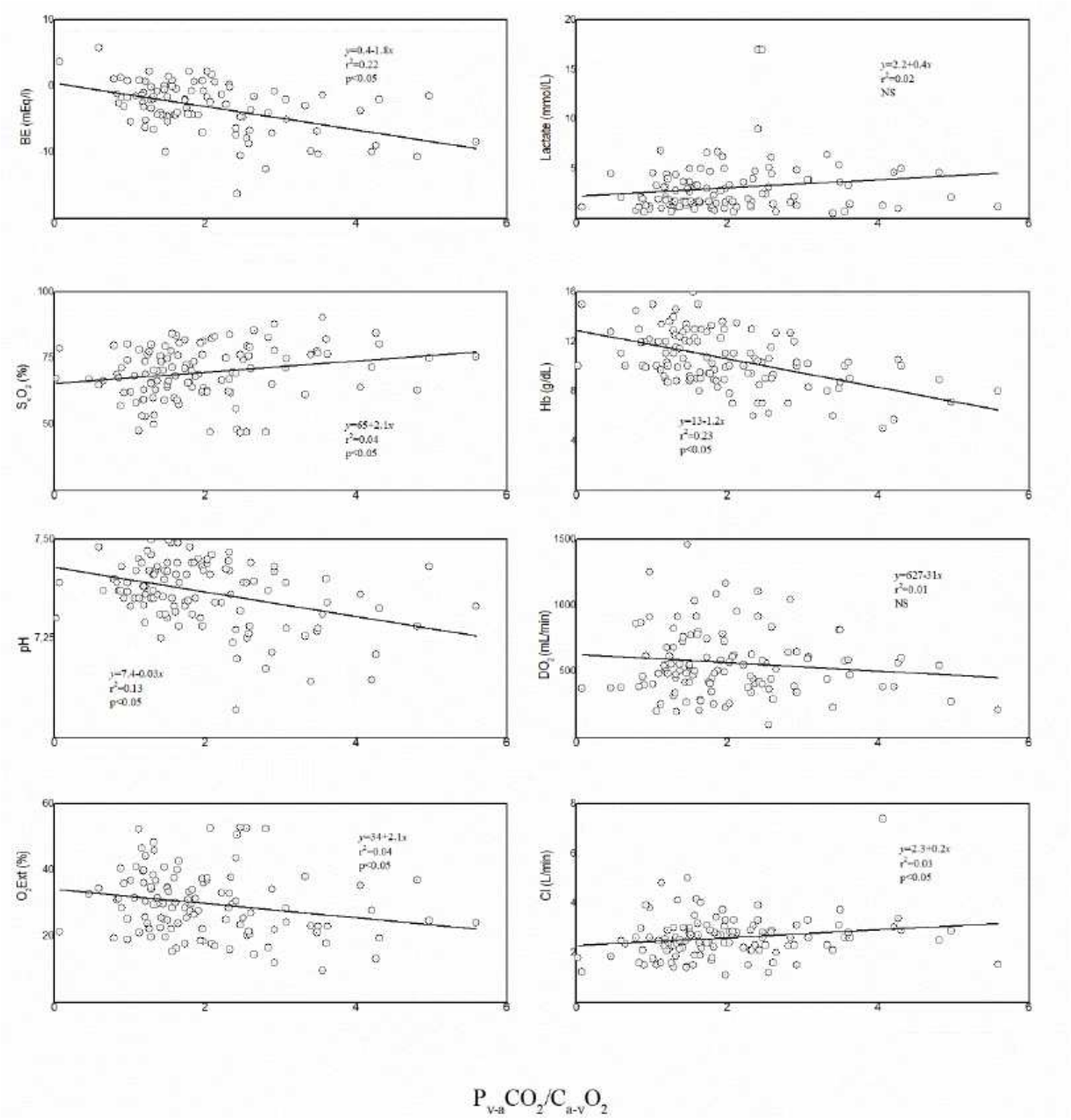

Figure 2

Correlation between mixed venous minus arterial CO2 partial pressure/arterial minus mixed venous oxygen content ratio (Pv-aCO2/Ca-vO2).

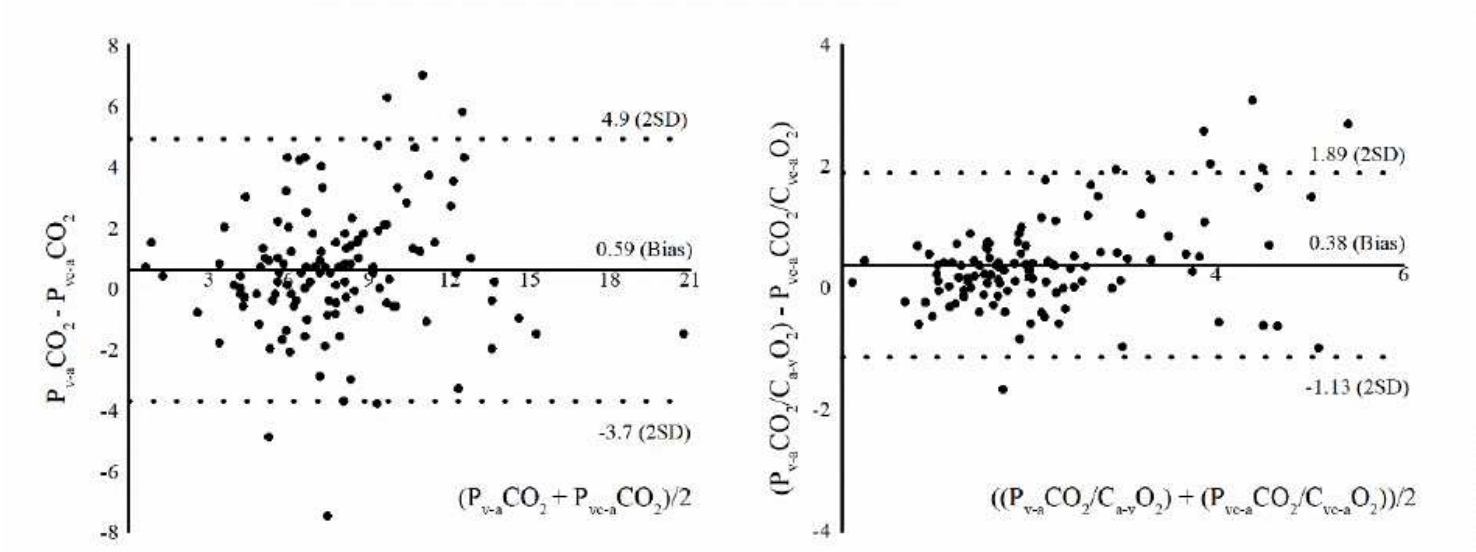

Figure 3

Left panel: Bland-Altman analysis between mixed venous and central venous CO2 partial pressure gradients (Pv-aCO2, Pvc-aCO2). Right panel: Bland-Altman analysis between mixed venous and central venous CO2 partial pressure gradients/arterial minus venous oxygen content ratios (Pv-aCO2/Ca-vO2, Pcv-aCO2/Ca-cvO2).

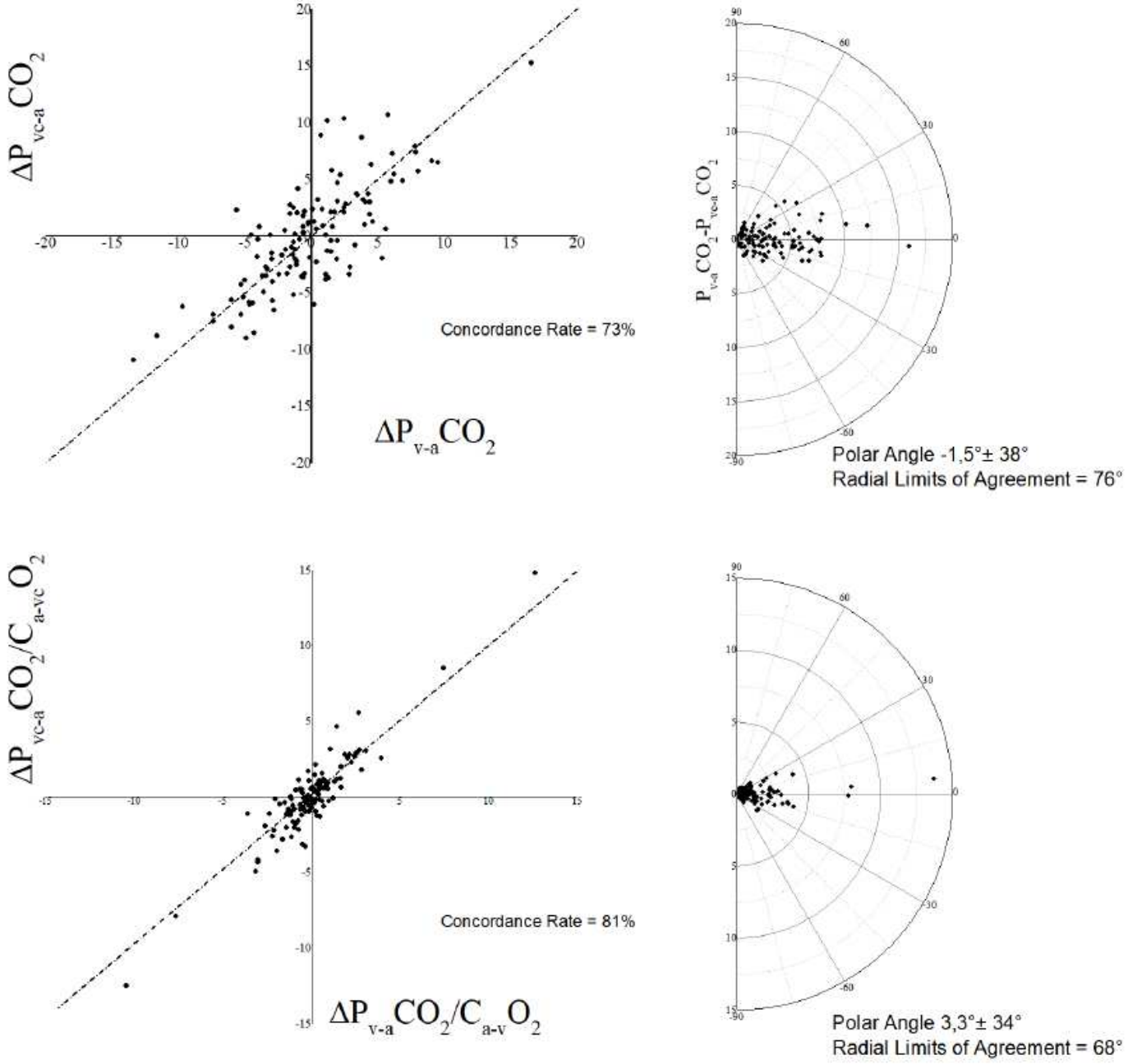

Figure 4

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 CO2 partial pressure gradients measured from mixed venous and central venous blood samples (ΔPv-aCO2, ΔPcv-aCO2). 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 CO2 partial pressure/arterial minus venous oxygen content ratios measured from mixed venous and central venous blood samples. (ΔPv-aCO2/Ca- vO2, ΔPcv-aCO2/Ca-cvO2).

Supplementary Files

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- SupplementaryTables.docx