Agreement between CO2 gap determined from peripheral blood and mixed venous blood in septic shock patients

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Abstract

***Purpose**:* The veno-arterial CO2 difference (Pv-aCO2) is a useful marker capable of identifying a subpopulation of shocked patients who present a cardiac output insufficient for the tissue metabolic demands. Some Authors have highlighted a linear relationship between Pv-aCO2 determined by mixed or central venous blood. This research aims to establish whether there is a linear relationship between Pv-aCO2 determined by peripheral venous blood (Pv-aCO2p) and mixed venous blood and the agreement between the two measures.

***Methods**:* Prospective, single-centre, observational clinical study on septic shocked and invasively ventilated patients during the first 24 hours from admission in ICU.

***Results**: On 38 determinations, t*he Bravais-Pearson r between Pv-aCO2 and Pv-aCO2p was 0.70 (95%CI 0.48 – 0.83; p-value = 1.25 x 10^-6). The Bland-Altman test's mean bias was 4.11 mmHg (95%CI 2.82 – 5.39); the repeatability coefficient was 11.05. The differential and proportional bias were 2.81 (95%CI 0.52 – 5.11) and 1.29 (95%CI 0.86 – 1.72), respectively, through the Taffé method.

***Conclusion**:* Pv-aCO2p could be used in clinical settings wider than the ICU alone, where central venous access is not routine, to establish early the adequacy of the circulation and, more specifically, of cardiac output versus tissue metabolic demands in septic patients.

Introduction

The clinical role of the veno-arterial CO2 difference (Pv-aCO2) lies in its ability to discriminate between a condition of low or maintained/high cardiac output [1–3]. Bakker et al. found that in a population of patients in septic shock, a Pv-aCO2 less/equal to or greater than 6 mmHg discriminated between two subpopulations of high cardiac output and low cardiac output [4]. Notably, the arterial lactate concentration was not significantly different between the two groups. Some Authors have therefore identified in Pv-aCO2 a useful marker capable of identifying a subpopulation of patients (mainly septic, in the clinical studies conducted up to now) who present a cardiac output insufficient for the tissue metabolic demands [5–7]. This data has direct clinical implications as it can modify the therapeutic approach at the patient's bedside. Some Authors have highlighted a linear relationship between Pv-aCO2 determined by mixed or central venous blood [8–10]. However, the studies conducted up to now have been developed in an intensive care environment, where the availability of at least one central venous access is routine. This research aims to establish whether there is a linear relationship between Pv-aCO2 determined by peripheral venous blood (Pv-aCO2p) and mixed venous blood. Furthermore, the correlation between Pv-aCO2p and a standard reference such as the cardiac index (as a measure of the cardiac output) determined through a pulmonary artery catheter was investigated. Finally, we established the measurement bias and the repeatability of the Pv-aCO2 from peripheral blood compared to classic Pv-aCO2 from mixed venous blood.

Methods

Study design: Prospective, single-centre, observational clinical study.

Inclusion criteria: clinical condition of septic shock according to literature definitions (sepsis + hypotension unresponsive to a fluid load and requiring the administration of vasopressor drugs) need for invasive monitoring via pulmonary artery catheter (PAC) and invasively measured blood pressure; the presence of at least one peripheral venous access.

Exclusion criteria: oxygenation via extracorporeal membrane system (ECMO), underage patients.

Setting: Clinical Intensive Care Unit, ASUFC University Hospital of Udine.

Primary aim: Evaluation of the linear correlation and agreement between the Pv-aCO2 measured on the peripheral and the mixed venous blood samples.

Secondary aims: Evaluation of the correlation between the Pv-aCO2 value measured on the peripheral blood sample and the cardiac index using PAC. Evaluation of the repeatability of the measurement.

Time intervals for evaluating the sampling: the measurement occured within the first 24 hours of admission of the eligible patients in the intensive care unit (ICU). For each patient, at least two separate measurements was performed for each type of venous blood sample (peripheral and mixed). As per internal protocol, the cardiac index was routinely established on the average of at least three measurements.

Sample size estimation: In calculating the required sample size, we considered a target power of 90%, an alpha error of 0.05, and a two-tailed distribution. Considering a linear regression coefficient of 0.51 (pessimistic estimate), we have estimated a required sample size of 36 measurements.

Data management and respect for privacy: the data were collected anonymously in protected databases which can only be accessed by the investigators described in the protocol. The CEUR of Friuli Venezia Giulia approved the study protocol on agenda 5.7 of 08/11/2022. The study followed the international and national regulations following the Declaration of Helsinki.

Statistical analysis: We applied regression analysis to verify the correlation between the variables under study, i.e. the Pv-aCO2 from peripheral venous blood and mixed venous blood (reference standard). We estimated the Bravais-Pearson r index to establish the degree of correlation. We used the Bland-Altman test to analyze the agreement between the two measures. We also applied the Taffé method, which consists in estimating the regression model through the marginal maximum likelihood (regardless of the variance), and estimating the posterior distribution through the Bayesian approach, to calculate the c.d. BLUP (best linear unbiased prediction) for the variables under study [11]. The second step of the Taffé method consists in estimating the bias value employing a regression equation using the OLS (ordinary least squares) method and Wald's test to estimate the confidence interval (similarly to the Bland-Altman

test but without assuming homoskedasticity of variance). Finally, the error measure's variance is recalibrated by removing the estimated differential and proportional biases.

Ancillary analyses were the correlation between Cardiac Index and variables under study and between these and oxygen-derived parameters (SvO2).

An alpha error of no more than 5% was adopted in the statistical analysis.

Statistical analysis was performed using the R-Cran open-source platform, implementing the following libraries: readODS; MethodCompare; car; ggplot2; tidyverse; SimplyAgree; mcr.

Results

We enrolled 18 patients for 38 blood gas determinations during the study period. Four patients were female; 7 cases were respiratory, 5 abdominal, and 2 neurological infections. In 4 cases, the source was not determined. Three patients underwent some CRRT (predominantly CVVHDF). The vital parameters, blood gas values and cardiac index are shown in Table 1.

Table 1. **Median values and interquartile range for vital signs, blood gas values, vasopressors and inotropes used and cardiac index.**

	Median value	25% percentile	75% percentile
MAP (mmHg)	78.5	65.0	91.5
HR (bpm)	102.5	85.0	111.5
Noradrenaline (mcg/Kg/min)	0.15	0.11	0.24
Adrenaline (mcg/kg/min)	0.11	0.10	0.22
Dobutamine (mcg/kg/min)	4.00	2.00	6.00
Vasopressine (mcg/kg/min)	0.035	0.020	0.035
PaO2 (mmHg)	105.0	91.5	119.0
PaCO2 (mmHg)	36.5	35.3	42.8
Lactate (mmol/L)	3.0	1.6	6.4
SvO2 (%)	76.0	67.9	78.0
PvCO2 (mmHg)	40.5	37.3	46.0
PvCO2p (mmHg)	46.0	40.0	50.8
Pv-aCO2 (mmHg)	4.0	2.0	6.0
Pv-aCO2p (mmHg)	7.5	4.0	13.0
CI (L/min/m^2)	2.7	2.0	3.2

MAP: mean arterial pressure; HR: heart rate; PaO2: arterial partial pressure of O2; PaCO2: arterial partial pressure of CO2; SvO2: oxygen saturation in mixed venous blood; PvCO2: partial pressure of CO2 in mixed venous blood; PvCO2p: partial pressure of CO2 in peripheral venous blood; Pv-aCO2: veno-arterial CO2 difference; Pv-aCO2p: veno-arterial difference of CO2 from peripheral venous blood; CI: cardiac index.

The linear correlation between Pv-aCO2p and Pv-aCO2 was statistically significant: β = 0.42; p-value = 1.25 x 10^-6; R^2= 0.48 and adjusted R^2= 0.47 (Breusch-Pagan test = 4.78, p-value = 0.029). The Bravais-Pearson r was 0.70 (95%CI 0.48 – 0.83; p-value = 1.25 x 10^-6)(*Figure 1*).

For the Bland-Altman test, the mean bias was 4.11 mmHg (95%CI 2.82 – 5.39; Giavarina test = +54.86%; LoA +212.41% – -102.70%) with a lower LoA of -3.47 (95%CI -5.80 – -1.34) and higher LoA of 11.69 (95%CI 9.55-14.01); repeatability coefficient was 11.05 (*Figure 2*). Note that for the Breusch-Pagan test, the distribution of the residuals is not homoskedastic, so the Bland-Altman test does not apply correctly.

Using the Taffé method, we estimated the differential and proportional bias: 2.81 (95%CI 0.52 - 5.11) and 1.29 (95%CI 0.86 -1.72), respectively (*Figure 3*).

Regarding the correlation between CI and Pv-aCO2: Pearson index was -0.52 (95%CI -0.72 – -0.24; p-value 0.0009; BP test= 0.45; p-value = 0.500); while for the correlation between CI and PvaCO2p: Pearson's r was -0.49 (95%CI -0.70 – -0.21; p-value = 0.002; BP = 0.90; p-value= 0.344) (*Figure 4 as Supplementary Material*). For the correlation between CI and SvO2: Pearson's r was 0.37 (95%CI: 0.06 – 0.62; p-value = 0.021; BP test = 0.49, p-value = 0.482) (*Figure 4 as Supplementary Material*). We found no statistically significant correlation between Pv-aCO2 and SvO2, lactatemia, or between Pv-aCO2p, SvO2 and lactatemia.

Discussion

Our analysis shows that Pv-aCO2 from peripheral venous blood correlates with Pv-aCO2 from mixed venous blood, showing a bias of about 55%. In particular, although the bias shows a linear increase, this increase in the bias between the two measures is theoretically not relevant from the clinical point of view, provided that the agreement on the cut-off value is maintained. For the clinical use of the Pv-aCO2 value adopted so far, this bias would not seem to affect the applicability of the Pv-aCO2p index. Bakker et al. have shown that 6 mmHg is the value above, and a net reduction in cardiac output compared to tissue metabolic needs occurs [4]. Ospina-Tascón et al. showed that beyond that cut-off value, the mortality of patients in septic shock increases exponentially [12]. Guo et al. found that this cut-off value has a sensitivity of 86% and a specificity of 67% for a Cardiac Index value lower than 2.2 L/(min x m^2) [13]. Given these premises, the cut-off of Pv-aCO2 from peripheral venous blood, identified as corresponding to Pv-aCO2, does not lose clinical significance.

Pv-aCO2 is determined by cardiac output and metabolic status, and in the literature, it has been taken as an indicator of the adequacy of venous blood flow in removing CO2 produced by peripheral tissues. The meta-analysis of Al Duhailib et al., summarizing the results of 21 studies (2,155 patients), finds that a Pv-aCO2 generically "high" (> 6 mmHg in most included studies) is a predictive factor of mortality in ICU (OR 2.22; 95%CI 1.30–3.82) [14].

While the predictive role of poor outcomes seems relatively established (at least in certain populations of patients hospitalized in intensive care, such as, for example, patients in the condition of septic shock) and despite the sum of the studies agree on the subsistence of the correlation of Pv-aCO2 with the cardiac output, several studies have shown the inconsistency of the Pv-aCO2/Ca-vO2 ratio in evidencing a condition of anaerobiosis [15]. Dubin et al. (on an animal model in which a hemodilution condition was experimentally induced compared to hemorrhagic loss) found that this ratio increases considerably in the first condition, regardless of oxygen consumption [16]. Similar results, through an experimental study on an animal model, comparing two conditions of artificially induced ischemic and hypoxic hypoxia (by arterial ligation and by reduction of the inspiratory fraction of oxygen), have shown that, in the first situation, the Pv-aCO2 shows an incremental trend. In contrast, in the second condition, it remains stable [17]. The Authors concluded that Pv-aCO2 is not a good marker for anaerobiosis. Due to the Haldane effect, the reduction in oxygen delivery is not followed proportionally by a similar increase in Pv-aCO2.

As for the concordance between Pv-aCO2 from mixed venous and central venous blood (from the superior vena cava), studies conducted so far have shown an excellent agreement: the bias is between a minimum of 3.0 mmHg and a maximum of 9.0 mmHg with a correlation value above 90% [8–10]. Some studies have been conducted to verify the agreement between PvCO2 values from arterial and peripheral venous blood [18]. Not unexpectedly, these studies showed poor agreement. The discrepancy found in these studies supports the role of Pv-aCO2 in discriminating between patients with adequate and inadequate cardiac output. The PCO2 along the venous sector strongly undergo the effect of "washing" of the blood flow brought by the cardiac output when the latter is inadequate; PCO2 increases disproportionately, especially in the venous sector, rather than in the arterial one.

A study conducted by Shastri et al. on an animal model in which hyper- and hypoventilation conditions were produced (Pv-aCO2 data compared on blood samples collected within the first 60 seconds after the introduction of the ventilator modification) found that, during hyperventilation, Pv-aCO2 increased rapidly while, conversely, during hypoventilation, Pv-aCO2 decreased [19]. These variations were due to a rapid reduction of PaCO2 (therefore in the arterial sector) during the increase in respiratory rate and, similarly but in the opposite direction, to a rapid increase of PaCO2 during hypoventilation. The Authors conclude that changes in the ventilator arrangement could change the Pv-aCO2 values and, therefore, the prognostic significance of this variable, at least within a certain time of blood sampling.

In the literature, to our knowledge, only one other study has evaluated the correlation between Pv-aCO2 and Pv-aCO2p. Gao et al. found a significantly higher correlation than our value (r-value 0.90 vs 0.69) over a larger population than ours [20]. However, beyond the methodological differences between the two studies, the correlation we found undergoes a great divergence, especially for values above the equivalent cut-off (about 10 mmHg according to the bias we found), beyond which the Pv-aCO2p values show a divergent trend for Pv-aCO2, probably linked to factors depending on the local blood circulation [21, 22]. In addition to the degree of correlation, evaluating the agreement between the two measures is crucial to apply this measure to clinical practice.

Several clinical settings deal with the management of the septic patient, at least in the early stages of the syndrome, such as pre-hospital medicine, emergency medicine, and hospital medicine. Our study indicates a good correlation between Pv-aCO2 and Pv-aCO2p. The correlation, however, is limited to patients in septic shock, subjected to an invasive mechanical ventilation regime, and within the first 24 hours of admission to the ICU (and therefore from the establishment of a condition of frank hemodynamic shock). The implications of this result, if confirmed on larger populations and externally validated, could develop in the direction of a less invasive and yet more accurate approach than current septic patient standards. Potentially, such results could lead to early and "tailored" management of the septic patient.

Limitations

Our study aimed to identify a clinically tolerable agreement between Pv-aCO2 and Pv-aCO2p. Before applying the Pv-aCO2p in clinical practice, our results should be validated by an RCT (i.e., ventilatory settings, administration of vasopressor or inotropic drugs, etc., have to be established within pre-defined margins by a research protocol). In addition, the correlation between Pv-aCO2/Pv-aCO2p and the cardiac index we found may not be clinically confirmed where the above experimental conditions (ventilation settings, hemodynamic management, etc.) are not controlled. Ospina-Tascòn et al., in a clinical study of 60 patients admitted to the Intensive Care, found a poor correlation (in the order of r^2 = 0.08–0.22) between Pv-aCO2 and cardiac index [23]. The concordance between low cardiac output values and Pv-aCO2 is greater for low flow values and, therefore, for the increased venous-arterial difference. However, as cardiac output increases, other factors may come into play, such as increased tissue metabolism induced by a condition of systemic inflammation response syndrome (e.g. SIRS), which could influence the microcirculation conditions and tissue oxygen extraction capability [21, 22]. Moreover, there is no reference standard for determining the adequacy of cardiac output. The cardiac index is insufficient to determine the adequacy of cardiac output concerning the metabolic needs of the body's tissues.

Conclusion

Pv-aCO2p could be used in clinical settings wider than the ICU alone, where central venous access is not routine, to establish early the adequacy of the circulation and, more specifically, of cardiac output versus tissue metabolic demands in septic patients. Pv-aCO2p shows a correlation with Pv-aCO2 of about 70%. The mean bias is approximately + 4.11 mmHg.

Declarations

Competing interests: The authors have declared that no competing interests exist.

Funding: The authors received no specific funding for this work.

Authors' contributions: DO designed the study, performed the statistical analysis, wrote the first draft, and supervised the final draft; CM, GB, VZ and VM collected the data; RC, NG, and TB supervised the final draft. All authors revised and approved the final draft.

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Figures

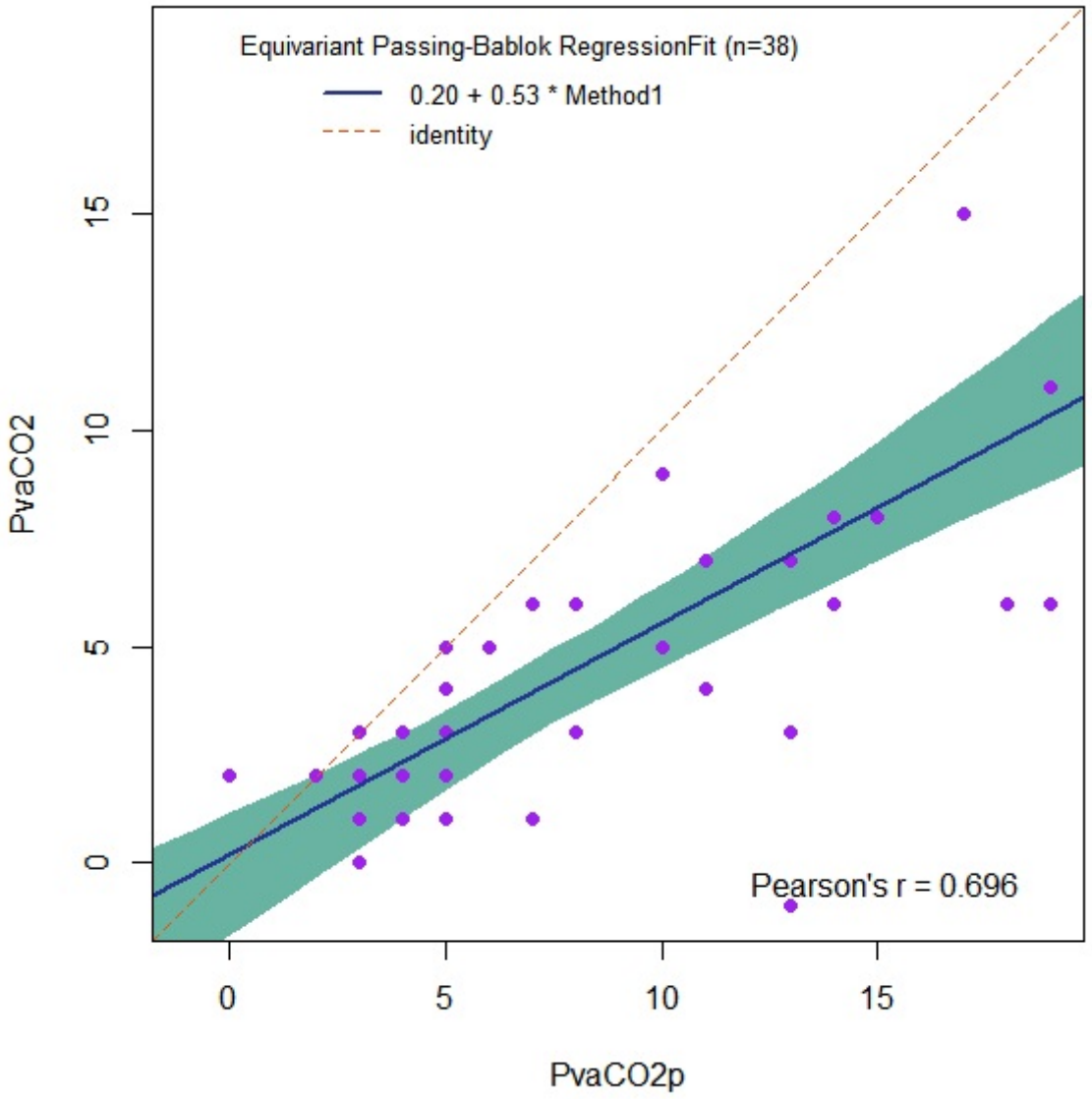

Figure 1

Linear correlation plot (via equivariant Passing-Bablok regression) between Pv-aCO2p and Pv-aCO2: β = 0.42; p-value = 1.25 x 10^-6; R^2= 0.48 and adjusted R^2= 0.47 (Breusch-Pagan test = 4.78, p-value = 0.029). The Bravais-Pearson r = 0.70 (95%CI 0.48 – 0.83; p-value = 1.25 x 10^-6). Note that for the Breusch-Pagan test, the distribution of the residuals is not homoskedastic, so the Bland-Altman test does not apply correctly.

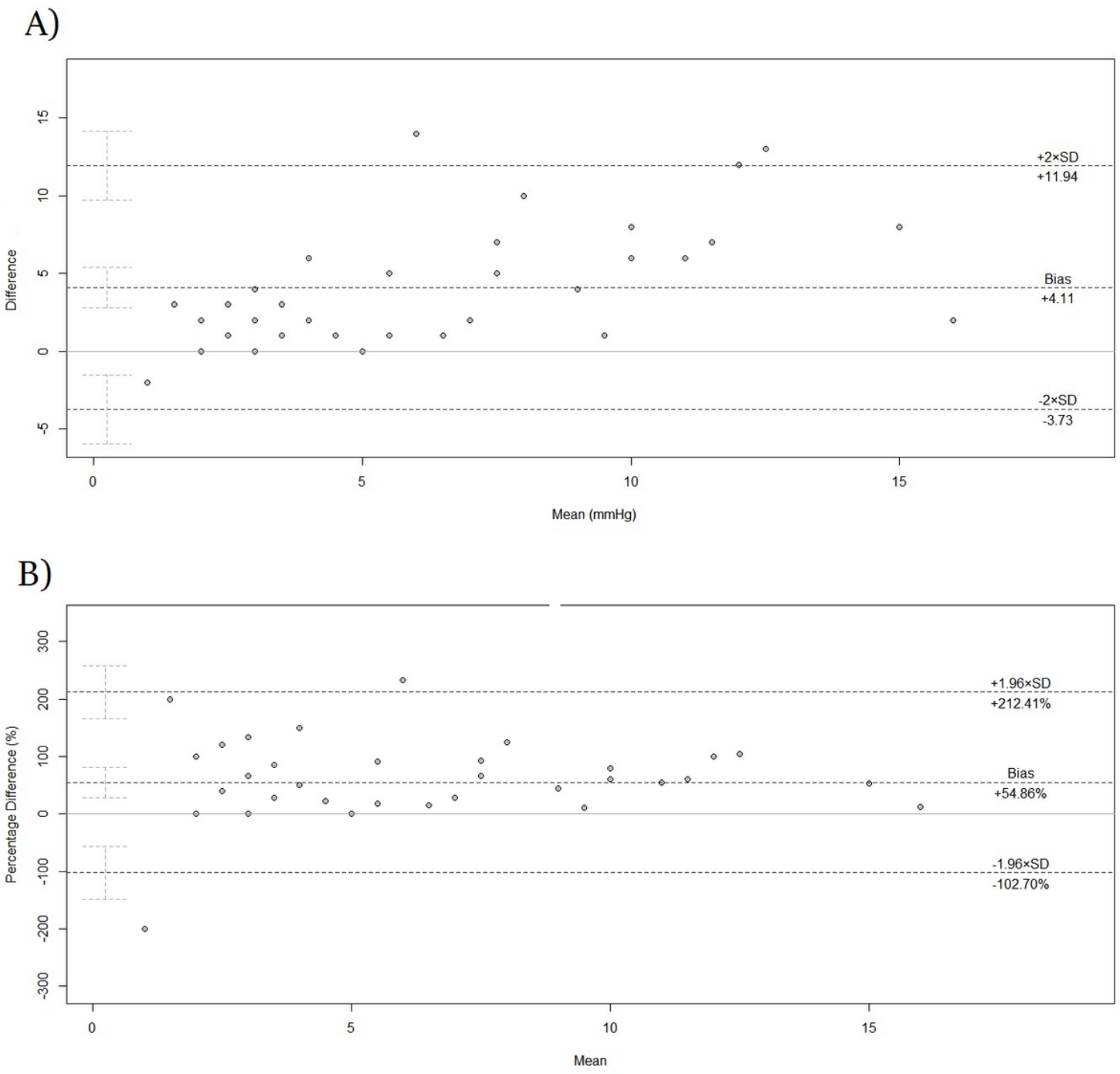

Figure 2

A) Bland-Altman plot. The mean bias is 4.11 mmHg (95%CI 2.82 – 5.39) with a lower LoA of -3.47 (95%CI -5.80 – -1.34) and higher LoA of 11.69 (95%CI 9.55-14.01); repeatability coefficient was 11.05. **B) Giavarina plot.** The mean bias is +54.86%; LoA +212.41% – -102.70%).

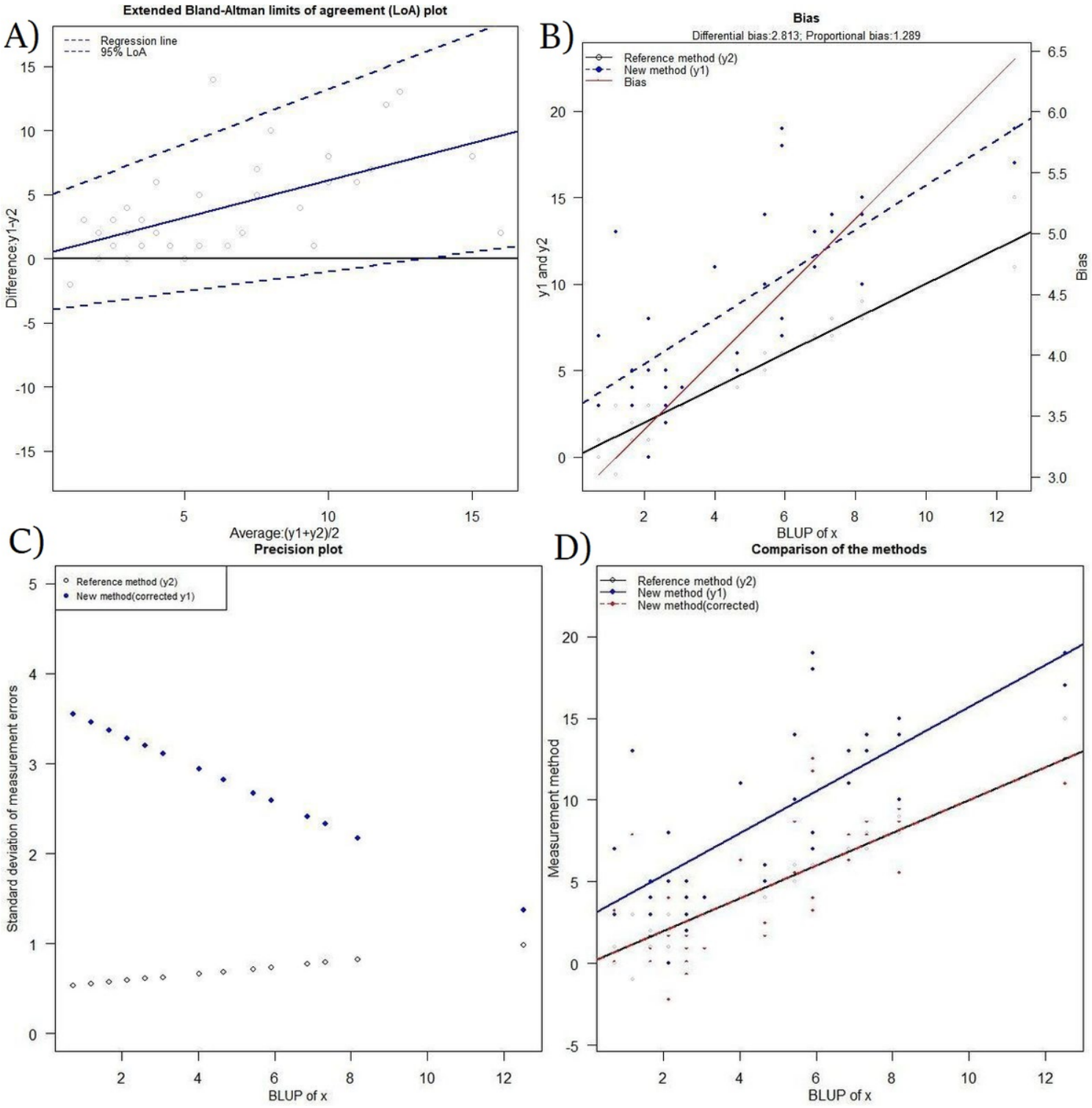

Figure 3

Estimation of the differential bias and the proportional bias (2.81; 95%CI 0.52-5.11 and 1.29; 95%CI 0.86 -1.72, respectively) using the Taffé method. Figure 8A represents the Bland-Altman graph according to Taffé's method and, Figure 8B shows the bias with respect to the BLUP (best linear unbiased prediction). Figure 8C illustrates the precision of the new method compared to the reference standard. Finally, figure 8D shows the recalibration of the new method once the bias has been removed.

Supplementary Files

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- Figure4.jpg