

RESEARCH ARTICLE

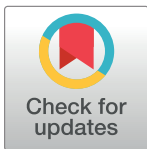
A comparison between measured and calculated central venous oxygen saturation in critically ill patients

Bruno De Oliveira¹, Malligere Prasanna¹, Malcolm Lemyze², Laurent Tronchon², Didier Thevenin², Jihad Mallat^{1,2*}

1 Department of Critical Care Medicine, Critical Care Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, UAE,

2 Department of Anesthesiology and Critical Care Medicine, Centre Hospitalier du Dr. Schaffner de Lens, Lens, France

* mallatjihad@gmail.com



Abstract

Background

Central venous oxygen saturation (ScvO₂) is often used to help to guide resuscitation of critically ill patients. The standard gold technique for ScvO₂ measurement is the co-oximetry (Co-oximetry_ScvO₂), which is usually incorporated in most recent blood gas analyzers. However, in some hospitals, those machines are not available and only calculated ScvO₂ (Calc_ScvO₂) is provided. Therefore, we aimed to investigate the agreement between Co-oximetry_ScvO₂ and Calc_ScvO₂ in a general population of critically ill patients and septic shock patients.

Methods

A total of 100 patients with a central venous catheter were included in the study. One hundred central venous blood samples were collected and analyzed using the same point-of-care blood gas analyzer, which provides both the calculated and measured ScvO₂ values. Bland and Altman plot, intra-class correlation coefficient (ICC), and Cohen's Kappa coefficient were used to assess the agreement between Co-oximetry_ScvO₂ and Calc_ScvO₂. Multiple linear regression analysis was performed to investigate the independent explanatory variables of the difference between Co-oximetry_ScvO₂ and Calc_ScvO₂.

Results

In all population, Bland and Altman's analysis showed poor agreement (+4.5 [-7.1, +16.1]%) between the two techniques. The ICC was 0.754 [(95% CI: 0.393–0.880), P< 0.001], and the Cohen's Kappa coefficient, after categorizing the two variables into two groups using a cutoff value of 70%, was 0.470 (P <0.001). In septic shock patients (49%), Bland and Altman's analysis also showed poor agreement (+5.6 [-6.7 to 17.8]%). The ICC was 0.720 [95% CI: 0.222–0.881], and the Cohen's Kappa coefficient was 0.501 (P <0.001). Four independent variables (PcvO₂, Co-oximetry_ScvO₂, venous pH, and Hb) were found to be associated with the difference between the measured and calculated ScvO₂ (adjusted R² = 0.8, P<0.001), with PcvO₂ being the main independent explanatory variable because of its

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highest absolute standardized coefficient. The area under the receiver operator characteristic curves (AUC) of PcvO₂ to predict Co-oximetry_ScvO₂ \geq 70% was 0.911 [95% CI: 0.837–0.959], in all patients, and 0.903 [95% CI: 0.784–0.969], in septic shock patients. The best cutoff value was \geq 36 mmHg (sensitivity, 88%; specificity, 83%), in all patients, and \geq 35 mmHg (sensitivity, 94%; specificity, 71%) in septic shock patients.

Conclusions

The discrepancy between the measured and calculated ScvO₂ is clinically not acceptable. We do not recommend the use of calculated ScvO₂ to guide resuscitation in critically ill patients. In situations where the Co-oximetry technique is not available, relying on PcvO₂ to predict the measured ScvO₂ value above or below 70% could be an option.

Introduction

Ensuring adequate oxygen delivery to organs and tissues is one of the primary objectives of organ support and goal-directed strategies in critical care. There are no readily available methods to monitor oxygen delivery to tissues directly in daily practice, and so physicians must instead rely on indirect measurements such as venous oxygen saturation.

Venous oxygen saturation is commonly used in the evaluation of patients in the intensive care unit (ICU) and may be of value in the management of septic patients [1] and post-cardiac surgery patients [2].

Mixed venous oxygen saturation (SvO₂) obtained from the pulmonary artery relates to oxygen consumption and oxygen delivery in the body. Central venous oxygen saturation (ScvO₂) obtained from central upper venous access is commonly used as a surrogate marker of SvO₂ since research has proven that ScvO₂ can be used in a less invasive manner to assess the balance between oxygen delivery and oxygen consumption [3].

The gold standard for ScvO₂ measurement is the analysis of the central venous blood sample by a Co-oximeter as this is a direct measurement of the effective amount of oxygen diluted in the sample. ScvO₂ can otherwise be inferred on standard blood gas analysis (ABG) machines by regression calculation based on the hemoglobin dissociation curve.

Previous studies have aimed at measuring the degree of agreement between these different techniques [4–6]. Most of these studies were done either in small numbers of patients, used different ABG machines for the same cohort of patients or were done in non-adult populations. They provided conflicting results regarding the use of a calculated ScvO₂ (Calc_ScvO₂) as a clinically acceptable surrogate of measured ScvO₂ (Co-oximetry_ScvO₂).

The primary aim of our study was to prospectively assess the agreement between Calc_ScvO₂ and Co-oximetry_ScvO₂ in an adult critically ill population in general, and in a sub-population of septic shock patients. The second aim of the study was to investigate if there is any variable that can predict a Co-oximetry_ScvO₂ value \geq 70% in the whole population and septic shock patients.

Materials and methods

Ethics statement

This prospective and observational study was conducted in a single, mixed medical, and surgical adult ICU between January and August 2017. This study was approved by the Institutional

Ethics Committee (comité d'éthique du centre Hospitalier du Dr. Shaffner de Lens). As the blood tests and data collected in this study were all standard clinical practice, the requirement for informed written consent was waived, and only oral consent was obtained. There were no measures taken to document to verbal consent procedure; nevertheless, the entire consent procedure was submitted to the ethics committee before they approved this study. If the patient or his/her next of kin refused consent, the patient's data were not entered into the analysis.

Patients

Patients were included if they met all of the following criteria: age >18 years, and central line with the tip confirmed by x-ray to be in the superior vena cava near or at the right atrium. Exclusion criteria were pregnancy and unstable condition, the latter being defined by >10% variation in heart rate, mean arterial pressure, and the need for clinical intervention within the 30-minute period before sampling.

Procedure

Venous blood gas samples were obtained from the central venous cannula, respectively, using a preheparinized 3-mL BG syringe (RAPIDLyte; Siemens Healthcare Diagnostic Inc, Deerfield, IL USA). As described in detail previously [7], immediately before sampling, the intravenous catheter was flushed using the standard flush solution of 0.9% sodium chloride without heparin. To reduce dilution effects, a 10-mL sample of blood was withdrawn into the syringe and discarded before drawing the 3-mL test samples. The tap in between the sampling port and administration set tubing was turned 45° while changing syringes to ensure that the solution from the proximal tubing could not enter the dead-space. Air bubbles were expelled, and the syringes were cupped and analyzed immediately, with temperature correction, using the GEM Premier 4000 (Instrumentation Laboratory Co, Paris, France). Maintenance, calibration, and quality control are performed on a regular basis by the central hospital laboratory. According to the manufacturer, the coefficient of variation for the PO₂ for the range of PcvO₂ was 1.66 to 3.31% and the coefficient of variation for Co-oximetry_ScvO₂ was 0.2 to 0.6%. The dead-space was 1.9 mL for the venous system.

No medical or nursing interventions were allowed while sampling was being performed.

Data collection

Demographic data, ICU admission diagnosis, and the Simplified Acute Physiology Score were obtained on the day of enrollment. Mean arterial pressure, the ventilation type (mechanical or spontaneous), and the use of vasopressor drugs were also registered. Septic shock was defined according to the Sepsis-3 criteria [8].

Central venous oxygen tension (PcvO₂), central venous carbon dioxide tension (PcvCO₂), measured central venous oxygen saturation (Co-oximetry_ScvO₂), calculated central venous oxygen saturation (Calc_ScvO₂), central venous pH, central venous blood lactate levels, hemoglobin concentration, and central venous base excess were measured using the GEM Premier 4000 (Instrumentation Laboratory Co, Paris, France). Co-oximetry ScvO₂ is determined by measuring the hemoglobin level of oxygen saturation based on a spectrophotometry optical system that monitors over 100 wavelengths in the absorbance spectra of oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin.

Both the Co-oximetry_ScvO₂ and Calc_ScvO₂ measurements were performed using the same point-of-care blood gas analyzer (GEM Premier 4000, Instrumentation Laboratory Co, Paris, France) on the same blood sample so that no additional blood withdraws was needed.

Sample size calculation

To calculate the sample size required to investigate the agreement between Co-oximetry_ScvO₂ and Calc_ScvO₂ by using Bland and Altman method [9], we decided to consider that a bias of 1% between the measured and calculated ScvO₂ with an estimated standard deviation of the difference of 1.5% [7] to be clinically pertinent and acceptable with a maximum allowed difference between the two methods of measurements of 5%. In order to achieve these requirements with a risk α of 0.05 and a power of 80%, 51 patients were needed to be included in the study.

Statistical analysis

Data are presented as mean \pm SD or as median (25–75%, interquartile range). Normality was evaluated using the Shapiro–Wilk test. Comparisons of continuous variables between septic shock and non-septic shock patients were assessed using Student's test or Mann-Whitney test as appropriate. Comparisons of categorical variables were performed using χ^2 -test or Fisher exact test as appropriate.

Agreement between Co-oximetry_ScvO₂ and Calc_ScvO₂ measurements was assessed using the Bland-Altman method [10]. Other methods used to evaluate the agreement are also described. There are the intra-class correlation coefficient (ICC) [11] and the Cohen's Kappa coefficient. According to Bland and Altman, most disagreements between measurements are expected to fall between limits called "limits of agreement" defined as $d \pm 1.96 SD_{diff}$ where d is the mean difference (bias) between the pairs of measurements, and SD_{diff} is the standard deviation of the differences [12]. The ICC equals variance between patients divided by variance between patients plus variance between measurements. The value of the ICC ranges from 0 to 1, 1 representing perfect agreement of the measurement. The Cohen's Kappa coefficient was calculated to assess the agreement between Co-oximetry_ScvO₂ and Calc_ScvO₂ after categorizing the two variables into two groups using a cutoff value of 70%. The values of the ICC and Cohen's Kappa coefficient range from 0 to 1, 1 representing perfect agreement of the measurements.

Simple linear regression analysis with the difference between Co-oximetry_ScvO₂ and Calc_ScvO₂ used as the dependent variable was performed, and variables with a P -value less than 0.2 or physiologically important were included in a multiple linear regression analysis model. Adjusted R^2 for the final model and each variable entry along with their standardized coefficients were also provided. The final model was tested for the presence of collinearity (VIF test).

Receiver operating characteristics (ROC) curves were constructed to evaluate the ability of the most explanatory variable of the Co-oximetry_ScvO₂ and Calc_ScvO₂ difference (found from the multiple linear regression model) to predict a Co-oximetry_ScvO₂ value $\geq 70\%$ in the whole population and septic shock patients. The best cutoff of a ROC curve was chosen with the highest Youden index [12]. Sensitivity, specificity, positive and negative predictive values along with their 95% confidence intervals were calculated.

Statistical analysis was performed using SPSS for Windows release 17.0 (Chicago, Illinois, USA) and MedCalc 18.6 (MedCalc Software, Mariakerke, Belgium). $P < 0.05$ was considered statistically significant. All reported P values are two-sided.

Results

One hundred patients were prospectively included in this study to have enough power for investigating the subgroup of septic shock patients. Basic characteristics of the cohort are presented in Table 1. The median age of patients was 66 [55–75] with a mean SAPS II score of 57

Table 1. Characteristics of the patients (n = 100).

Age, yrs	66 [55–75]
Sex, (Male/Female)	37/63
ICU mortality, n	37
Mechanical ventilation, n	68
SAPS II	57±22
Septic shock, n	49
Norepinephrine, n	49
Reason for admission in ICU, n	
Pneumonia	41
Peritonitis	30
Pancreatitis	8
Cardiac failure	7
Status epilepticus	6
Others	5
Venous pH, (minimum, maximum)	(7.05, 7.53)
PcvO ₂ , mmHg (minimum, maximum)	(22, 86)
PcvCO ₂ , mmHg (minimum, maximum)	(27, 89)
Co-oximetry_ScvO ₂ , % (minimum, maximum)	(46, 98)
Calc_ScvO ₂ , % (minimum, maximum)	(40, 96)
Base Excess, mmol/L (minimum, maximum)	(-18, +17)
Bicarbonate, mmol/L (minimum, maximum)	(11, 46)
Lactate, mmol/L (minimum, maximum)	(0.5, 13.3)
Hemoglobin, g/dL (minimum, maximum)	(4, 17)

ICU, intensive care unit; SAPS, simplified acute physiologic score; Co-oximetry-ScvO₂, Co-oximetry central venous oxygen saturation; Calc_ScvO₂, calculated central venous oxygen saturation; PcvO₂, central venous oxygen tension; PcvCO₂, central venous carbon dioxide tension. Data are expressed as mean ± SD, count, or median [interquartile, 25–75].

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±22. Forty-nine patients had septic shock, and 68% were mechanically ventilated. The comparisons of blood gas parameters between septic shock and non-septic shock patients are displayed in Table 2. Overall, septic shock patients were more acidotic and had higher lactate levels.

The whole population

Fig 1A shows the Bland-Altman diagram comparing ScvO₂ values measured with co-oximetry and the calculated ScvO₂ values. We found a high mean difference (bias) between the two methods (4.5±6.0%), which was significantly different from zero (P < 0.001). Furthermore, the limits of agreement were wide (-7.1, +16.1).

The agreement between the two parameters expressed as ICC was 0.754 [(95% CI: 0.393–0.880), P < 0.001]. We also calculated the agreement between the two parameters after categorized them into S_{cv}O₂ values less than 70% and higher or equal to 70%. We found a moderate agreement with a Cohen’s Kappa coefficient of 0.470 (P < 0.001).

Agreement according to septic and non-septic shock patients

In septic shock patients, the mean difference between Co-oximetry_ScvO₂ and Calc_ScvO₂ was 5.6±6.0% (Table 2) with limits of agreement ranged from -6.7 to 17.8% (Fig 1B). In non-

Table 2. Comparisons of blood gas parameters between septic shock and non-septic shock patients.

	All patients (n = 100)	Septic shock (n = 49)	Non-Septic shock (n = 51)	P-value
Mean arterial pressure, mmHg	80±15	77±14	83±16	0.057
Co-oximetry_ScvO ₂ , %	73±10	74±10	68±11	0.454
Co-oximetry_ScvO ₂ < 70%, n (%)	35 (35)	17 (35)	18 (35)	0.950
Calc_ScvO ₂ , %	68±11	68±11	68±11	0.878
Calc_ScvO ₂ < 70%, n (%)	47 (47)	23 (47)	24 (47)	0.909
(Co-oximetry_ScvO ₂ -Calc_ScvO ₂), %	4.5±6.0	5.6±6.0	3.5±5.5	0.082
Venous pH	7.36 [7.32–7.42]	7.35 [7.28–7.38]	7.40 [7.33–7.43]	0.005
PcvO ₂ , mmHg	38 [33–43]	38 [33–43]	36 [32–43]	0.269
PcvCO ₂ , mmHg	43 [38–50]	43 [39–48]	45 [38–53]	0.159
Bicarbonate, mmol/L	25.4±6.2	23.0±5.8	27.7±5.7	<0.001
Base Excess, mmol/L	-0.3±6.3	-2.8±6.4	2.1±5.3	<0.001
Lactate, mmol/L	1.6 [1–2.6]	2.5 [1.5–3.9]	1.1 [0.8–1.6]	<0.001
Hemoglobin, g/dL	10.7±2.2	11.1±2.4	10.4±1.9	0.096

Co-oximetry_ScvO₂, Co-oximetry central venous oxygen saturation; Calc_ScvO₂, calculated central venous oxygen saturation; PcvO₂, central venous oxygen tension; PcvCO₂, central venous carbon dioxide tension. Data are expressed as mean± SD or as median [interquartile range, 25–75].

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septic shock patients, the mean difference between Co-oximetry_ScvO₂ and Calc_ScvO₂ was 3.5±5.5%, and the limits of agreement were wide from -7.2 to 14.2% (Fig 1C). There was no significant difference between the two groups regarding the mean difference between the two techniques (Table 2).

The ICC was a little bit higher in non-septic shock compared with septic shock patients (0.799 [95% CI: 0.534–0.902] vs. 0.720 [95% CI: 0.222–0.881]).

In septic shock patients, among the 23 patients with Calc_ScvO₂ < 70%, 9 (39%) had Co-oxymetry_ScvO₂ > 70% (P = 0.001). The Cohen’s Kappa coefficient was 0.501 (P < 0.001). Among the 24 patients, in non-septic shock group, with Calc_ScvO₂ < 70%, 10 (42%) had Co-oxymetry_ScvO₂ > 70% (P = 0.002). The Cohen’s Kappa coefficient was 0.441 (P = 0.001).

Factors affecting the mean difference between Co-oximetry_ScvO₂ and Calc_ScvO₂ in the whole population

The best multiple regression analysis model constructed from the data found that PcvO₂, Co-oximetry_ScvO₂, venous pH, and Hb were the independent determinants of Co-oximetry_ScvO₂ and Calc_ScvO₂ difference (adjusted R² = 0.80; P < 0.001) (Table 3). Variables were excluded from the model if they did not change the adjusted R². PcvO₂ was the main independent explanatory variable to predict the Co-oximetry_ScvO₂ and Calc_ScvO₂ difference because of its highest absolute standardized coefficient and the highest changes made in adjusted R² when it was entered in the model (Table 3). The model did not reveal collinearity (all VIFs were < 5 and all tolerances were > 0.2).

Ability of PcvO₂ to predict Co-oximetry_ScvO₂ ≥ 70%

The ability of PcvO₂ to predict Co-oximetry_ScvO₂ value ≥ 70%, in all patients, was excellent with AUC of 0.911 [95% CI: 0.837–0.959] (Fig 2A). The best cutoff value was ≥ 36 mmHg with a sensitivity of 88% [95% CI: 77–94%], specificity of 83% [95% CI: 66–93%], positive predictive value of 90% [95% CI: 82–95%], and negative predictive value of 78% [95% CI: 65–88%] (Table 4).

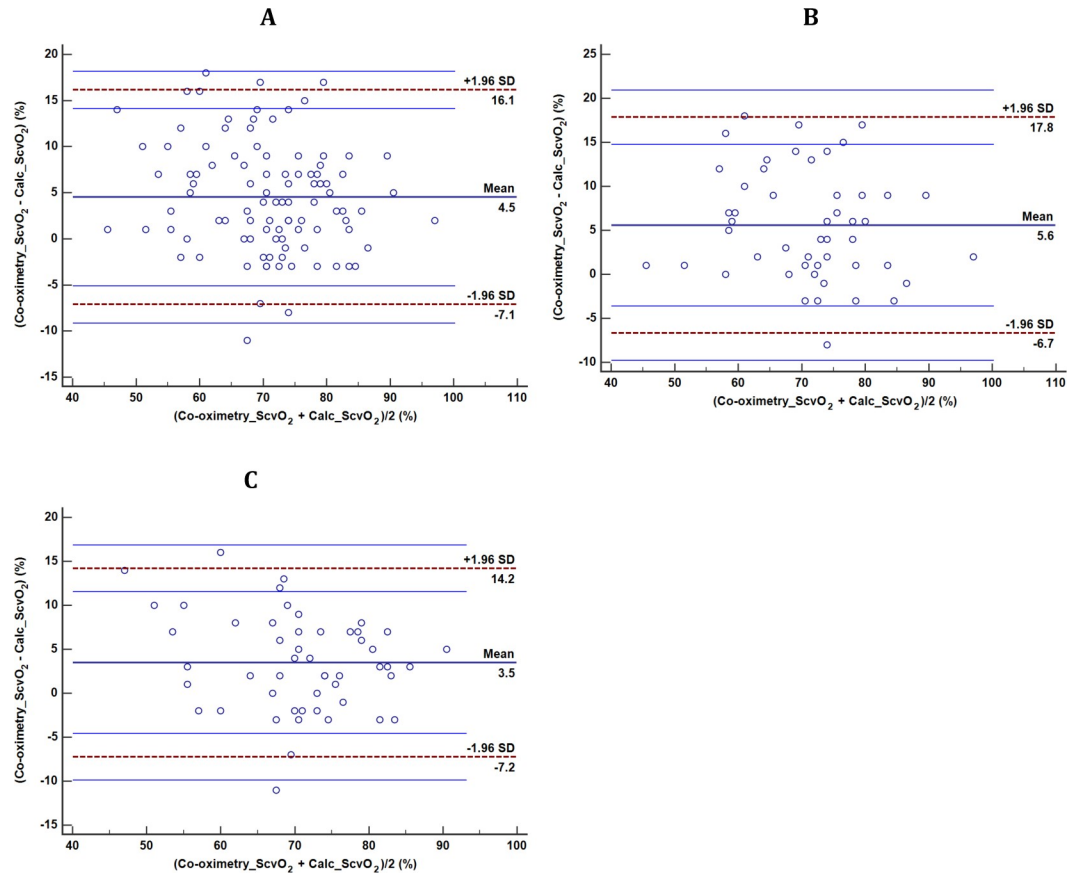


Fig 1. Bland and Altman plot of the difference against the mean of Co-oximetry ScvO₂ and the calculated ScvO₂. The solid line (dark blue) represents the mean difference (bias) between both techniques. The dashed lines represent the upper and lower limits of agreement, whereas the solid lines (light blue) surrounding the upper and lower limits of agreement represent their 95% confidence intervals. (A) The whole population, (B) Septic shock patients, and (C) Non-septic shock patients.

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Furthermore, we found that, in septic shock patients, the ability of PcvO₂ to predict Co-oximetry_ScvO₂ value $\geq 70\%$ was, also, excellent with AUC of 0.903 [95% CI: 0.784–0.969] (Fig 2B). The best cutoff value was ≥ 35 mmHg with a sensitivity of 94% [95% CI: 79–99%], specificity of 71% [95% CI: 44–90%], positive predictive value of 86% [95% CI: 74–93%], and negative predictive value of 86% [95% CI: 60–96%] (Table 4).

Also, in non-septic shock population, the ability of PcvO₂ to predict Co-oximetry_ScvO₂ value $\geq 70\%$ was, also, excellent with AUC of 0.920 [95% CI: 0.809–0.977] (Fig 2C). The best

Table 3. Multiple linear regression model for the difference between co-oximetry ScvO₂ and calculated ScvO₂ (Co-oxym_ScvO₂ - Calc_ScvO₂).

(Co-oximetry_ScvO ₂ - Calc_ScvO ₂)	Coefficients	95% CI	P-value	Standardized Coefficients
Venous pH	-65.64	-73.50 to -57.80	<0.001	-0.92
PcvO ₂	-1.18	-1.31 to -1.04	<0.001	-1.60
Co-oximetry_ScvO ₂	0.76	0.66 to 0.87	<0.001	1.19
Hemoglobin	-0.16	-0.42 to 0.09	0.210	-0.06

PcvO₂, central venous oxygen tension; Co-oximetry_ScvO₂, Co-oximetry central venous oxygen saturation; Calc_scvO₂, calculated central venous oxygen saturation; CI, confidence interval.

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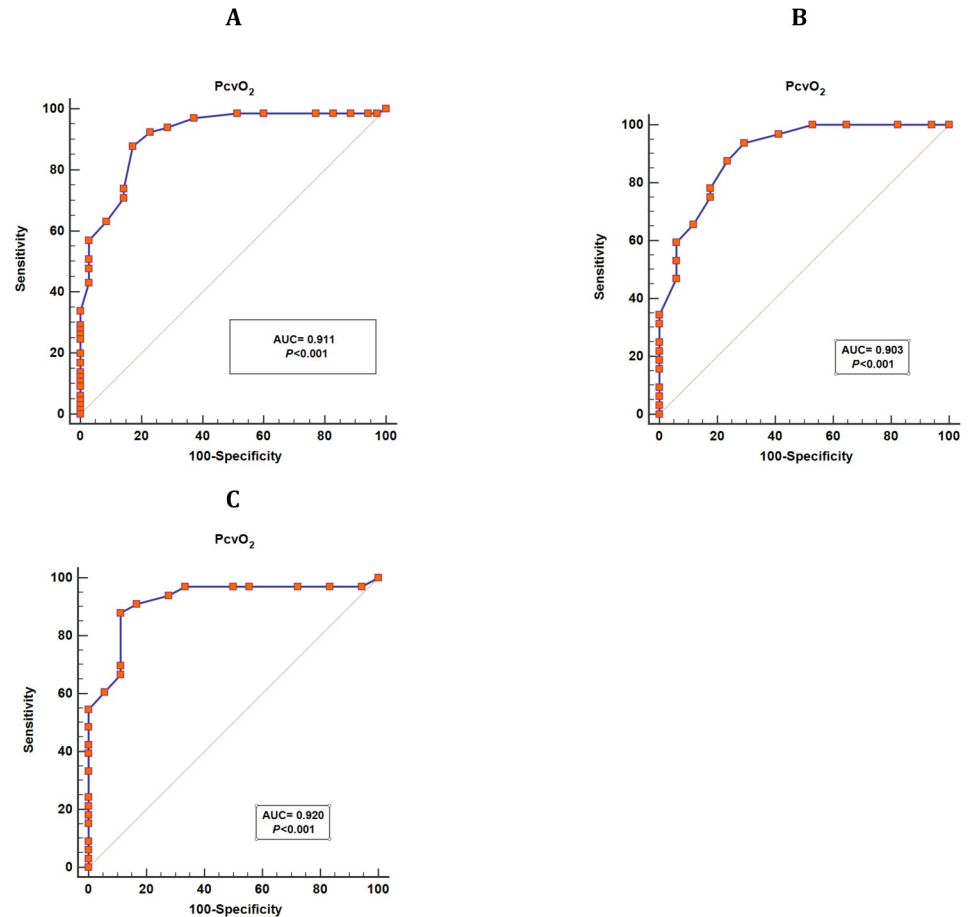


Fig 2. Receiver operator characteristic (ROC) curve showing the ability of the central venous oxygen pressure (PcvO₂) to predict Co-oximetry ScvO₂ greater than or equal to 70% in all patients. (A) The whole population, (B) Septic shock patients, and (C) Non-septic shock patients.

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cutoff value was ≥ 36 mmHg with a sensitivity of 89% [95% CI: 72–97%], specificity of 89% [95% CI: 65–99%], positive predictive value of 94% [95% CI: 80–98%], and negative predictive value of 80% [95% CI: 61–91%] (Table 4).

Discussion

The main findings of our study were that (1) the agreement between the CO-oximetry_ScvO₂ and the calculated ScvO₂ was poor in all population as well as in septic shock patients; (2) PcvO₂ was the primary independent variable that could explain the difference between ScvO₂

Table 4. Predictive values of PcvO₂ to detect Co-oximetry_ScvO₂ value $\geq 70\%$ in different populations. The best cutoff PcvO₂ value was ≥ 36 mmHg for the whole and non-septic shock patients, and ≥ 35 mmHg for septic shock patients.

	AUC [95%CI]	Se [95 CI] (%)	Spe [95 CI] (%)	PPV [95% CI] (%)	NPV [95% CI] (%)
Whole population	0.911 [0.837–0.959]	88 [77–94]	83 [66–93]	90 [82–95]	78[65–88]
Septic shock	0.903 [0.784–0.969]	94[79–99]	71[44–90]	86[74–93]	86[60–96]
Non septic shock	0.920 [0.809–0.977]	89[72–97]	89[65–99]	94[80–98]	80[61–91]

AUC, area under the curve; Se, sensitivity; Spe, specificity; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

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measured by CO-oximetry and the calculated ScvO₂; (3) PcvO₂ had an excellent ability to predict CO-oximetry_ScvO₂ values $\geq 70\%$ in all population as well as in septic shock patients.

Calculated and measured ScvO₂

Venous blood gas analysis allows for the direct and accurate determination of a series of oxygen-related parameters including the partial pressure of oxygen in venous blood or PvO₂. The saturation of oxygen may be directly measured by CO-oximetry, or it may be calculated.

The oxygen saturation reflects only the oxygen that is bound to hemoglobin. It is an expression of the total percentage of oxygen binding sites within the hemoglobin molecules that are occupied by oxygen. It is, in fact, a measure of the oxygen-carrying capacity that is in use. This represents almost all of the oxygen present in the venous blood (over 98%) the rest is dissolved in plasma and expressed as a partial pressure of O₂. Even if representing just a very small percentage of the total oxygen content of venous blood the partial pressure of O₂ is relevant as it is the main determinant of hemoglobin affinity to oxygen. This change of hemoglobin affinity is traditionally expressed by the oxygen dissociation curve where the higher the oxygen partial pressure, the higher the hemoglobin affinity becomes.

Before the current generation of blood gas analyzer machines, ScvO₂ and arterial oxygen saturation could only be obtained by relying on the direct determination of the oxygen partial pressure and estimating the saturation using a mathematical representation of the oxygen dissociation curve. One can understand that this comes with some potential for errors as it considers that the only factor influencing the shape and position of the dissociation curve is PvO₂. However, other factors, namely (5): temperature, pH, the partial pressure of CO₂, the concentration of non-oxygen binding hemoglobin (carboxyhemoglobin and methemoglobin) and the concentration of 2,3-diphosphoglycerate also affect the oxygen dissociation curve. Furthermore, the influence of 2,3-diphosphoglycerate, a three-carbon isomer of the glycolytic intermediate 1,3-bisphosphoglyceric acid, maybe even more relevant at lower oxygen partial pressures since it binds with higher affinity to deoxygenated hemoglobin [13,14].

The use of the mathematical equivalent of a standard hemoglobin dissociation curve also assumes standard conditions namely a pH of 7.4, temperature of 37°C, partial pressure of CO₂ of 40 mmHg, normal concentrations of 2,3-diphosphoglycerate and normal levels of methemoglobin and carboxyhemoglobin. Some changes in these parameters such as higher temperature, higher CO₂ partial pressure, acidosis, increased 2,3-diphosphoglycerate, will displace the curve to the right (lower saturation at a given PcvO₂). The opposite changes of these parameters: lower temperature, lower CO₂ partial pressure, alkalosis, low 2,3-diphosphoglycerate and higher concentrations of others hemoglobin will have the opposite effects by displacing the curve to the left, which means higher saturation for a given partial pressure).

The blood gas analyzer machine will attempt to mitigate these sources of errors by employing complex algorithms and taking into account more than just PcvO₂. It requires the input of pH, PcvCO₂, temperature and calculated base excess. No model integrates the concentration of 2,3-diphosphoglycerate or concentrations of the others hemoglobin to calculate ScvO₂. The inaccuracy resulting from these models was shown in arterial samples by Gothgen et al. almost thirty years ago [15]. There might an even more significant potential for errors in the critical illness where patients have severe acid-base or temperature disturbances and are possibly hypoxemic and also when using venous samples that have lower PO₂ values than their arterial counterparts.

Modern blood gas analyzers also allow for the direct measurement of oxygen saturation: CO-oximetry is based on spectrophotometric analysis of blood. Spectrophotometry is a tool that hinges on the quantitative analysis of molecules depending on how much light is absorbed

by colored compounds. It was first applied for dosing of total hemoglobin concentration in blood [16]. The multiple subspecies of hemoglobin present in blood, oxyhemoglobin, deoxyhemoglobin, methemoglobin, and carboxyhemoglobin have each a specific light absorption and transmission wavelength and can thus be quantified [17].

Knowing the measured oxygenated and non-oxygenated hemoglobin concentrations, one can directly deduce the saturation of oxygen in the sample as follows: $SvO_2 = cO_2Hb / (cO_2Hb + HHb)$ where cO_2Hb is the oxyhemoglobin concentration in venous blood and $cHHb$ is the concentration of deoxyhemoglobin in venous blood.

Contrary to the calculated oxygen saturation, the measured by CO-oximetry is not dependent on pH, temperature, hemoglobin concentration, 2,3-diphosphoglycerate or any other parameter that may displace the hemoglobin dissociation curve.

Agreement between CO-oximetry_ScvO₂ and Calc_ScvO₂

We found significant differences between measured and calculated ScvO₂ for this study population. The Bland and Altman plot analysis shows a large bias and wide limits of agreement (Fig 1A). Also, the interclass correlation coefficient (ICC) was found to have a large confidence interval, which is in favor of non-agreement between CO-oximetry_ScvO₂ and Calc_ScvO₂. Moreover, the Cohen's Kappa coefficient, which measures the inter-rater agreement for qualitative (categorical) items, and is believed to be a more robust test than the simple percent agreement calculation was low. This, also, points for lack of agreement between the two methodologies.

One might suppose that this disagreement in methods would be limited to extreme physiological conditions as in shock. We found that, indeed, the septic shock sub-group was significantly different in various physiological variables that impact the hemoglobin dissociation curve, namely pH, venous bicarbonate concentration and venous lactate concentration. Our results show poor agreement between Co-oximetry_ScvO₂ and Calc_ScvO₂ in septic shock patients (Fig 1B). Overall, we have demonstrated that the discrepancy between the measured and calculated ScvO₂ extends to all patient groups regardless of shock (Fig 1C).

Our findings are in line with previous results [5,6]. Indeed, a prior study by Romero et al. [5] in 16 septic shock patients with 111 pairs of measurements also showed lack of agreement between Co-oximetry_ScvO₂ and calculated ScvO₂ with wide apart limits of agreement on Bland and Altman plot analysis. A recent study using 141 paired samples from 82 pediatric ICU patients by Subramanian et al. [6] also failed to show adequate agreement between the two methodologies. Inversely, only one earlier study [4], which included 28 critically ill patients with 46 pairs measurements, found an insignificant systematic difference between measured and calculated ScvO₂ (0.78%) with smaller limits of agreement (-5.52 to 4.96%). However, the characteristics of the population were not provided in that study [4].

We should also consider that this discrepancy between measured and calculated ScvO₂ could have immediate clinical and treatment consequences. Indeed, 23 patients in septic shock would have presumably needed new interventions (possibly fluids or additional vasopressor) because their Calc_ScvO₂ values were < 70% when these same patients were found to be within the recommendations targets of a measured ScvO₂ over 70%. Likewise, for the non-septic shock population, 24 patients would be erroneously classified as having a low ScvO₂ (Co-oximetry_ScvO₂).

Four independent variables, in a multiple linear regression model, were found to be the main determinant of the disagreement between CO-oximetry_ScvO₂ and Calc_ScvO₂ with PcvO₂ being the most explanatory variable with the highest standardized coefficient (Table 4). Our multiple regression' model proved to be strong as it had a high adjusted R² (0.8). With an

AUROC of 0.911, PcvO₂ found to be an excellent predictor for CO-oximetry_ScvO₂ value above 70%. A cut-off ≥ 36 mmHg was demonstrated to be the best discriminative value for all population and ≥ 35 mmHg for septic patients. Our results are also in agreement with previously published data by Romero et al. [5] who found, in septic shock patients, an excellent AUROC (0.87) but a little different cut-off point (40 mmHg) to predict CO-oximetry_ScvO₂ values $> 70\%$. From a practical standpoint, considering that CO-oximetry_ScvO₂ is not readily available in all institutions and that the primary intent of a physician when ordering a test aimed at determining venous oxygen saturation is to know if the patients saturation is under or over the 70% threshold, we found that using PcvO₂ is highly specific and sensitive to predict CO-oximetry_ScvO₂ above 70%.

To our knowledge, this is the first prospective study comparing calculated saturation and CO-oximetry in a large ICU population of septic shock and non-septic shock patients. The strengths of our study compared to the others [4–6] are: (1) only 1 measurement per patient was performed whereas the other studies [4,5] included fewer patients with multiple measurements per patient without adjusting for that [18], introducing potential errors in the results; (2) Co-oximetry_ScvO₂ and Calc_ScvO₂ values were provided by the same point-of-care blood gas analyzer (GEM 4000) while in the other studies two different machines were used to compare the two methodologies, which could increase the pre-analytical errors (by increasing the waiting time for each sample to be analyzed by two devices) and the analytical errors related to each machine; (3) we used different methods to examine the agreement between the two variables, and sample size calculation with power analysis was performed.

Our findings are of clinical importance. Indeed, our results are a step forward in raising awareness that these two methods of determining ScvO₂ are not equivalent in any circumstance in the ICU population and following calculated saturation may lead to diagnosis missteps and unwarranted therapeutic interventions in almost half of our patients.

Some limitations must be recognized for our study. First, it took place in a single center using a unique brand and model of analyzer. Second, we did not process 2,3-diphosphoglycerate concentrations and temperature levels. However, the venous blood gas variables were corrected for temperature level, and no one of our patients was profoundly hypo or hyperthermic. Also, our multiple linear regression model was very good (adjusted $R^2 = 0.8$) without including temperature and 2,3-diphosphoglycerate levels. Furthermore, our findings are in line with the results of other studies [5,6].

Conclusion

No agreement was found between the measured and calculated ScvO₂ in the whole population as well as in septic shock patients. Our results do not recommend the use of calculated ScvO₂ to guide resuscitation in critically ill patients. In situations where the Co-oximetry technique is not available, relying on PcvO₂, measured by any blood gas analyzer, to predict the Co-oximetry_ScvO₂ value above or below 70% could be an option.

Supporting information

S1 File. Datasets supporting the conclusions of this article.
(XLSX)

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Author Contributions

Conceptualization: Jihad Mallat.

Formal analysis: Jihad Mallat.

Investigation: Malcolm Lemyze, Laurent Tronchon, Didier Thevenin, Jihad Mallat.

Methodology: Jihad Mallat.

Writing – original draft: Bruno De Oliveira, Malligere Prasanna.

Writing – review & editing: Jihad Mallat.

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