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SCIENTIFIC ARTICLE

# Influence of perfusion status on central and mixed venous oxygen saturation in septic patients

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**KEYWORDS**
Sepsis;
Venous oxygen saturation;
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**Abstract**
*Background and objectives:* Although there is controversy regarding the role of venous oxygen saturation in the initial resuscitation of septic patients with hypoperfusion these markers are still widely used. This study aimed to evaluate the correlation and concordance between central ($ScvO_2$) and mixed ($SvO_2$) oxygen saturation in septic shock patients with or without hypoperfusion in addition to the impact of these differences in patient conduction.
*Methods:* Patients with septic shock were monitored with pulmonary artery catheter and the following subgroups of hypoperfusion were analyzed: 1) lactate > 28 mg.dL$^{-1}$; 2) base excess $\leq -5$ mmol.L$^{-1}$; 3) venoarterial $CO_2$ gradient > 6 mmHg; 4) $SvO_2$ < 65%; 5) $ScvO_2$ < 70%; 6) lactate > 28 mg.dL$^{-1}$ and $SvO_2$ < 70%; 7) lactate > 28 mg.dL$^{-1}$ and $ScvO_2$ < 75%.
*Results:* Seventy-seven samples from 24 patients were included. There was only a moderate correlation between $SvO_2$ and $ScvO_2$ ($r = 0.72$, $p = 0.0001$) and there was no good concordance between these variables (7.35% bias and 95% concordance limits of −3.0% to 17.7%). Subgroup analysis according to the presence of hypoperfusion showed no differences in concordance between variables. There was discordance regarding clinical management in 13.8% ($n = 9$) of the cases.
*Conclusions:* There is a moderate correlation between $SvO_2$ and $ScvO_2$; however, the concordance between them is inadequate. It was not possible to demonstrate that the presence of hypoperfusion alters the concordance between $SvO_2$ and $ScvO_2$. The use of $SvO_2$ instead of $ScvO_2$ may lead to changes in clinical management in a small but clinically relevant portion of patients.
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**PALAVRAS-CHAVE**
Sepse;
Saturação venosa de oxigênio;
Saturação mista de oxigênio

**Influência do *status* perfusional nas saturações venosas de oxigênio central e mista em pacientes sépticos**

**Resumo**
*Justificativa e objetivos:* Embora haja controvérsias sobre o papel das saturações venosas de oxigênio na ressuscitação inicial do paciente séptico com hipoperfusão, esses marcadores são ainda bastante usados. Este estudo procurou avaliar a correlação e a concordância entre as saturações venosas central ($ScvO_2$) e mista ($SvO_2$) de oxigênio em pacientes com choque séptico, na presença ou não de hipoperfusão, além do impacto dessas diferenças na condução clínica do paciente.
*Métodos:* Foram incluídos pacientes com choque séptico monitorados com cateter de artéria pulmonar e analisados os seguintes subgrupos de hipoperfusão: 1) Lactato > 28 mg.dL$^{-1}$; 2) Excesso de bases $\leq$ -5 mmoL.L$^{-1}$; 3) Gradiente venoarterial de $CO_2$ > 6 mmHg; 4) $SvO_2$ < 65%; 5) $ScvO_2$ < 70%; 6) Lactato > 28 mg.dL$^{-1}$ e $SvO_2$ < 70%; 7) Lactato > 28 mg.dL$^{-1}$ e $ScvO_2$ < 75%.
*Resultados:* Foram incluídas 70 amostras de 24 pacientes. Houve apenas correlação moderada entre $SvO_2$ e $ScvO_2$ (r = 0,72; $p$ = 0,0001) e não houve boa concordância entre essas variáveis (viés de 7,35% e limites de concordância de 95% de -3,0%-17,7%). A análise dos subgrupos de acordo com a presença de hipoperfusão não mostrou diferenças na concordância entre as variáveis. Houve discordância na conduta clínica em 13,8% dos casos (n = 9).
*Conclusões:* Existe correlação moderada entre $SvO_2$ e $ScvO_2$, entretanto a concordância entre elas é inadequada. Não foi possível demonstrar que a presença de hipoperfusão altera a concordância entre a entre $SvO_2$ e $ScvO_2$. O uso da $SvO_2$ em vez da $ScvO_2$ pode levar a alterações na conduta clínica numa parcela pequena, porém clinicamente relevante, dos pacientes.
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## Introduction

Sepsis is defined as an infection followed by systemic manifestations resulting from the host's deleterious inflammatory response. It affects millions of people worldwide and has a high mortality rate ranging from 20% to 80%.[1–5] Rivers et al. used central venous oxygen saturation ($ScvO_2$) as one of the components of early goal-directed therapy (EGDT) and showed a significant mortality reduction in patients who met the proposed goals.[6] Subsequently, other studies that involved a greater number of patients did not reproduce these results and suggested that there was no benefit in the improvement guided by this variable.[7–9] However, these studies were performed in places with high-quality primary care, resulting in low mortality rate in the control groups, a reality quite different from that found in countries with limited resources.[10,11] It should also be considered that pre-randomization interventions resulted in an already improved $ScvO_2$ in most patients included. The impact of interventions for $ScvO_2$ normalization in patients who persisted at low values prior to randomization was not assessed. Moreover, enhancement based on classical EGDT was not associated with increased adverse events. For all these reasons, the Sepsis Survival Campaign has chosen to maintain the $ScvO_2$ measurement as one of the possible therapeutic targets in patients with initial signs of hypoperfusion.[12]

$ScvO_2$ measurement is quicker, easier, and involves lower costs and risks than mixed venous saturation ($SvO_2$), which requires the insertion of a pulmonary artery catheter (PAC), a more invasive device whose usefulness remains questionable. Furthermore, there is no consensus regarding the behavior of these oxygenation variables. Some argue that $ScvO_2$ and $SvO_2$, although numerically different, are related, have similar trends during patient evolution, and both are clinically useful.

$ScvO_2$ differs from $SvO_2$ by reflecting the oxygen content in blood after its consumption by the upper limbs and cephalic segment, as it is measured through the blood collected from the superior vena cava. $SvO_2$, in its turn, indicates the blood oxygen content after this gas extraction throughout the body, including the heart.[13] If there is splanchnic hypoperfusion, there is an increase in the rate of oxygen extraction in this region; so that, in theory, $ScvO_2$ and $SvO_2$ would be even more disparate. Thus, the primary objective of this study was to evaluate if there is correlation and agreement between the values of $ScvO_2$ and $SvO_2$ in patients with severe sepsis or septic shock and whether the presence of hypoperfusion alters the relationships between these two variables. The secondary objective was to evaluate the impact of using these two variables in the clinical management of the patient.

## Methods

A prospective observational study performed in three intensive care units of a university hospital with 35 clinical-surgical beds. The study was approved by the Research Ethics Committee of the institution under the number CEP-Unifesp 1518/11, and all patients or their legal guardians gave written informed consent (WIC).

Patients older than 18 years with septic shock less than 48 h after vasopressor initiation and monitored with PAC (Vigilance®, Edwards Lifesciences, Irvine, CA, USA) were included in the study. Sepsis was defined according to the consensus conference of the Society of Critical Care Medicine and the American College of Chest Physician[14] and septic shock was defined as hypotension refractory to volume replacement in need of vasopressors. Exclusion criteria were gestation, hemoglobin less than 7.0 g.dL$^{-1}$, hepatic cirrhosis, tricuspid valvulopathy, pulmonary valvulopathy, and known intracardiac shunts.

Demographic data, comorbidities, general characteristics of sepsis, the severity of the Acute Physiological and Chronic Health Evaluation (Apache II) scores, and the Sequential Organ Failure Assessment (Sofa) were recorded.

Blood samples were simultaneously collected from the pulmonary artery (distal lumen of PAC), superior vena cava (central venous catheter), and invasive blood pressure catheter. Arterial blood lactate was measured. In order to avoid contamination with liquids infused into catheters, 5 mL were aspirated from their lumen before collecting each sample. Up to four measurements were performed per patient with a minimum interval of 6 h between each sample collection. PAC and central venous catheter were inserted through the internal or subclavian jugular vein and their correct placement were confirmed by the pulmonary artery and right atrium curves and chest X-ray. In addition, hemodynamic and tissue perfusion parameters, hematimetry, and use and dose of vasoactive drugs were recorded at the time of sample collection.

Samples were immediately sent to laboratory for processing. For arterial and venous blood gas and arterial lactate examination, a microtechnique was used in a gas analyzer (ABL 700 Radiometer, Copenhagen, Dinamarca). Blood gases with hyperoxia, with partial arterial oxygen pressure ($PaO_2$) greater than 150 mmHg were excluded.

To evaluate the clinical agreement, the same investigator assessed the hemodynamic and respiratory data sets, the diagnoses and vasoactive drug dosages, and defined whether any approach toward hemodynamic improvement would be necessary. Considering that $ScvO_2$ was the parameter validated by Rivers in his study,[8] the percentage of times in which the use of $SvO_2$ generated different clinical approaches was evaluated.

Moreover, we opted to analyze a subgroup in which the presence of hyperlactatemia and changes in venous saturation were jointly evaluated. Patients with lactate greater than 28 mg.dL$^{-1}$ associated with $SvO_2 < 70\%$ or $ScvO_2 < 75\%$ were included in this subgroup. These limits were defined in order to exclude cases of hyperlactatemia secondary to low oxygen use due to cytopathic hypoxemia or hyperflow. As the concomitant use of adrenaline could compromise the assessment of the presence of hyperlactatemia, patients taking this medication were included in this group only if $SvO_2$ or $ScvO_2$ were below 65% or 70%, respectively. To define other groups considered as being under hypoperfusion, the following limits were used: lactate > 28 mg.dL$^{-1}$ or base excess (BE) less than 5 mmol.L$^{-1}$ or $CO_2$ venoarterial gradient (delta $CO_2$) greater than 6 mmHg or $SvO_2 < 65\%$ or $ScvO_2 < 70\%$. Patients were also classified according to their cardiac index, using as reference 3.5 L.min$^{-1}$.m$^{-2}$.

## Statistical analysis

In order to calculate the sample we sought to determine the existence of a correlation between two quantitative variables, with two-tailed test, 0.05 significance level, and 0.80 test power. It was considered as an optional hypothesis the existence of correlation with $r = 0.8$ and null hypothesis as no correlation with $r = 0.4$. The calculated sample size was 44. Calculations were performed using the STPLAN software version 4.1 for correlation tests of one-sample with normal approximation. Considering the possible asymptotic distribution of the variable and the possibility of analyzing subgroups according to the presence or absence of hypoperfusion, the sample was recalculated in 65 pairs.

The continuous variables distribution pattern was analyzed using the Kolmogorov-Smirnov test, with normal distribution presented as mean and standard deviation and non-normal distribution as median and 25th and 75th percentile. Categorical variables were presented as a percentage. Mann–Whitney test or Student's *t*-test was used to compare the continuous variables, according to their distribution. The correlation between paired samples was assessed using Spearman's correlation test and concordance using the Bland–Altman test, where the 95% limits of agreement represent the bias (mean absolute difference) ± 2 standard deviations. Clinical agreement was reported only in a descriptive way.

In all tests, a *p*-value <0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 19.0 and the software GraphPad Prism version 5.0.

## Results

Twenty-four patients were included, or 70 paired blood samples. Five samples were excluded due to hyperoxia, three of them from the same patient, who were excluded from the study. Patient characteristics and sample collection time are available (Table 1). In 61 samples (93.8%) the patient was taken noradrenaline; in 26 samples (40%) the patient was taken adrenaline; and in 15 samples (23.1%), the patient was taken dobutamine.

The Bland–Altman test in all patients showed no good agreement between $SvO_2$ and $ScvO_2$, with 7.35% bias and LC 95%: −3.0% to 17.7% (Fig. 1). There was a moderate correlation between these variables ($r = 0.72$; $p = 0.0001$).

Only 10 samples (15.4%) met the hypoperfusion criterion; that is, the presence of normal or low $SvO_2$ and/or $ScvO_2$ associated with hyperlactatemia – in only four of these situations both venous saturations were below the established limits. There was no good agreement among them because, although there was a small bias, the limits of agreement were wide (3.15%, LC 95%: −7.25% to 13.76%) (Fig. 2).

$ScvO_2 < 70\%$ was found in only eight samples, whereas $SvO_2 < 65\%$ occurred in 12 of them. Bland–Altman test also did not show good agreement between these variables in both situations (Figs. 3 and 4). There were 20 samples (30.8%) with a widened delta $CO_2$ (>6 mmHg) and 29 samples (44.6%) with BE < −5.0 mmol.L$^{-1}$. The Bland–Altman analysis also showed low agreement between $SvO_2$ and $ScvO_2$ in these subgroups. Hyperlactatemia was present in 29

**Table 1** General characteristics of patients and data at the sample collection time.

| Characteristics | Results |
|---|---|
| **Patients** | (*n* = 26) |
| *Sex* | |
| Male | 15 (65.2) |
| Female | 8 (34.8) |
| *Age (years)* | 65 (55–71) |
| *Apache* II | 20 (17–27) |
| *Admission Sofa* | 8 (6–12) |
| *Infectious focus* | |
| Gastrointestinal tract | 9 (39.1) |
| Pulmonary | 8 (34.8) |
| Genitourinary tract | 1 (4.3) |
| Skin | 2 (8.7) |
| Central nervous system | 1 (4.3) |
| Other | 2 (8.7) |
| *Outcome* | |
| ICU discharge | 6 (26.1) |
| Death | 17 (73.9) |
| **Sample collection time** | (*n* = 65) |
| *Sofa on sample collection* | 8 (8–12) |
| *Shock time (hours)* | 37.0 ± 18.9 |
| *$SvO_2$ (%)* | 71.0 (65.5–73.0) |
| *$SvcO_2$ (%)* | 78.0 (74.0–81.5) |
| *$SaO_2$ (%)* | 97 (95–98) |
| *CI ($L.min^{-1}.m^{-2}$)* | 3.5 ± 0.9 |
| *BE ($mmol.L^{-1}$)* | −4.3 ± 6.9 |
| *Delta $CO_2$* | 4.4 (2.7–7.0) |
| *MAP (mmHg)* | 73.4 ± 7.7 |
| *HR (beats per minute)* | 105.9 ± 20.8 |
| *CVP (mmHg)* | 10.3 ± 4.0 |
| *PAOP (mmHg)* | 11.2 ± 5.2 |
| *PASP (mmHg)* | 41.1 ± 13.5 |
| *Noradrenaline ($mcg.kg^{-1}.min^{-1}$)* | 0.56 ± 0.50 |
| *Adrenalin ($mcg.kg^{-1}.min^{-1}$)* | 0.13 ± 0.20 |
| *Dobutamine ($mcg.kg^{-1}.min^{-1}$)* | 1.4 ± 4.0 |

Apache II, acute physiology and chronic health evaluation; BE, excess of bases; HR, heart rate; CI, cardiac index; MAP, mean arterial pressure; PAOP, pulmonary artery occlusive pressure; PASP, pulmonary artery systolic pressure; CVP, central venous pressure; $SaO_2$, arterial oxygen saturation; Sofa, sequential organ failure assessment; $SvcO_2$, central venous oxygen saturation; $SvO_2$, mixed venous oxygen saturation; ICU, intensive care unit.
Results are presented as number (percentage), mean ± standard deviation or median 25%–75%.

samples (44.6%). The Bland–Altman test analysis of groups with or without hyperlactatemia revealed inadequate agreement between mixed and central venous saturations in both situations (Fig. 5).

Regarding CI, 29 samples (44.6%) presented with high values, higher than 3.5 $L.min^{-1}.m^{-2}$, with an inadequate agreement between saturations in both CI conditions. All subgroup analysis results are summarized in Table 2.

Regarding the clinical approach assessment, there was disagreement as to the need for intervention in nine situations (13.8%) when $SvO_2$ or $SvcO_2$ was informed to the investigator, in addition to the other hemodynamic

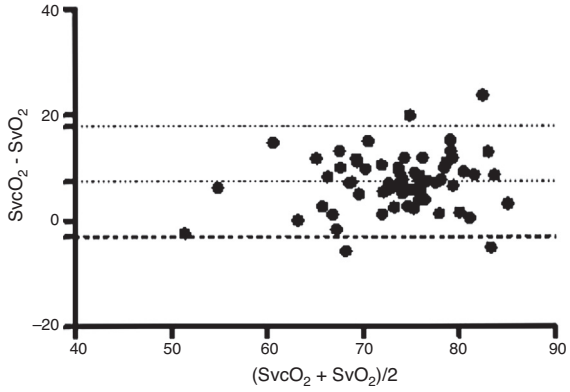


**Figure 1** Concordance analysis between central venous saturation ($SvcO_2$) and mixed venous saturation ($SvO_2$) in global sample. Data show 7.35% bias and 95% limits of agreement of 3.0%–17.7%.

and respiratory parameters. Considering $SvcO_2$ as a gold standard and a predictor or not for treatment, the treatment based on $SvO_2$ would have been excessive in six situations because $SvcO_2$ was already improved. In two situations the presence of elevated $SvcO_2$ would have led to a reduction of medication intake, which did not occur when the observer was based on $SvO_2$. In a single situation (1.5%) the patient would no longer be treated on the basis of $SvO_2$, when the approach should have been considered in view of $SvcO_2 < 70\%$.

## Discussion

In this study there was no good agreement between $SvcO_2$ and $SvO_2$, regardless of the presence or absence of tissue hypoperfusion, characterized by hyperlactatemia, reduced venous saturation, metabolic acidosis with BE fall or $CO_2$ delta ratio enlargement. There was disagreement in clinical management in a small, though clinically significant, portion of the cases (13.8%) when using a $SvcO_2 < 70\%$ as gold standard.

The use of venous saturation as a therapeutic target in critically ill patients has been the subject of numerous studies. Initial analyzes based on $SvO_2$ obtained through pulmonary artery catheter failed to demonstrate that its use resulted in reduced morbidity and mortality.[15–17] However, the use of this parameter was delayed by these studies, which may have impaired the ability to correctly evaluate its validity as a resuscitation target. Based on current knowledge we know that the hemodynamic care and improvement of these patients should be performed early.[18]

The first study to validate the use of venous saturations as a therapeutic target was conducted by Rivers et al.[6] This study was criticized for several reasons, among them the finding of very low levels of $SvcO_2$ no longer reproduced in other case series, and a mortality rate in the control group higher than in other studies. Subsequently, another randomized study showed a reduction in mortality with the strategy described by Rivers.[19] Despite these controversies a $SvcO_2$ of 70% continued to be used for the resuscitation of patients with severe sepsis or septic shock.

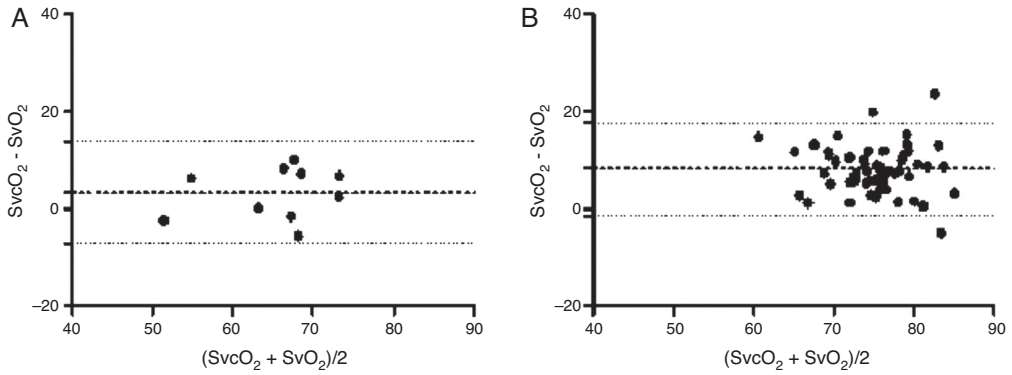


**Figure 2** Analysis of agreement between mixed ($SvO_2$) and central ($SvO_2$) venous saturations in subgroups of $SvcO_2$ and/or $SvO_2$ and lactate joint analysis. (A) Low $SvcO_2$ and/or $SvO_2$ associated with hyperlactatemia. Bias: 3.15% and LC 95%: −7.25% to 13.76%. (B) $SvcO_2$ and/or normal $SvO_2$ associated with hyperlactatemia. Bias: 8.11% and LC 95%: −1.6% to 17.83%.

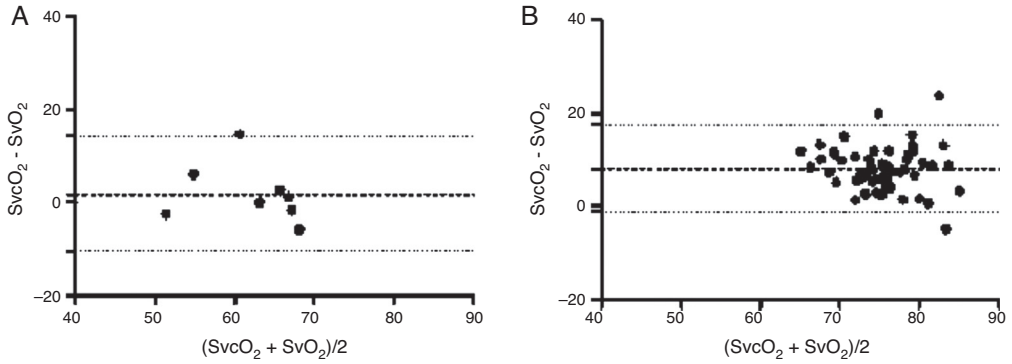


**Figure 3** Analysis of agreement between mixed ($SvO_2$) and central ($SvO_2$) venous saturations in subgroups of $SvcO_2$. (A) $SvcO_2 < 70\%$. Bias: 1.94% and LC 95%: −10.43% to 14.31%. (B) $SvcO_2 \geq 70\%$. Bias: 8.1% and LC 95%: −1.18% to 17.34%.

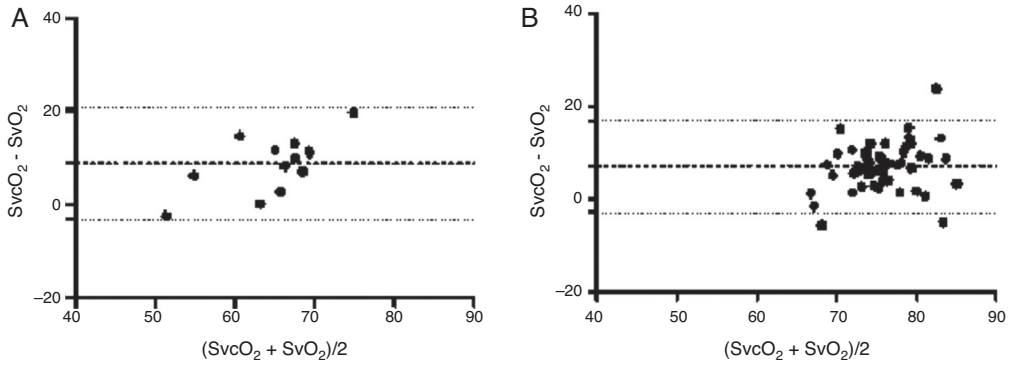


**Figure 4** Analysis of agreement between mixed ($SvO_2$) and central ($SvO_2$) venous saturations in $SvO_2$ subgroups. (A) $SvO_2 < 65\%$. Bias: 8.83% and LC 95%: −3.16% to 20.82%. (B) $SvO_2 \geq 65\%$. Bias: 6.98% and LC 95%: −2.93% to 16.89%.

Recently, three randomized multicenter studies have shown no differences in mortality rate between groups of patients randomized to conventional treatment (no use of $SvcO_2$) and the goal-guided therapy of Rivers et al.[7–9] The limitations of these studies should be kept in mind, as all of them were conducted in high-quality centers in rich countries, with relatively low mortality rate in control groups. This makes it difficult to apply their results in countries with limited resources or inadequate quality of care. The $SvcO_2$ mean values at the time of randomization in groups of patients undergoing EGDT $\geq 70\%$ (ProCESS: $SvcO_2 = 71\%$; ARISE: $SvcO_2 = 72.7\%$; ProMISe: $SvcO_2 = 70\%$%)

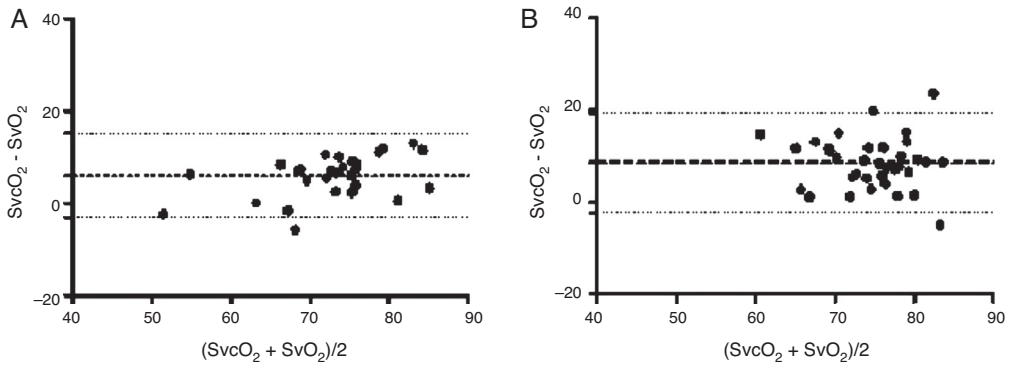


**Figure 5** Analysis of agreement between mixed ($SvO_2$) and central ($SvO_2$) venous saturations in lactate subgroups. (A) Lactate $\leq 28\,mg.dL^{-1}$. Bias: 6.04% and LC 95%: −3.07% to 15.14%. (B): lactate $\leq 28\,mg.dL^{-1}$. Bias: 8.56% and LC 95%: −2.28% to 19.41%.

**Table 2** Agreement between central venous saturation and mixed venous saturation in the various subgroups.

| Subgroup | Bias (%) | 95% limits of agreement (%) |
|---|---|---|
| *Global* | 7.35 | −3.00 to 17.70 |
| *Hypoperfusion* | | |
| Yes | 3.15 | −7.25 to 13.76 |
| No | 8.11 | −1.60 to 17.83 |
| *$ScvO_2$* | | |
| $ScvO_2 < 70\%$ | 1.94 | −10.43 to 14.31 |
| $ScvO_2 \geq 70\%$ | 8.10 | −1.18 to 17.34 |
| *$SvO_2$* | | |
| $SvO_2 < 65\%$ | 8.83 | −3.16 to 20.82 |
| $SvO_2 \geq 65\%$ | 6.98 | −2.93 to 16.89 |
| *Delta $CO_2$* | | |
| Delta $CO_2 > 6$ mmHg | 7.19 | −5.28 to 19.66 |
| Delta $CO_2 \leq 6$ mmHg | 7.43 | −1.97 to 16.83 |
| *BE* | | |
| $BE < -5\,mmol.L^{-1}$ | 7.42 | −2.74 to 17.6 |
| $BE \geq -5\,mmol.L^{-1}$ | 5.85 | −16.42 to 28.14 |
| *Lactate* | | |
| Lactate $> 28\,mg.dL^{-1}$ | 6.04 | −3.07 to 15.14 |
| Lactate $\leq 28\,mg.dL^{-1}$ | 8.56 | −2.28 to 19.41 |
| *CI* | | |
| $CI \leq 3.5\,L.min^{-1}.m^{-2}$ | 7.78 | −1.41 to 16.97 |
| $CI > 3.5\,L.min^{-1}.m^{-2}$ | 7.00 | −4.30 to 18.30 |

BE, base excess; CI, cardiac index; $ScvO_2$, central venous oxygen saturation; $SvO_2$, mixed venous oxygen saturation.
Results are presented as number (percentage).

indicated that most patients were already adequately resuscitated, possibly due to volume replacement received prior to randomization.[7–9] Furthermore, it is not a study comparing hemodynamic improvement in patients who persist with low saturation after initial resuscitation. Thus, we remain without evidence of the best management in these situations: persist with resuscitation or observation. Finally, the studies had their samples calculated with the estimation of mortality rates higher than those actually found in the studies. None of the studies showed increased adverse events in groups undergoing EGDT. Thus, the Sepsis Survival Campaign continues to include among the options for hemodynamic improvement the measurement of $ScvO_2$ or $ScvO_2$ as variables that reflect the body supply and consumption of oxygen. Therefore, the object of our study continues to have relevance for these patients monitoring.

Although pulmonary artery catheter has been poorly used for being more invasive and due to the difficult interpretation of hemodynamic data, in cases in which it is used it would be important to define what would be the values corresponding to $ScvO_2$ previously validated by Rivers et al.[6] In the guidelines of the Sepsis Survival Campaign, the cut-off point of 65% is recommended.[18] However, this value has little support in the literature. Our results are in line with several studies showing poor agreement between $ScvO_2$ and $SvO_2$.[20–22] However, it would be more appropriate to evaluate these possible differences in patients with signs of hypoperfusion, as it is in this clinical situation that $ScvO_2$ improvement or non-improvement has relevance. In our study, agreement between venous saturations is also inadequate in hypoperfusion situations, with limits of agreement.

Other authors have suggested a worse agreement between $ScvO_2$ and $SvO_2$ when $ScvO_2$ <60%.[22] It is known that circulatory failure in the early stages of sepsis is related to hypovolemia, myocardial pressure, hypercatabolic state, and abnormal vasoregulation, with a pathological oxygen supply dependency in this period. In theory, the presence of splanchnic hypoperfusion would make $ScvO_2$ and $SvO_2$ more divergent due to an increase in the rate of oxygen extraction by the viscera, measurable in the blood returning to the heart via the inferior vena cava and not via the superior vena cava. In our study, there was no difference between subgroups evaluated according to venous oxygen saturation. It was not possible to identify a relationship pattern between $ScvO_2$ and $SvO_2$ in any of the subgroups with signs of hypoperfusion. One hypothesis for our findings would be the fact that abdominal splanchnic hypoperfusion is not primarily responsible for the reduction of $SvO_2$. It is believed that the main component responsible for a lower $SvO_2$ value compared to $ScvO_2$ would be the mixed blood from the coronary

sinus.[20] Thus, this reduction could be the result of cardiac output impairment and not necessarily of increased visceral consumption. In myocardial depression low oxygen consumption could lead to a relative increase in $SvO_2$, narrowing its relationship with $SvcO_2$. However, it was not possible to demonstrate agreement differences in the subgroup of patients with high or low cardiac output. This analysis is limited both by the fact that there were no situations in our group in which cardiac index was reduced in absolute numbers (below 2.5 $L.min^{-1}.m^{-2}$) and by the difficult interpretation of the cardiac output adequacy to the body need.

The clinical agreement analysis demonstrated a management disagreement in 13.8% of cases, suggesting that the use of the proposed 65% limit for $SvO_2$ could trigger treatment for hemodynamic parameter supranormalization, although it was not possible to demonstrate this clearly. It is known that hypertreatment is associated with increased morbidity and mortality with excessive use of fluids, dobutamine, and blood transfusion in an attempt to increase cardiac output.[23] Although there have been few cases of inadequate management in our study, on an individual level this could bring harm to that particular patient.

The present study has some strength points. We analyzed a relevant group of patients with septic shock, in which management standardization is necessary to eventually reduce morbidity and mortality. We sought to make a detailed analysis of the perfusional status and create different forms of evaluation based on different laboratory profiles. In addition, the analysis was not restricted to statistical procedures of correlation and concordance evaluation, but rather to the impact of using $SvO_2$ or $SvcO_2$ in clinical practice.

This study also has a number of limitations. First, the small sample size resulted in a limited number of situations in each of the subgroups evaluated for perfusion status. Second, the patients were no longer in the first hours of resuscitation, which may limit the findings application in this clinical setting. In addition, as a result of this inclusion window, most patients were already adequately resuscitated, which restricted the number of patients in a state of hypoperfusion. Third, more than one sample was collected from each patient, which may have generated bias in interpreting the relationships between venous saturations. Finally, the evaluation of isolated measures, rather than the venous saturation behavior in response to interventions, also constitutes a limitation in the definition of clinical behavior, even if minimized by the fact that the observer has taken into account other perfusion variables.

In conclusion, this study showed that although there is a moderate correlation between $SvO_2$ and $SvcO_2$, the agreement between them is inadequate. It was not possible to demonstrate that the presence of hypoperfusion alters the agreement between $SvO_2$ and $SvcO_2$. In addition, the use of $SvO_2$ instead of $SvcO_2$ may lead to changes in clinical management in a small but clinically relevant portion of patients

## Conflicts of interest

The authors declare no conflicts of interest.

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