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## Central and mixed venous oxygen saturation in septic shock: is there a clinically relevant difference?

*Saturação venosa central e mista de oxigênio no choque séptico: existe diferença clinicamente relevante?*

### ABSTRACT

**Introduction:** Central venous oxygen saturation (SvcO<sub>2</sub>) has been proposed as an alternative for mixed venous oxygen saturation (SvO<sub>2</sub>), with a variable level of acceptance according to available data. This study aimed to evaluate possible differences between SvO<sub>2</sub> and SvcO<sub>2</sub> or atrial venous saturation (SvaO<sub>2</sub>), with emphasis on the role of cardiac output and their impact on clinical management of the septic patient.

**Methods:** This is an observational, prospective study of patients with septic shock monitored by pulmonary artery catheter. Blood was obtained simultaneously for SvcO<sub>2</sub>, SvO<sub>2</sub> and SvaO<sub>2</sub> determination. Linear correlation (significant if p≤0.05) and agreement analysis (Bland-Altman) were performed with samples and subgroups according to cardiac output. Moreover, agreement about clinical management based on these samples was evaluated.

**Results:** Sixty one measurements from 23 patients were obtained, median age of 65.0 (49.0-75.0) years and mean APACHE II of 27.7±6.3. Mean values of SvO<sub>2</sub>, SvcO<sub>2</sub> and SvaO<sub>2</sub> were 72.20±8.26%, 74.61±7.60% and 74.64±8.47%. Linear correlation test showed a weak correlation between SvO<sub>2</sub> and SvcO<sub>2</sub> (r=0.61, p<0.0001) and also between SvO<sub>2</sub> and SvaO<sub>2</sub> (r=0.70, p<0.0001). Agreements between SvcO<sub>2</sub>/SvO<sub>2</sub> and SvaO<sub>2</sub>/SvO<sub>2</sub> were -2.40±1.96 (-16.20 and 11.40) and -2.40±1.96 (-15.10 and 10.20), respectively, with no difference in the cardiac output subgroups. No agreement was found in clinical management for 27.8% of the cases, both for SvcO<sub>2</sub>/SvO<sub>2</sub> and for SvaO<sub>2</sub>/SvO<sub>2</sub>.

**Conclusion:** This study showed that the correlation and agreement between SvO<sub>2</sub> and SvcO<sub>2</sub> is weak and may lead to different clinical management.

**Keywords:** Oximetry/methods; Oxygen/blood; Sept, shock/blood

### INTRODUCTION

Tissue hypoxia is considered to be one of the most important factors in the development of organ dysfunction in septic patients.<sup>(1)</sup> Unfortunately, clinical findings, vital signs and urine output are not sufficiently precise to detect it.<sup>(2)</sup> Monitoring of mixed venous oxygen saturation (SvO<sub>2</sub>) has been used to evaluate the balance between oxygen delivery and consumption. Although studies including patients with a long duration organ dysfunction have failed to demonstrate its role as a therapeutic target,<sup>(3)</sup> Rivers et al., in 2001, showed that in the early hours of hemodynamic resuscitation in severe sepsis, its optimization should be the objective in a protocol known as Early Goal Directed Therapy (EGDT).<sup>(4)</sup> However, these authors used central venous oxygen saturation (SvcO<sub>2</sub>), measured by means of an optical

fiber catheter located in the superior vena cava.

Due to risks associated with pulmonary artery insertion, costs and controversies regarding benefits, associated with the routine use of central venous oxygen saturation in the intensive care units, measurement of SvcO<sub>2</sub> has been proposed as an alternative to evaluate the global relationship between oxygen delivery and consumption. Studies in critical care medicine show that SvcO<sub>2</sub> is on the average 4% to 7% higher than SvO<sub>2</sub> and that there is a good relation between them.<sup>(5-7)</sup> However, the extent of agreement is not satisfactory and available data is still not conclusive regarding ability to adequately display SvO<sub>2</sub>.

This difference in the venous oxygen content could possibly be explained by the mixture with blood drained through the inferior vena cava, as well as that shed from the coronary sinus and thebesian veins. It is well known that myocardial oxygen extraction fraction is quite high and that the resulting blood may have saturation levels as low as 30-40%. Some authors believe that this mixture with blood from the coronary sinus would be the probable explanation for this difference.<sup>(5)</sup> Behavior of the difference between SvcO<sub>2</sub> and SvO<sub>2</sub> in different cardiac output profiles has not yet been well evaluated. Cardiac output in septic patients can vary widely, with a decrease due to an inadequate preload or sepsis induced myocardial depression. At the same time, some patients can present a high output as a natural consequence of the decrease in afterload. In these clinical situations an analysis of the differences between SvO<sub>2</sub> and SvcO<sub>2</sub> may be very interesting.

Moreover, these studies generally use different sites, right atrium (SvaO<sub>2</sub>) or superior vena cava (SvcO<sub>2</sub>), for the determination of venous saturation, with controversial results.

Another aspect to be considered, besides the correlation or agreement between these two ways of measurement from the statistical point of view, is agreement with the clinical point of view. None of the cited authors evaluated if the differences found would lead to clinical repercussion in the clinical conduct assumed.<sup>(5-7)</sup>

As such, this study aimed to evaluate the possible differences between SvO<sub>2</sub> and SvcO<sub>2</sub> or SvaO<sub>2</sub>, emphasizing the interference of cardiac output and their impact on clinical conduct of the septic patient.

## METHODS

This is a clinical, prospective, observational study performed at a 16-beds mixed intensive care unit of a

tertiary university hospital. This study was approved by the Ethics Research Committee of the institution and all patients or their legal representatives agreed with the participation, signing an informed consent.

Patients more than 18-years old with septic shock that had a central venous catheter in place and under monitoring by arterial pulmonary catheter were included. Septic shock was defined as the presence of volume refractory hypotension according to the 1992 Consensus.<sup>(8)</sup> This hypotension should be clearly secondary to the septic process, that is to say the presence of an infectious source.

Patients with known tricuspid valvulopathy associated with pulmonary valve insufficiency, interatrial or interventricular communication, oval foramen, patent ductus arteriosus or diseases associated with intracardiac shunt were excluded.

Demographic data and Acute Physiological and Chronic Health Evaluation II (APACHE II) score were registered.<sup>(9)</sup> All patients were monitored with a 7.5 F and 110cm length pulmonary artery catheter (Edwards Lifesciences<sup>®</sup>) inserted through the jugular or subclavian vein. Position of the venous catheter in the superior vena cava was confirmed by thorax X-ray. Position of the pulmonary artery catheter proximal port was confirmed by a typical right atrial pressure curve. Each patient was submitted to a maximum of 4 sets of hemodynamic and respiratory parameters, within a 4 hours minimal interval. Each set comprised a blood gas analysis obtained simultaneously through proximal (SvaO<sub>2</sub>) and distal (SvO<sub>2</sub>) port of the pulmonary artery catheter and from the central venous catheter. To avoid contamination with fluids infused in the catheter, before each sample a 5 ml of blood was drawn from both ports of the pulmonary artery catheter as well as the central line. Samples were immediately sent to the laboratory and processed. Hemodynamic parameters were registered immediately prior to samples collection, with emphasis on cardiac output measured by thermodilution.

The set of hemodynamic and respiratory data, as well as the baseline diagnosis and doses of vasoactive drugs in use, were presented to an intensivist board-certified by the Brazilian Critical Care Association who, without knowing the site that originated each set of data, among a spectrum of options, defined the conduct to be carried out. This conduct was not transmitted to the team responsible for the patient and did not influence patient's management. The spectrum of options comprised the following: maintain the actual conduct, fluid replacement, red blood cells transfusion, increase or de-

crease doses of noradrenaline infusion, start, increase or decrease the rate of dobutamine infusion or administer diuretics. Moreover, at a second phase, the intensivist was informed about which of the blood bases were drawn from the distal port of pulmonary artery catheter and was asked to reevaluate his conduct, considering as appropriate a mixed venous oxygen saturation of 65%

### STATISTICAL ANALYSIS

Sample size was calculated to determine presence of correlation between two quantitative variables, using a two-tailed test, with a significance level of 0.05 and a power of 0.80. The alternative hypothesis was considered as the existence of correlation with  $r=0.8$  and the null hypothesis as the inexistence of correlation with  $r=0.4$ . Calculated sample size was 44. All analyses were carried out in the Stplan software version 4.1 for correlation tests in normal distribution samples.

Results were expressed as mean  $\pm$  standard deviation or median (25-75% interval). Statistical analysis was performed using paired T-Student test and linear correlation. Results were considered significant if  $p \leq 0.05$ . In agreement analysis between venous oxygen saturation the Bland-Altman test was applied for the following comparison: superior vena cava versus pulmonary artery and right atrium versus pulmonary artery. Results were expressed as bias  $\pm$  standard deviation (limits of agreement). In this analysis, individuals were classified in two subgroups: patients with cardiac index below or above  $3.5 \text{ l/min/m}^2$ .

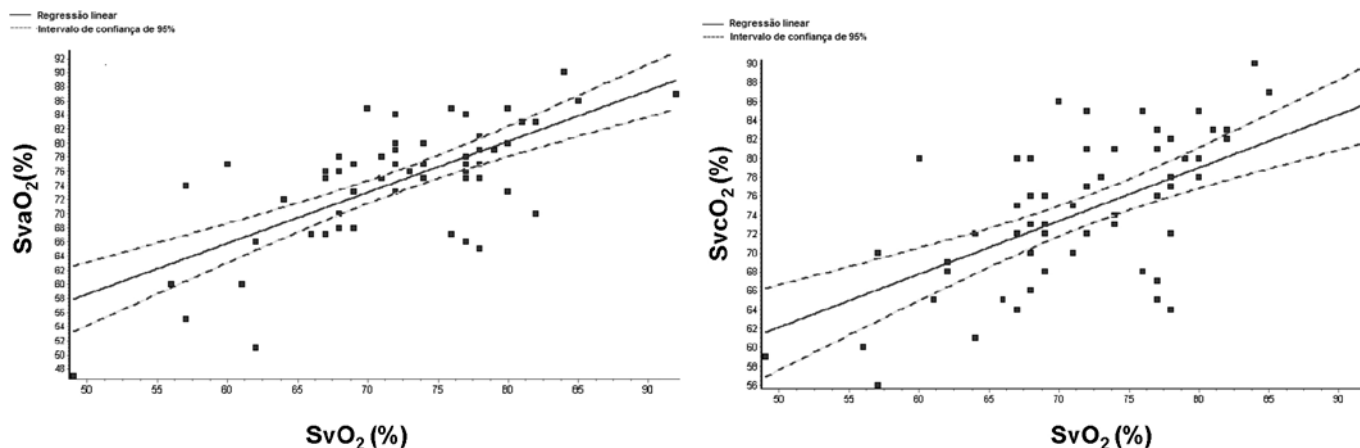
### RESULTS

Sixty-one measurements from 23 patients were analyzed, 10 were men (43.5%) and 13 women (56.5%), median age of 65.0 (49.0-75.0) years and mean APACHE II of  $27.7 \pm 6.3$ . Patients were distributed as follows: 43.5% elective surgery, 34.8% emergency surgery and 21.7% clinical.

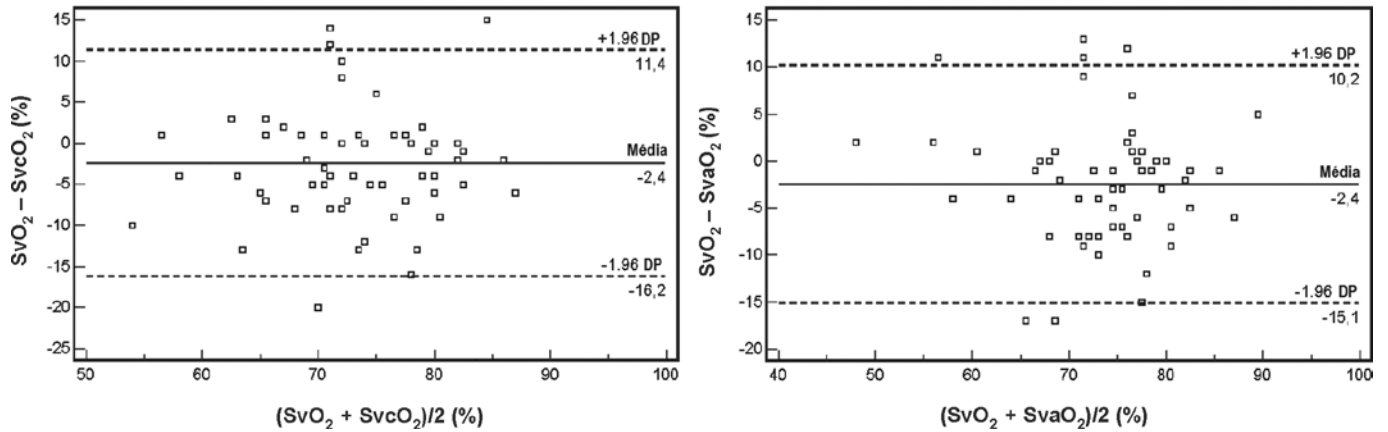
Mean values for  $\text{SvO}_2$ ,  $\text{SvcO}_2$  and  $\text{SvaO}_2$  were  $72.20 \pm 8.26\%$ ,  $4.61 \pm 7.60\%$  and  $74.64 \pm 8.47\%$ , respectively, with a significant difference both for  $\text{SvcO}_2$  ( $p=0.01$ ) and for  $\text{SvaO}_2$  ( $p=0.04$ ) when compared to  $\text{SvO}_2$ . Linear correlation test showed a weak correlation between  $\text{SvO}_2$  and  $\text{SvcO}_2$  ( $r=0.61$ ,  $p<0.0001$ ) and between  $\text{SvO}_2$  and  $\text{SvaO}_2$  ( $r=0.70$ ,  $p<0.0001$ ), with a stronger correlation in the latter case (Figure 1). When analyzed by Bland-Altman agreements between  $\text{SvcO}_2/\text{SvO}_2$  and  $\text{SvaO}_2/\text{SvO}_2$  were, respectively,  $-2.40 \pm 1.96$  (-16.20 and 11.40) and  $-2.40 \pm 1.96$  (-15.10 and 10.20) (Figure 2).

When the subgroup of patients with high cardiac index ( $>3.5 \text{ l/min/m}^2$ ) was considered, results of Bland-Altman showed a bias of  $-2.20 \pm 1.96$  (-18.30 and 15.80) and  $-2.90 \pm 1.96$  (-16.40 and 10.60), respectively for  $\text{SvcO}_2/\text{SvO}_2$  and  $\text{SvaO}_2/\text{SvO}_2$  (Figure 3). In patients with cardiac index below  $3.5 \text{ l/min/m}^2$  these values were  $-2.20 \pm 1.96$  (-13.20 and 8.00) and  $-1.90 \pm 1.96$  (-13.50 and 9.80) (Figure 4).

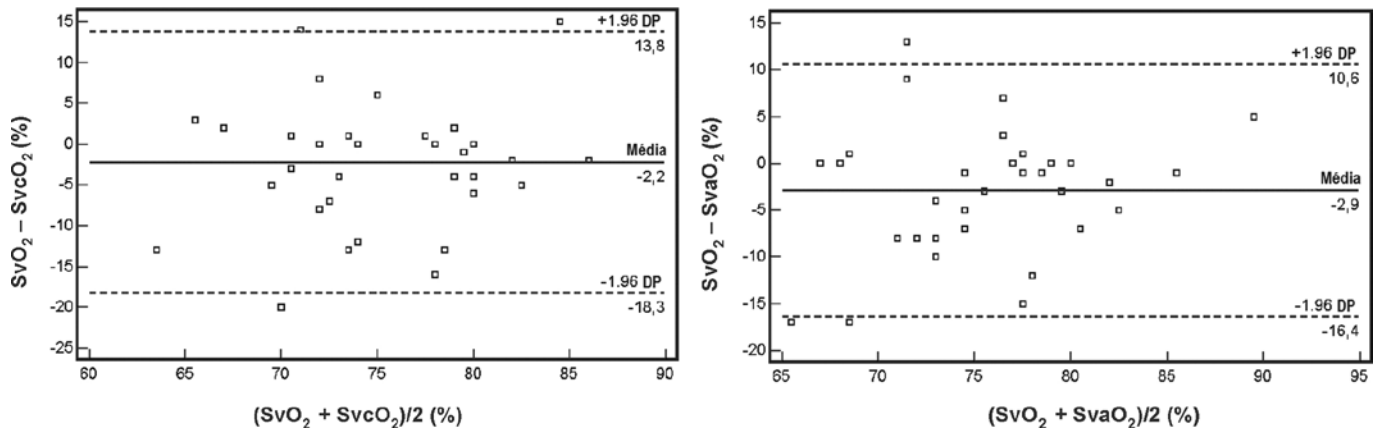
There was no agreement in the clinical management for 27.8% of cases, neither for comparison between  $\text{SvcO}_2/\text{SvO}_2$  or for  $\text{SvaO}_2/\text{SvO}_2$  analysis. In most cases (57 samples, 93.4%), both measurements ( $\text{SvcO}_2$  and  $\text{SvaO}_2$ ) agreed or disagreed simultaneously from  $\text{SvO}_2$ .



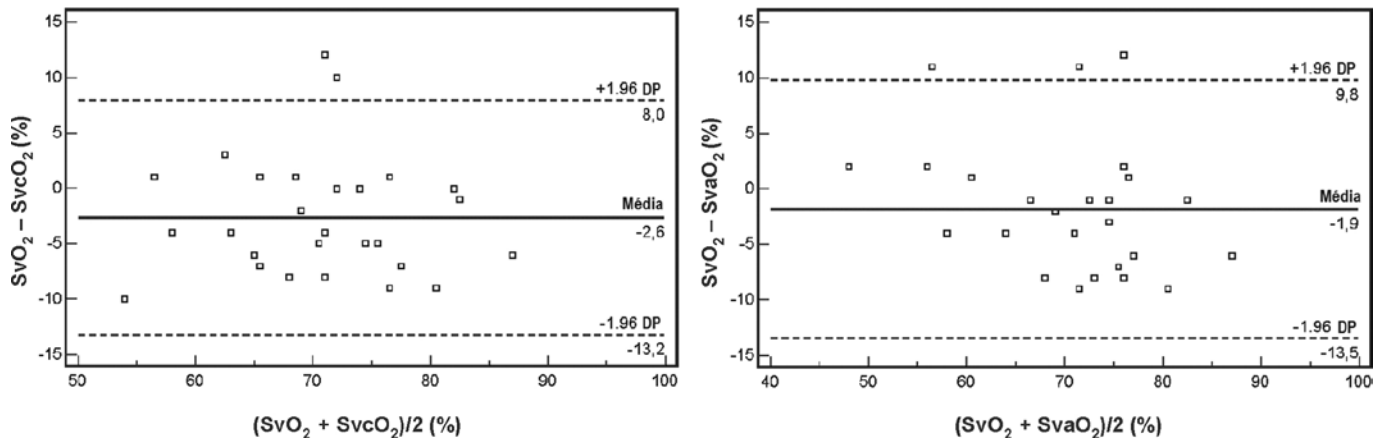
**Figure 1 – Linear correlation between measurements.** Linear correlation test showed a weak correlation between mixed venous oxygen saturation ( $\text{SvO}_2$ ) and central venous oxygen saturation ( $\text{SvcO}_2$ ) as well as between  $\text{SvO}_2$  and atrial venous oxygen saturation ( $\text{SvaO}_2$ ).



**Figure 2 – Agreement between measurements.** Bland-Altman test showed a reasonable bias but high limits of agreement between mixed venous oxygen saturation ( $SvO_2$ ) and central venous oxygen saturation ( $SvcO_2$ ) as well as between  $SvO_2$  and atrial venous oxygen saturation ( $SvaO_2$ ).



**Figure 3 – Agreement analysis in the subgroup of patients with cardiac index above 3.5l/min/m<sup>2</sup>.** Bland-Altman test showed a reasonable bias but high limits of agreement between mixed venous oxygen saturation ( $SvO_2$ ) and central venous oxygen saturation ( $SvcO_2$ ) as well as between  $SvO_2$  and atrial venous oxygen saturation ( $SvaO_2$ ).



**Figure 4 – Agreement analysis in the subgroup of patients with cardiac index below 3.5l/min/m<sup>2</sup>.** Bland-Altman test showed a reasonable bias but high limits of agreement between mixed venous oxygen saturation ( $SvO_2$ ) and central venous oxygen saturation ( $SvcO_2$ ) as well as between  $SvO_2$  and atrial venous oxygen saturation ( $SvaO_2$ ).

Only four patients disclosed a divergent behavior: two cases where  $SvaO_2$ , but not  $SvcO_2$ , agreed with  $SvO_2$  and two with the opposite situation (agreement with  $SvcO_2$  but not with  $SvaO_2$ ). When the intensivist was oriented to consider adequate a mixed venous saturation of 65%, the percentage of disagreement was 11.5% both for  $SvcO_2$  and for  $SvaO_2$ .

## DISCUSSION

This study showed a weak correlation between  $SvcO_2$  and  $SvO_2$  ( $r=0.61$ ). Moreover, although the bias shown by Bland-Altman is relatively small (-2.40), limits of agreement were very high as shown in previous studies.<sup>(5-7)</sup> In relation to  $SvaO_2$ , correlation values were better, but limits of agreement remained high. These results indicated that, at least from the statistical point of view, replacement of  $SvO_2$  for  $SvcO_2$  or  $SvaO_2$  remains questionable. This hypothesis was confirmed in the assessment of clinical agreement when, in most cases, different conducts were adopted based upon these measurement.

It is noteworthy that when the role of measuring venous oxygen saturation as a therapeutic target in hemodynamic resuscitation is analyzed, the best evidences come from the study by Rivers et al.<sup>(4)</sup> This study, of patients admitted to an emergency room with severe sepsis or septic shock, demonstrated a 15% mortality reduction when a  $SvcO_2$  above 70% was reached, in addition to maintain arterial pressure, central venous pressure and urinary output at predefined levels. In other words, to date, the only study, that validated venous saturation as a target, used  $SvcO_2$  and not  $SvO_2$ .

Therefore and due to the statistical and clinical disagreement herein shown it could be question if, in patients monitored with pulmonary artery catheter,  $SvO_2$  could be used in place of  $SvcO_2$  during the resuscitation phase with the same value used by Rivers et al., as therapeutic target.<sup>(4)</sup> This controversy was already addressed and, based on previous studies,<sup>(5-6)</sup> an agreement was reached that the target value should be changed to 65%. Currently, the *Surviving Sepsis Campaign* also endorses this recommendation as part of the initial management of patients with severe sepsis. Our study, however, does not support this recommendation as shown by the high limits of agreement and variations in clinical management, even when the target was set at 65% for  $SvO_2$ .

Knowing the determinants for these differences between  $SvO_2$  and  $SvcO_2$  might assist in the correct inter-

pretation of the results found.<sup>(10)</sup> As such it could initially be believed that cardiac output would influence the agreement between  $SvcO_2$  and  $SvO_2$ . In situations of high cardiac output we hypothesized that this difference might be greater, as the blood drained from the coronary sinus tends to have a lower saturation due to increased myocardial oxygen consumption. However, it should be noted that the oxygen extraction fraction is already very high and that myocardial capacity to significantly increase extraction remains questionable.<sup>(11)</sup> The reversal rationale is also possible. In conditions of inadequate cardiac output a more pronounced difference is to be expected as, in these situations, a redistribution of blood flow to brain and heart instead of a splanchnic and renal circulation, would lead to decreased saturation of the blood coming from the inferior vena cava. Some authors demonstrated that the difference between  $ScvO_2/SvO_2$  was inversely correlated with cardiac output.<sup>(7, 12)</sup> This reinforces the importance of the latter hypothesis to explain the influence of different profiles of cardiac output on the relation between  $SvO_2$  and  $SvcO_2$ . However, our study did not find any difference in the venous oxygen saturation agreement when patients were classified according to the cardiac index ( $>$  or  $<$   $3.5l/min/m^2$ ). This finding could be due to the fact that patients were, in general, adequately resuscitated. In the early phase of resuscitation there would be a greater chance of finding patients with an inadequate cardiac output and, consequently, a decrease of splanchnic venous oxygen saturation, with consequent decrease of inferior vena cava oxygen saturation. In this situation, it would be easier to identify possible correlations of cardiac output with the differences in saturations. Furthermore it is known that the absolute value of cardiac output does not define adequacy of this output to metabolic demand.

The better correlation found between  $SvaO_2$  and  $SvO_2$  corroborated the hypothesis of an important role for inferior vena cava saturation in the determination of agreement between  $SvcO_2$  and  $SvO_2$ , as previously demonstrated.<sup>(13)</sup> This suggests that a mixture of blood from superior and inferior cava really occurs at atrial level and reinforces this hypothesis as a responsible factor for the difference found between  $SvO_2$  and  $SvcO_2$ . However, it should be emphasized that this study did not aim to directly compare  $SvaO_2$  with  $SvcO_2$ .

Our study has some strengths. It analyzed a reasonably homogeneous population, including only septic patients. Sample collection was performed in a prospective manner with technical adequacy to assure the

quality of the blood gases analysis. Moreover, determination of the sample size and assessment of the clinical agreement were made *a priori* besides the adequate statistical analysis. In this clinical assessment, the intensivist was blind, without knowing to which subgroup patients belonged.

Some limitations should be pointed out. The first is that it included more than one measurement from the same patient. This can influence the analysis, if more samples from patients with a low agreement between SvO<sub>2</sub> and SvcO<sub>2</sub> were used.<sup>(10)</sup> Another issue, from the methodological point of view was related to the atrial sample, as the position of the catheter was confirmed only by presence of a typical pressure curve. Samples could have been collected from different points at atrial level and this could have influenced results.<sup>(13)</sup> Moreover, no analysis was performed considering the time of resuscitation in the patients and this fact, as already stated, may influence the agreement between saturations. Finally, use of an isolated measurement and not the trend in face of interventions can also be considered a limitation for clinical assessment, even when minimized because the intensivist took into account the entire clinical picture and other perfusion measures.

## CONCLUSION

This study shows that correlation and agreement between SvO<sub>2</sub> and SvcO<sub>2</sub> are weak and can lead to different clinical conducts. Moreover, using a SvO<sub>2</sub> of 65% as an equivalent therapeutic target to a SvcO<sub>2</sub> of 70% might be inadequate.

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## RESUMO

**Introdução:** A medida da saturação venosa central de oxigênio (SvcO<sub>2</sub>) tem sido proposta como alternativa a saturação venosa mista (SvO<sub>2</sub>), com grau de concordância variável nos dados atualmente disponíveis. Esse estudo objetivou avaliar as possíveis diferenças entre a SvO<sub>2</sub> e a SvcO<sub>2</sub> ou saturação venosa atrial de oxigênio (SvaO<sub>2</sub>), com ênfase na interferência do débito cardíaco, e o impacto delas no manejo clínico do paciente séptico.

**Métodos:** Estudo prospectivo observacional em pacientes com choque séptico monitorizados com cateter de artéria pulmonar. Foi obtido sangue simultaneamente para determinação da SvcO<sub>2</sub>, SvO<sub>2</sub> e SvaO<sub>2</sub>. Realizado testes de correlação linear (significativos se p<0,05) e análise de concordância (Bland-Altman) entre as amostras e nos subgrupos de débito cardíaco. Além disso, foi avaliada a concordância entre condutas clínicas baseadas nessas medidas.

**Resultados:** Foram obtidas 61 medidas de 23 pacientes, mediana de idade de 65,0 (49,0-75,0) anos, APACHE II médio de 27,7±6,3. Os valores médios encontrados foram 72,20±8,26%, 74,61±7,60% e 74,64±8,47% para SvO<sub>2</sub>, SvcO<sub>2</sub> e SvaO<sub>2</sub>. O teste de correlação linear mostrou baixa correlação tanto entre a SvO<sub>2</sub> e a SvcO<sub>2</sub> (r=0,61, p<0,0001) quanto entre a SvO<sub>2</sub> e a SvaO<sub>2</sub> (r=0,70, p<0,0001). As concordâncias entre SvcO<sub>2</sub>/SvO<sub>2</sub> e SvaO<sub>2</sub>/SvO<sub>2</sub> foram, respectivamente, de -2,40±1,96 (-16,20 e 11,40) e -2,40±1,96 (-15,10 e 10,20), sem diferença nos subgrupos de débito cardíaco. Não houve concordância na conduta clínica em 27,8% dos casos, tanto entre SvcO<sub>2</sub>/SvO<sub>2</sub> como de SvaO<sub>2</sub>/SvO<sub>2</sub>.

**Conclusão:** Esse estudo mostra que a correlação e a concordância entre SvO<sub>2</sub> e SvcO<sub>2</sub> é baixa e pode levar a condutas clínicas diferentes.

**Descritores:** Oximetria/métodos; Oxigênio/sangue; Choque séptico/sangue

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