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Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock

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Abstract *Objective:* Central venous oxygen saturation ($ScvO_2$) in initial resuscitation is included in the Surviving Sepsis Campaign guidelines. $ScvO_2$ monitoring has also been suggested to be comparable to mixed venous oxygen saturation (SvO_2) for clinical purposes. The aim of our study was to assess the correlation and agreement of $ScvO_2$ and SvO_2 and compare $ScvO_2$–SvO_2 difference to lactate, oxygen-derived and hemodynamic parameters in early septic shock in ICU after initial resuscitation. *Design and setting:* Prospective clinical study with 16 patients with septic shock at two university hospital ICUs. A dose of norepinephrine over 0.1 μg/kg/min was required for inclusion. *Measurements and results:* Five paired $ScvO_2$ and SvO_2 samples at 6-h intervals, altogether 72 samples, were collected during 24 h. The mean SvO_2 was below the mean $ScvO_2$ at all time points. Bias of difference was 4.2% and 95% limits of agreement ranged from –8.1% to 16.5%. The difference correlated significantly to CI and DO_2. *Conclusions:* The difference between paired $ScvO_2$ and SvO_2 varies highly. Therefore, SvO_2 may not be estimated on the basis of $ScvO_2$ in treatment of septic shock after resuscitation period in ICU.

Keywords Sepsis · Septic shock · Hemodynamic monitoring · Outcome

Introduction

Early goal-directed therapy (EGDT), aiming at central venous oxygen saturation ($ScvO_2$) over 70% during the first 6 h, has been shown to reduce mortality among patients with severe sepsis and septic shock [1], and the use of $ScvO_2$ in initial resuscitation has been applied also to sepsis guidelines [2]. While $ScvO_2$ is an excellent tool in the resuscitation period of shock, there is still controversy as to whether it is a suitable parameter for follow-up afterwards during ICU treatment.

Mixed venous oxygen saturation (SvO_2) is commonly used to monitor patient hemodynamics in ICUs. SvO_2 predicts mortality in sepsis [3, 4], although there is no clear evidence of its value as a treatment target. Instead of SvO_2, $ScvO_2$ monitoring has been suggested to be useful for clinical purposes [5, 6]. This is mainly based on the fact that low $ScvO_2$ indicates even lower SvO_2, and that the trends of $ScvO_2$ generally agree with those of SvO_2 [6, 7, 8]. However, most studies that have investigated the relationship of $ScvO_2$ and SvO_2 in critically ill patients have shown marked differences between the two, with $ScvO_2$ being higher than SvO_2 [9, 10, 11, 12]. Individual values in shock state may differ up to 18–22% [6, 10, 12]. In fact, none of the previous studies confirms $ScvO_2$ either as an independent predictor of mortality or as

Table 1 Studies relating SvO_2 and $ScvO_2$ in septic patients with Bland–Altman analysis

Study	Patients No.		No. paired samples	Bias	95% Limits of agreement
	All patients	Patients with sepsis			
Edwards et al. [10]	30	11	30	2.9%	–14.4%, 21.6%
Martin et al. [31]	7	7	580**	1.1%	–18.9%, 21.1%
Tumaoglu et al. [9]	73	41	41*	6.4%*	–7.1%, 14.1%
Chawla et al. [37]	53	13	53	5.2%	–5.2%, 15.5%
Reinhart et al. [6]	29	11	150	7.1%	–0.9%, 15.0%

* Only sepsis patients included
** Continuous measurement

a measure to guide the treatment after initial resuscitation phase.

Our assumption is that an acceptable level of $ScvO_2$ during ICU treatment, when $ScvO_2$ is mostly normal or elevated, is not straightforward, and $ScvO_2$ cannot be used as a surrogate of SvO_2 or as a target in the treatment of septic shock after the resuscitation period. Although this difference has been evaluated in a few previous investigations (Table 1), no study has assessed its value in a homogeneous group of early severe septic shock defined as a moderate need of norepinephrine to maintain adequate perfusion pressure. The aim of our study was to evaluate the correlation and agreement of $ScvO_2$ and SvO_2 and also compare the $ScvO_2$–SvO_2 difference to lactate, oxygen-derived and hemodynamic parameters during early severe septic shock in ICU after initial resuscitation.

Materials and methods

Our prospective study was conducted in two Finnish ICUs from November 2004 to June 2005 after approval by the local ethics committees. Sixteen patients with septic shock fulfilling the criteria set by the APCCP/SCCM Consensus Conference [13] – known or suspected infection with systemic inflammatory response syndrome, sepsis-induced hypotension, and need for vasopressor after adequate fluid resuscitation – were included. Norepinephrine dose over 0.1 μg/kg/min for maintaining mean arterial blood pressure over 65 mmHg was required for inclusion. Standard management of septic shock included fluid resuscitation and the use of norepinephrine as the primary vasopressor and dobutamine as the primary inotrope according to the SCCM sepsis guidelines [2]. The treatment targets were mean arterial pressure (MAP) over 65 mmHg, pulmonary artery occlusion pressure (PAOP) of 12–16 mmHg, and SvO_2 over 65%. All patients required ventilator treatment. Propofol or midazolam infusions combined with fentanyl were used for sedation.

An arterial catheter and a four-lumen pulmonary artery catheter (PAC) with introducer (7.5 F Paceport Oximetry TD Catheter with AMC Thromboshield 780HF75, Edwards Lifesciences LCC, Irvine, CA, USA) were inserted for hemodynamic monitoring. A typical wedge pressure tracing with the balloon inflated and chest X-ray confirmed the correct placement of the catheter in the zone-3 position. The correct location of the introducer tip in the superior vena cava (SVC) was confirmed with chest X-ray. For the measurements, SvO_2 samples were simultaneously drawn slowly from the distal port of the unwedged PAC, $ScvO_2$ samples from the side port of the introducer and arterial samples via the arterial catheter. The side port of the introducer instead of the proximal port of the PAC was chosen for more reliable placement in the SVC.

Baseline samples were drawn immediately after patient inclusion and every 6 h thereafter up to 24 h. Altogether five paired $ScvO_2$ and SvO_2 samples were obtained for each patient unless the patient expired or because of technical reasons. Blood gas analyses were performed and oxygen saturations were determined photospectrometrically with a CO oximeter (Ciba-Corning 850 and 855, Medfield, MA, USA). Hemodynamic measurements were performed immediately after blood sampling. Cardiac output (CO) was determined with thermodilution method by injecting 10 ml of isotonic saline through proximal port of PAC. Ice-cold solution was used if cardiac index (CI) was found to be below 2.5 l/min/m^2. CI was computed by dividing CO by the patient's body surface area. Three to five measurements were obtained and averaged. Oxygen extraction rates (O_2ER), oxygen delivery (DO_2) and oxygen consumption (VO_2) were calculated by using standard formulas. Arterial plasma lactate level was measured with a photometric method.

Statistical analysis

To evaluate the agreement between $ScvO_2$ and SvO_2, bias (systematic error) was determined by the method described by Bland and Altman [14], where bias is expressed as the mean of the differences between paired values ($\Delta[ScvO_2–SvO_2]$). Ninety-five percent limits of agreement were calculated. Correlation between $ScvO_2$ and SvO_2 was determined with intraclass correlation, and comparison of saturation values in different time points and according to different levels of $ScvO_2$ was performed with the nonparametric Friedman test. The normality of

continuous variables was tested with the Kolmogorow–Smirnov test. $\Delta[ScvO_2–SvO_2]$ was compared to common hemodynamic and perfusion variables with Spearman correlation for assessing possible factors affecting to the $ScvO_2–SvO_2$ gradient.

Results

Altogether 72 paired blood samples were obtained from 16 patients with septic shock. Patient characteristics are shown in Tables 2 and 3. The source of sepsis was pneumonia in six cases (38%), peritonitis in six (38%), meningitis in one (6%), pyelonephritis in one (6%), and undetermined or unknown in two cases (13%). Five patients (31%) had positive blood culture. The first blood samples were taken 5.0 h (range 2.8–14.0 h) after ICU admission and 8.5 h (3.3–12.6 h) after onset of severe sepsis. One patient died within 24 h. Five paired samples were missed due to technical reasons. The hospital mortality was 38% (6 of 16).

Simultaneous values of $ScvO_2$ and SvO_2 are shown in Fig. 1. The intraclass correlation of paired $ScvO_2$ and

Table 2 Characteristics of the patients ($n = 16$), expressed as median (interquartile range) or number (percentage)

Age	51 (44–62)
Gender male	13 (81%)
APACHE II	23 (18–29)
SOFA day 1	10 (9–12)
Dose of norepinephrine (microg/kg/min)*	0.26 (0.16–0.36)
MAP (mmHg)*	69 (64–75)
Paop (mmHg)*	17 (13–20)
Lactate (mmol/L)*	2.8 (1.4–4.9)
CVP (mmHg)*	15 (10–17)
Dobutamine	9 (56%)
Hydrocortisone substitution	8 (50%)
Activated protein C	2 (13%)
Hospital mortality	6 (38%)

* On the time of first blood samples

Table 3 Oxyhemoglobin Saturations and Hemodynamic parameters during study ($n = 72$ samples)

SvO_2 (%)	68 (60–73)
$ScvO_2$ (%)	70 (63–80)
SaO_2 (%)	97 (93–99)
Paop (mmHg)	17 (13–20)
CVP (mmHg)	14 (10–16)
Cl (L/min/m2)	3.5 (2.8–4.3)
SVR (dyn × s/cm^5)	655 (479–824)
DO_2 (mL/min)	921 (723–1245)
VO_2 (mL/min)	285 (223–346)
B-Hb (mg/L)	97 (85–109)
Body temperature (°C)	37.1 (36.5–37.9)

Values are expressed as median (interquartile range)

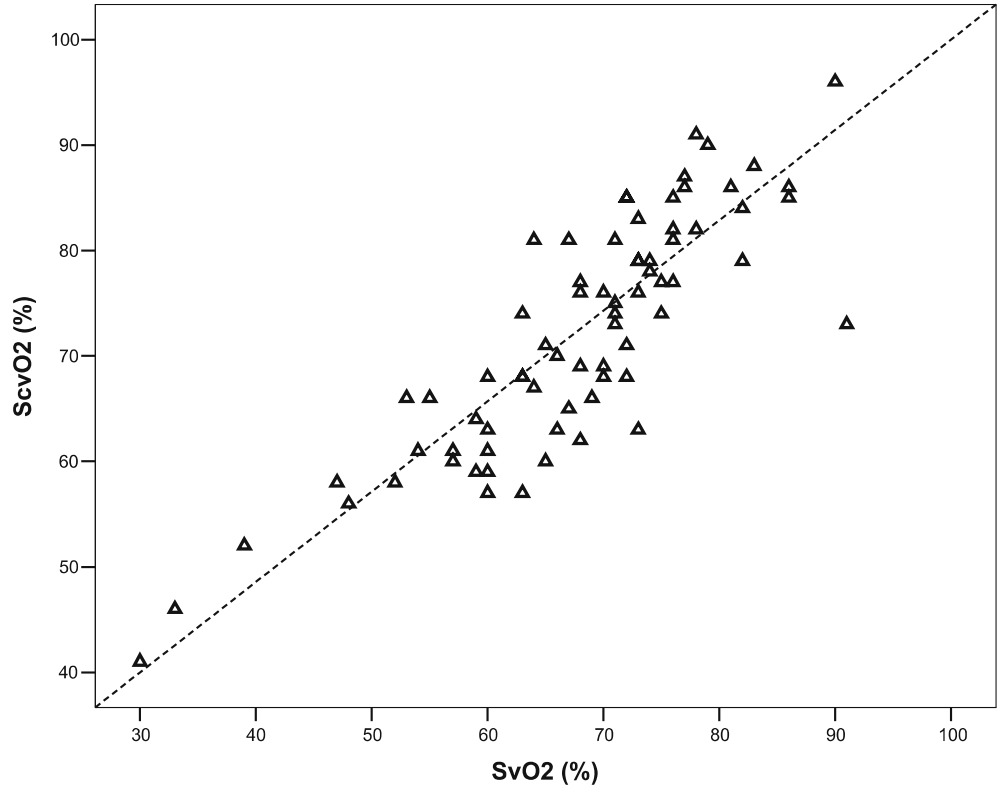

Fig. 1 Paired samples of mixed venous oxygen saturation (SvO_2) and central venous oxygen saturation ($ScvO_2$): $n = 72$, intraclass correlation coefficient 0.89 (95% CI 0.82–0.93, $p < 0.001$). The *dotted line* represents the line of equality

SvO_2 was highly significant (intraclass correlation coefficient 0.89, 95%CI 0.82–0.93, $p < 0.001$). Mean SvO_2 was below mean $ScvO_2$ at all time points (Fig. 2). The agreement between $ScvO_2$ and SvO_2 by Bland–Altman plot is presented in Fig. 3, where the bias of difference is 4.2% and 95% limits of agreement were –8.1% to 16.5%. The Bland–Altman plots at each time point separately showed bias of difference from 1.9% to 5.6% (95% limits of agreement ranging from –14.1% to –5.2% to 14.5%–17.9%). These are shown in the Electronic Supplementary Material (ESM, S.F1–F5) as well as the individual oximetric and hemodynamic values during study (ESM, S.T1). $\Delta[ScvO_2–SvO_2]$ correlated inversely to CI ($p = 0.036$) (Fig. 4) and to DO_2 ($p = 0.007$), but no correlation to other measured variables or to dose of norepinephrine was detected (Table 4).

No significant change was found in average $\Delta[ScvO_2–SvO_2]$ over time (Fig. 2), but $\Delta[ScvO_2–SvO_2]$ was dependent on the level of $ScvO_2$ when values of $< 60\%$, 60–70%, 70–80% and $> 80\%$ were analyzed separately. The mean $\Delta[ScvO_2–SvO_2]$ values were 5.2%, 1.5%, 2.9% and 8.1%, respectively. This showed statistical significance ($p = 0.003$).

Changes in $ScvO_2$ and SvO_2 were parallel in 55% (95% CI 41%–69%) of two successive measurements (both measurements changed at the same time to the same direction compared with previous measurements, ESM S.F6).

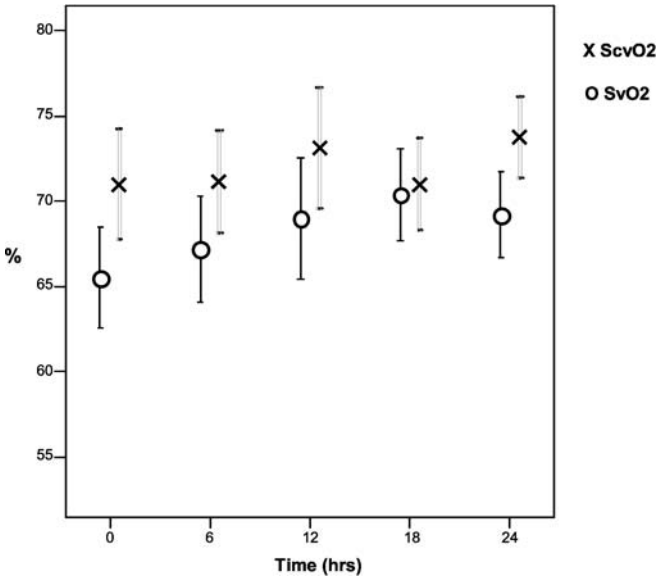

Fig. 2 Mean SvO_2 (*circles*) and $ScvO_2$ (*crosses*) with SE at different time points during the study. The difference between SvO_2 and $ScvO_2$ in different time points was not statistically significant by Friedman test ($p = 0.48$)

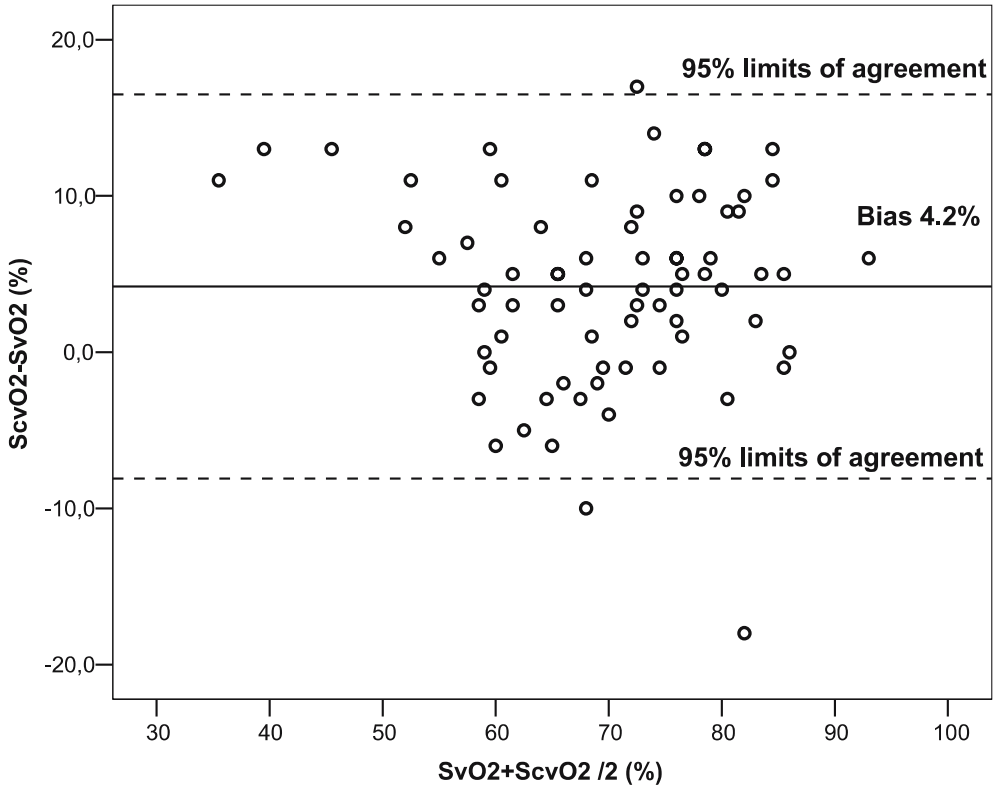

Fig. 3 Bland–Altman plot of the differences between SvO_2 and $ScvO_2$ against their mean values. The *unbroken line* indicates the mean difference (bias), the *broken lines*, the 95% limits of agreement.

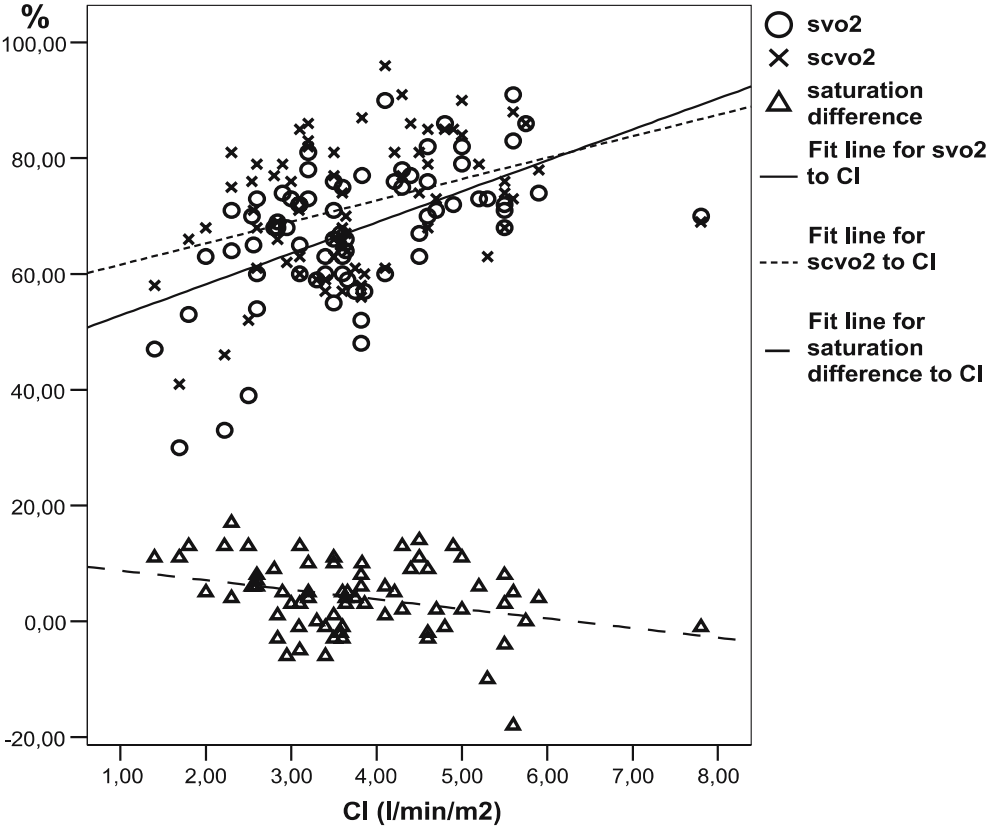

Fig. 4 SvO_2, $ScvO_2$ and $\Delta[ScvO_2–SvO_2]$ correlation to cardiac index (CI). *Circles* SvO_2, *crosses* $ScvO_2$, *triangles* $\Delta[ScvO_2–SvO_2]$; $n = 72$; $r = 0.52$ for SvO_2–CI, $r = 0.38$ for $ScvO_2$–CI, $r = –0.25$ for $\Delta[ScvO_2–SvO_2]$–CI by Spearman correlation

Table 4 Spearman correlations of SvO_2, $ScvO_2$ and $\Delta[ScvO_2–SvO_2]$ with hemodynamic, oxygen-derived and laboratory variables

	SvO_2	$ScvO_2$	$\Delta[ScvO_2–SvO_2]$
PaO_2	0.44**	0.43**	0.09
$PaCO_2$	0.23	0.23	0.05
SaO_2	0.25*	0.27*	0.15
pH	0.12	0.13	–0.09
BE	0.26	0.36	0.04
MAP	0.39**	0.42**	–0.06
Paop	–0.11	–0.27	0.03
Cl	0.52**	0.38**	–0.25*
CO	0.38**	0.26*	–0.28*
DO_2	0.42**	0.24*	–0.33**
VO_2	–0.31**	–0.38**	–0.15
O_2ER	–0.87**	–0.74**	0.19
P-lactate	–0.33	–0.41	–0.13
Body temperature	–0.21	–0.19	0.01
B–Hb	0.16	0.12	–0.13

* $p < 0.05$
** $p < 0.01$

Discussion

Our study showed that in early severe septic shock, despite a statistically significant correlation, the agreement of $ScvO_2$ and SvO_2 is not adequate. For clinical use this variability makes the accurate conception of the values difficult. $\Delta[ScvO_2–SvO_2]$ was not dependent on the time point of treatment but the difference varied according to the level of $ScvO_2$, being greatest in very low and high values. Low oxygen delivery and cardiac output led to increased difference between $ScvO_2$ and SvO_2. In addition, for clinical decisions it is noteworthy that $ScvO_2$ and SvO_2 changed in the same direction in only 55% of cases.

$ScvO_2$ is a mixture of venous blood from the upper body, while SvO_2 reflects the flow-weighted oxygen balance of the whole body. In early shock, despite its etiology, both saturation values are commonly decreased and thus $ScvO_2$ has been shown to be excellent in emergency

departments to detect a shock in emergency situations [15, 16, 17, 18]. $ScvO_2$ reflects accurately hypovolemia, which is common in septic patients first presenting in ED [19, 20]. The EGDT study showed that $ScvO_2$ is useful in guiding the resuscitation of early septic shock targeting to $ScvO_2$ over 70% during the first 6 h in ED [1]. However, whether we can extrapolate this goal to patients who are treated after the resuscitation period in ICUs is not clear at all.

In the study conducted by Reinhart et al., evaluating critically ill patients during an average of 56 h with continuous measurement of $ScvO_2$, over 87% of the values of nonsurvivors and 95% of those of survivors were over 70% [6]. According to our opinion this may suggest that $ScvO_2$ of 70% as a treatment goal in septic shock after the resuscitation period is insensitive for the detection of tissue oxygen demand. In our previous study we showed that the area of SvO_2 values under 70% in the first 24 h of treatment in ICU was a significant predictor of mortality independent of cardiac output or arterial saturation [4]. Because $\Delta[ScvO_2–SvO_2]$ varies extensively, the estimation of adequacy of SvO_2 on the basis of $ScvO_2$ level seems impossible. In general, this pronounced variability is in agreement with other studies, although inclusion criteria similar to our study have not been used, and also non-septic critically ill patients have been included in most of them. Table 1 shows the degree of bias and limits of agreement (ranging from –18 to +21%) of paired SvO_2 and $ScvO_2$ in previous studies. However, there is only indirect evidence that the use of SvO_2 to guide the treatment is beneficial either. Pölönen and colleagues found reduced hospital stay and morbidity with SvO_2-targeted goal-oriented postoperative treatment after cardiac surgery [21], but using SvO_2 as a treatment goal has not improved outcome in prospective trial [22].

The gradient between SvO_2 and $ScvO_2$ depends on the oxygen consumption and the amount of blood flow in various organs between the upper and the lower body. We found a reversed correlation of $\Delta[ScvO_2–SvO_2]$ to CI and DO_2. Distribution of blood flow in low-flow condition away from renal, splanchnic and mesenteric circulation toward cerebral and myocardial perfusions are likely to explain this phenomenon. The significant differences in CI and DO_2I depending on the difference between $ScvO_2$ and SvO_2 were also noted by Turnaoglu and colleagues [9], and the correlation between SvO_2 and $ScvO_2$ in general has been poorer in hypodynamic shock [12, 23]. In sepsis, the possible reasons for $\Delta[ScvO_2–SvO_2]$ also include increased oxygen consumption in the hepatosplanchnic region and mixing of the less saturated blood from the coronary sinus in the right atrium, which both decrease the SvO_2, while decreased cerebral oxygen uptake during sedation increases $ScvO_2$.

Tissue hypoxia in the splanchnic area is considered to be an important cofactor in the pathogenesis of multiple organ failure in sepsis [24], and inadequate regional perfusion in the hepatosplanchnic area may also influence the outcome [25]. Hepatic venous saturation may be highly depressed in sepsis, and perfusion is even further influenced by the use of vasoactive treatment [26, 27, 28]. The hypoperfusion within the hepatosplanchnic region may persist even after the early correction of hypovolemia when global hemodynamic variables appear adequate [29, 30]. Regional hypoperfusion is not detected accurately with SvO_2 measurement [26, 27], but theoretically it is better detected with SvO_2 than with $ScvO_2$. To the best of our knowledge, the relationship between oximetric values from hepatic vein or inferior vena cava and $ScvO_2$ have been investigated only in one study. In this study the difference was more pronounced between inferior vena cava and $ScvO_2$ than for SvO_2, but the patient population was small [12]. Nearly 20% of abrupt changes over 10% of SvO_2 cannot be detected with $ScvO_2$ in severe sepsis or septic shock [31], and 33% of sudden changes of SvO_2 cannot be explained by therapeutic interventions or alterations in hemodynamic measurements. These differences are probably caused by fluctuations in tissue oxygen demands in hepatosplanchnic region [32].

Coronary venous oxygen saturation is very low in the normal situation due to the high oxygen extraction rate of the myocardium [33]. In sepsis, coronary blood flow is increased as a consequence of coronary vasodilatation while oxygen extraction remains high [34]. This leads to the elevation of $\Delta[ScvO_2–SvO_2]$ by the mixing of coronary venous blood of lower oxygen saturation in the right atrium.

The impact of coronary mixing was highlighted in a recent trial that detected a decrease not only in oxygen saturations but also in lactate concentrations when comparing samples from proximal and distal ports of PAC in critically ill patients. Because the lactate concentration in coronary venous blood is very low, unlike in inferior venous blood, the authors suggested that the decrease between $ScvO_2$ and SvO_2 originate from mixing the coronary blood, not the inferior venous blood. They concluded that the phenomenon might reflect changes in myocardial energy requirement [35]. Insufficient oxygen supply to the myocardium with respect to its metabolic needs may itself lead to diminished contractility and low output [36], which in turn may further increase $\Delta[ScvO_2–SvO_2]$.

A limitation of our study is small sample size. However, our patient group was homogeneous with regard to the severity and timing of septic shock. Concerning clinical decisions, not a statistically significant correlation but individual bias between the measurements is relevant, and therefore our results, a clear bias and wide limits of agreement between paired $ScvO_2$ and SvO_2, are of importance in septic shock. In correlation analysis, samples are pooled from several time points, which may have affected the results. However, we find that unlikely since the results are in accordance with previous findings.

In conclusion, both $ScvO_2$ and SvO_2 are low in early septic shock and are useful parameters in the detection of shock and during the resuscitation period. Later in the ICU

treatment period, the difference between these two oxygen saturation parameters varies highly even with comparable vasoactive treatment. Therefore, SvO_2 is not estimated on the basis of $ScvO_2$. However, the usefulness of SvO_2 itself in guiding the treatment in septic shock needs to be re-evaluated in a randomized trial using goal-oriented therapy and continuous measurements.

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