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ORIGINAL RESEARCH

Prospective evaluation of regional oxygen saturation to estimate central venous saturation in sepsis

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Abstract Current treatment guidelines for sepsis claim an early goal-directed hemodynamic optimization including fluid resuscitation, use of vasopressors and inotropic agents. We investigated the correlation between the prominent treatment goal central venous saturation ($ScvO_2$) and the frontal and the thenar regional oxygen saturation (rSO_2) measured by near infrared spectroscopy. Secondary, we examined the value of $ScvO_2$, lactate levels and rSO_2 as surrogate markers of an impaired tissue oxygenation for outcome prediction in sepsis. This prospective, observational study was performed at the surgical intensive care unit of the University Hospital Giessen. A total of 50 patients with sepsis, severe sepsis or septic shock were included. $ScvO_2$, rSO_2 and lactate were measured at sepsis diagnosis (baseline), 24 and 48 h, thereafter. We investigated the predictive value of frontal and thenar rSO_2 for a decreased $SvcO_2$ under 70 %. For survivor and non-survivors $ScvO_2$, rSO_2 and lactate were analysed. Patients with $ScvO_2$ >70 % showed a trend to higher levels of fontal rSO_2 (62.81 ± 8.06 vs. 53.54 ± 15.48; $p = 0.058$). ROC-analysis revealed a minor prediction of a decreased $ScvO_2$ by frontal rSO_2 levels at baseline (AUC = 0.687; 95 % CI 0.511–0.863; $p = 0.047$). Combined measurements of lactate and ScvO2 showed significantly elevated mortality for patients with ScvO2 ≥70 % and lactate levels ≥2.5 mmol/l (log rank test $p = 0.004$). In the group with $ScvO_2$ <70 % and lactate levels <2.5 mmol/l no patients died during the observation period. Frontal rSO_2 correlates with $ScvO_2$ but both frontal and thenar rSO2 do not exactly discriminate between patients with high or low ScvO2 in sepsis. The combination of elevated lactate >2.5 mmol/l and $ScvO_2$ >70 % is highly associated with poor outcome in ICU patients with sepsis, severe sepsis and septic shock.

Keywords Sepsis · Spectroscopy · Near infrared · Lactic acid · Central venous saturation · Oxygen consumption · Outcome assessment

1 Introduction

Severe sepsis is responsible for 6–15 % of admissions to the intensive care unit (ICU) [1–3]. In non-cardiac ICUs, sepsis is the second-leading cause for mortality with an estimated mortality rate of 30–50 %. Current treatment guidelines for sepsis, severe sepsis, and septic shock claim for early source control, antimicrobial treatment and hemodynamic stabilization including fluid resuscitation, use of vasopressors and inotropic agents [4]. Rivers et al. [5] showed that an early goal directed therapy including monitoring of the central venous oxygen saturation ($ScvO_2$) is able to improve patients' outcome in severe sepsis and septic shock. Cardiovascular failure in sepsis often induces disturbance in oxygen delivery. Following tissue hypoxia could lead to elevated lactate concentrations [6]. Numerous studies have demonstrated the use of lactate as a diagnostic and prognostic marker of global tissue

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hypoxia in critical ill and septic patients [7, 8] [9]. Current sepsis guidelines recommend an early goal directed approach including $ScvO_2$ and lactate measurements [4].

Measurement of $ScvO_2$ has been clinically approved to assess changes in oxygen delivery and consumption in various clinical settings [10]. Unfortunately this method requires frequent blood draws from a central venous catheter or the use of expensive spectrophotometric $ScvO_2$ catheters. Non-invasive monitoring methods of tissue oxygenation may provide useful information about the state of tissue oxygenation and microcirculation. A potential gain of information may be offered by near-infrared spectroscopy (NIRS).

NIRS uses computer analysis of spectra in the near-infrared range (680–800 nm) to assign regional tissue haemoglobin (Hb) oxygen saturation (rSO_2) [11]. It is used to determine cerebral and somatic tissue saturation rSO_2 via sensors placed on patients' forehead or somatic areas (thenar muscle, nephral tissue). Measurement of frontal rSO_2 by NIRS has been correlated with central venous saturation in animals and children [12, 13]. Detection of rSO_2 is also used as a surrogate for hemodynamic function [13, 14]. Even thenar rSO_2 was shown to correlate with severity of illness and outcome in sepsis [14–17]. In a previous preliminary study, we found a significant correlation between frontal rSO_2 and $ScvO_2$ in patients with severe sepsis and septic shock. A $ScvO_2$ <70 % was indicated by a rSO_2 <56.5 % with a sensitivity and specificity of 75 and 100 %, respectively [18].

The aim of the study was to investigate the correlation between $ScvO_2$ and rSO_2. As secondary aim, we examined the value of $ScvO_2$, lactate levels and rSO_2 as surrogate markers of an impaired tissue oxygenation for outcome prediction in sepsis.

2 Materials and methods

2.1 Study population

This prospective observational study was performed at the surgical ICU of the University Hospital of Giessen (Trial registration: DRKS00003327). Ethical approval for this study (ethics proposal number AZ 57/12) was obtained from the Ethics Committee of the Faculty of Medicine at the Justus-Liebig-University Giessen, Giessen, Germany (Chairman Prof. H. Tillmanns) on 12 June 2012. Patients or their legal representative gave written informed consent before study inclusion. We enrolled 50 patients within the first 6 h after onset of sepsis, severe sepsis or septic shock, defined according to the definition of the International Sepsis Definitions conference [19]. Exclusion criteria were age <18 years, history of cerebral bleeding or stroke. All patients received standardized treatment including source control, fluid infusion, catecholamine infusion, glucose control and organ failure support or replacement therapy according to the surviving sepsis guidelines [4]. Thus, the early resuscitation was goal-directed to achieve a heart rate (HR) <100/min, a mean arterial pressure (MAP) ≥60 mmHg, a central venous pressure of 8 to 12 mmHg, a urinary output ≥0.5 ml/kg/hour, and a $ScvO_2$ ≥70 %.

2.2 Measurements

For all enrolled patients we obtained and calculated values at baseline (T1) (baseline), 24 h (T2), and 48 h (T3) after inclusion. Recorded variables were age, ICU and hospital mortality, length of stay in ICU and hospital, septic focus, acute physiology and chronic health evaluation II score (APACHE II), sequential organ failure (SOFA) score, simplified acute physiology II score (SAPS II), ventilator parameters, norepinephrine dosage, HR, MAP, arterial and $ScvO_2$, Hb, arterial and venous lactate, arterial and blood gas values, and Horowitz-Index.

The INVOS 5100C oximeter (Somanetics, Troy, MI, USA) was used to obtain frontal and thenar rSO_2 measurements. The principle of clinical used NIRS is the non-invasive measurement of the attenuation of light by Hb, where the emitted light is in a wavelength range longer than visible light [20, 21]. Near-infrared spectroscopy wavelengths approximately 700–850 nm are generated by a light source of the sensor and penetrate the skin and the bone. Within the brain tissue in 2.5 cm depth the light is either absorbed or reflected to the sensor. Therefore, NIRS provides the total tissue oxy- and deoxyhemoglobin in a quantitative and qualitative manner to obtain oxygen supply and demand [20]. The measured results were expressed as a percentage of oxygen at the corresponding monitor.

The oxymetric sensors were placed after cleaning the forehead and thenar skin with alcoholic pads. Following a 5-min stabilization period, we assessed the rSO_2.

2.3 Statistical analysis

Descriptive statistics were performed for demographics, clinical characteristics, hemodynamic values and laboratory findings. Continuous variables are presented as means and standard deviations or medians with interquartile ranges, and categorical variables as numbers and percentages. Comparisons between groups were analysed by *t* test. Comparisons of categorical variables were generated by the Pearson χ^2 test. The predictive value of rSO_2 for $SvcO_2$ was calculated using receiver operator characteristic (ROC) curves and the area under the curve (AUC) was computed. Mortality analysis where performed by using Kaplan–Meier-Curves. A logistic regression analysis was

performed to investigate predictors for mortality. Probability p values ≤ 0.05 were considered statistically significant. The entire statistical analysis was performed with SPSS®, version 19.0.0 (SPSS Inc., IBM, Chicago, Illinois).

3 Results

3.1 Baseline characteristics

A total number of 50 consecutive patients with severe sepsis or septic shock were enrolled in this study. Baseline characteristics of the study population are shown in Table 1. Patients' mean age was 68.02 ± 13.52 years. The population was characterized by a significant morbidity reflected by high APACHE II Score (25.24 ± 6.76). The majority of patients required a norepinephrine therapy (84 %) to achieve an adequate circulatory status (Table 2). Almost 60 % of the patients suffered from septic shock at the time of inclusion. In the vast majority of patients, intra-abdominal or pulmonary infections were the cause of sepsis. The observed hospital mortality was 52 %. The mean rSO_2 measured at baseline (T1) was 60.4 ± 11.1 %. At least, 25 % of patients included did not achieve a $ScvO_2$ above 70 %. At baseline, 13 (26 %) patients represented $ScvO_2$ below 70 %. Surprisingly, the number of patients with a decreased $ScvO_2$ increased at the two following days compared to the initial stabilization phase (T2: 17 (43.6 %), T3: 10 (32.3 %)) (Table 2). In about 42 % of patients the measured arterial lactate was higher than 2.5 mmol/l.

At baseline, frontal rSO_2 was significantly higher than the thenar rSO_2 (Table 3). Nevertheless, higher rSO_2 thenar values were found in 24 % of the patients at T1. At baseline and for the pooled study data (T1-T3), we revealed a moderate correlation between frontal and thenar rSO_2 (T1: Pearson $r = 0.451$, $p = 0.001$; T1–T3: $r = 0.442$, $p < 0.001$).

Survivors and non-survivors represented no significant differences between their frontal and thenar rSO_2 values ($p = 0.24$). Also the proportion of patients who revealed greater thenar than frontal rSO_2 did not differ.

3.2 Relationship between rSO_2 and $ScvO_2$

We further stratified patients according to their $ScvO_2$ to investigate the relationship between rSO_2 and $SvcO_2$ (Table 4). Patients were divided into patients with a $ScvO_2$ <70 % and patients with a $ScvO_2$ ≥70 %. We found no significant differences in APACHE II, SAPS II, SOFA,

Table 1 Study population

	n = 50
Gender male	36 (72)
Age (years)	68.02 ± 13.52
Height (cm)	173.68 ± 8.51
Weight (kg)	80.72 ± 26.33
Hospital length of stay before inclusion (days)	10.56 ± 17.12
Hospital length of stay after inclusion (survivors) (days)	30.08 ± 24.42
Length of stay in ICU (days)	17.28 ± 19.27
APACHE II	25.24 ± 6.76
SOFA Score	6.42 ± 2.29
SAPS II	50.62 ± 15.17
History of coronary artery disease	10 (20)
Heart insufficiency (NYHA ≥III)	15 (30)
Peripheral artery occlusive disease	12 (24)
Renal disease	17 (34)
Chronic obstructive pulmonary disease	18 (36)
Diabetes mellitus	16 (32)
Arterial Hypertension	37 (74)
Septic shock at inclusion	28 (56)
ICU mortality	25 (50)
Hospital mortality	26 (52)
ICU days non-survivor (days)	12.58 ± 17.13

ICU intensive care unit; *APACHE II* acute physiology and chronic health evaluation II score; *SOFA* sequential organ failure assessment score; *SAPS II* simplified acute physiology II score. Data are shown as mean ± standard deviation or numbers (%)

Table 2 Clinical variables and therapy goals

	T1 (n = 50)	T2 (n = 39)	T3 (n = 31)
MAP (mmHg)	77.54 ± 14.74	83.38 ± 13.36	81.42 ± 14.57
Patients treated with vasopressors	42 (84.0)	27 (69.2)	21 (67.7)
Norepinephrine dosage (μg/kg·min)	0.33 ± 0.33	0.22 ± 0.16	0.15 ± 0.15
Dobutamin treatment	6 (12.0)	9 (23.1)	6 (12.0)
Dobutamine dosage (μg/kg·min)	2.88 ± 0.72	1.88 ± 1.15	1.94 ± 1.15
PaO_2 (mmHg)	107.19 ± 54.30	96.71 ± 21.86	127.36 ± 164.22
Arterial CO_2 (mmHg)	40.98 ± 7.94	40.63 ± 7.42	41.69 ± 6.43
PEEP (mbar)	6.22 ± 4.18	6.46 ± 4.30	6.78 ± 6.12
Respiratory rate (1/min)	16.46 ± 4.82	16.74 ± 5.12	16.35 ± 4.84
FiO_2 (%)	51.28 ± 22.24	44.51 ± 14.91	41.58 ± 15.75
Horowitz Index	236.63 ± 120.97	241.24 ± 116.64	234.61 ± 106.21
Intubated and mechanicaly venitalated patients	35 (70)	23 (59)	16 (50)
Frontal rSO_2 (%)	60.40 ± 11.10	60.24 ± 12.03	59.10 ± 10.95
Thenar rSO_2 (%)	50.90 ± 14.64	51.41 ± 11.83	55.84 ± 10.48
$ScvO_2$ (%)	73.86 ± 8.58	70.69 ± 9.68	71.29 ± 7.81
$ScvO_2$ <70 %	13 (26.0)	17 (44.7)	10 (33.3)
Arterial Lactate (mmol/l)	4.08 ± 4.73	2.20 ± 2.10	1.90 ± 2.02
Arterial Lactate ≥2, 5 mmol/l	21 (42.0)	9 (23.1)	5 (16.1)
Venous Lactate (mmol/l)	4.11 ± 4.57	2.35 ± 2.22	1.97 ± 1.87
SaO_2 (%)	96.07 ± 5.25	96.81 ± 2.74	95.98 ± 5.18
Hemoglobine (g/dl)	10.12 ± 1.60	10.25 ± 2.51	10.18 ± 1.31

MAP mean arterial pressure; *PaO_2* arterial oxygen pressure; *FiO_2* fraction of inspired oxygen; *$ScvO_2$* central venous oxygen saturation. Data are shown as mean ± standard deviation or numbers (%)

Table 3 Comparison of frontal and thenar measured rSO_2 divided by outcome

		All (T1: n = 50; T2: n = 39; T3: n = 31)		Survivors (T1: n = 24; T2: n = 21; T3: n = 17)		Non-survivors (T1: n = 26; T2: n = 18; T3: n = 14)		*p*
		frontal	thenar	frontal	thenar	frontal	thenar	
T1	rSO_2	60.40 ± 11.10	50.90 ± 14.64	61.13 ± 11.89	49.21 ± 13.95	59.73 ± 10.52	52.46 ± 15.36	
	Difference $rSO_{2\ frontal}$—$rSO_{2\ thenar}$	9.50 ± 13.82		11.92 ± 12.05		7.27 ± 15.16		0.24
	Patients with $rSO_{2frontal}$ >$rSO_{2\ thenar}$	38 (76.0)	12 (24.0)	20 (83.3)	4 (16.7)	18 (69.2)	8 (30.8)	0.24
T2	rSO_2	60.24 ± 12.03	51.41 ± 11.83	59.76 ± 13.55	49.33 ± 12.56	60.81 ± 10.32	53.83 ± 10.74	
	Difference $rSO_{2\ frontal}$—$rSO_{2\ thenar}$	8.83 ± 12.12		10.43 ± 9.94		6.97 ± 14.32		0.38
	Patients with $rSO_{2frontal}$ >$rSO_{2\ thenar}$	34 (87.2)	5 (12.8)	19 (83.3)	2 (9.5)	15 (83.3)	3 (16.7)	0.51
T3	rSO_2	59.10 ± 10.95	55.84 ± 10.48	58.12 ± 12.97	53.71 ± 12.40	60.29 ± 8.17	58.43 ± 7.14	
	Difference $rSO_{2\ frontal}$—$rSO_{2\ thenar}$	3.26 ± 11.35		4.41 ± 12.01		1.86 ± 10.78		0.54
	Patients with $rSO_{2frontal}$ >$rSO_{2\ thenar}$	20 (64.5)	11 (35.5)	12 (70.6)	5 (29.4)	8 (57.1)	6 (42.9)	0.44

Data are absolute numbers (%) or mean ± standard deviation

thenar rSO_2, arterial lactate, venous lactate, SaO_2, blood pressure, dose of norepinephrine, FiO_2, positive end-expiratory pressure (PEEP), Horowitz Index and central venous pressure (CVP) between the groups. Patient characteristics solely differ in body weight (74.11 ± 18.4 vs. 99.54 ± 36.0; $p = 0.028$, data not shown). Patients with $ScvO_2$ ≥70 % showed a trend towards higher levels of a frontal rSO_2 (62.81 ± 8.06 vs. 53.54 ± 15.48; $p = 0.058$).

Table 4 Patients characteristics depending on central venous saturation

	$ScvO_2$ ≥70 %	$ScvO_2$ <70 %	*p*
APACHE II T1	25.68 ± 6.92	24.00 ± 6.37	0.45
SAPS II T1	52.14 ± 14.31	46.31 ± 17.28	0.24
SOFA T1	6.46 ± 2.45	6.31 ± 1.84	0.84
Septic Shock	20 (54.1)	8 (61.5)	0.64
rSO_2 frontal T1 (%)	62.81 ± 8.06	53.54 ± 15.48	0.058
rSO_2 thenar T1 (%)	50.51 ± 14.76	52.00 ± 14.83	0.76
$ScvO_2$ T1 (%)	77.80 ± 5.43	62.62 ± 5.18	<0.001
Arterial Lactate T1 (mmol/l)	4.30 ± 5.20	3.43 ± 3.06	0.57
Venous Lactate T1 (mmol/l)	4.37 ± 5.09	3.38 ± 2.64	0.51
Arterial Lactate T1 ≥2.5 mmol/l	15 (40.5)	6 (46.2)	0.72
SaO_2 T1 (%)	96.69 ± 4.01	94.30 ± 7.70	0.16
Horowitz Index T1	235.19 ± 119.77	240.71 ± 129.20	0.89
MAP T1 [mmHg] (mmHg)	76.70 ± 14.25	79.92 ± 16.43	0.50
Norepinephrine dose (µg/kg/min)	0.28 ± 0.35	0.27 ± 0.28	0.96
Hemoglobine T1 (g/dl)	10.26 ± 1.54	9.73 ± 1.75	0.31
ICU Mortality	21 (56.8)	4 (30.8)	0.11
Hospital Mortality	22 (59.5)	4 (30.8)	0.07

ICU intensive care unit; *SAPS II* simplified acute physiology score; *APACHE II* acute physiology and chronic health evaluation score; *SOFA* sequential organ failure assessment score; *MAP* mean arterial pressure. Data are shown as mean ± standard deviation or numbers (%)

ROC-analysis revealed just a minor prediction of a decreased $ScvO_2$ by frontal rSO_2 levels at baseline (AUC = 0.687; 95 % CI 0.511–0.863; $p = 0.047$) (Fig. 1). Even after the combined analyses of the data from T1, T2 and T3, the prediction of $ScvO_2$ by frontal rSO_2 could not be improved (AUC 0.687; 95 % CI 0.512–0.721; $p = 0.039$). Regarding the pooled data we could only measure a weak correlation between thenar rSO_2 and $ScvO_2$ (Pearson: $r = 0.223$; $p = 0.015$) (Fig. 3).

However, multivariate logistic regression analysis revealed frontal rSO_2 as an independent predictor for a $ScvO_2$ <70 % (OR 0.867; 95 % CI 0.784–0.958); $p = 0.005$). Other parameters did not show any significant relationship (Table 5).

3.3 Explorative analysis of survivors and non-survivors

Regarding the differences between survivors and non-survivors, we revealed a raised APACHE II Score (22.04 ± 5.61 vs. 28.19 ± 6.46; $p = 0.001$), and SAPS II Score (44.79 ± 14.21 vs. 56.00 ± 14.24; $p = 0.008$), lower MAP (T1) (mmHg) (84.50 ± 14.86 vs. 71.12 ± 11.55; $p = 0.001$), and therefore higher doses of norepinephrine (µg/kg/min) (0.18 ± 0.18 vs. 0.37 ± 0.4; $p = 0.04$) (Table 6). In addition, in the group of non-survivors, we detected higher (arterial and venous) lactate levels (mmol/l) (arterial 2.14 ± 2.16 vs. 5.86 ± 5.70; $p = 0.004$), and also surprisingly significantly raised $ScvO_2$ (71.10 ± 8.09 vs. 76.41 ± 8.37; $p = 0.027$) at T1.

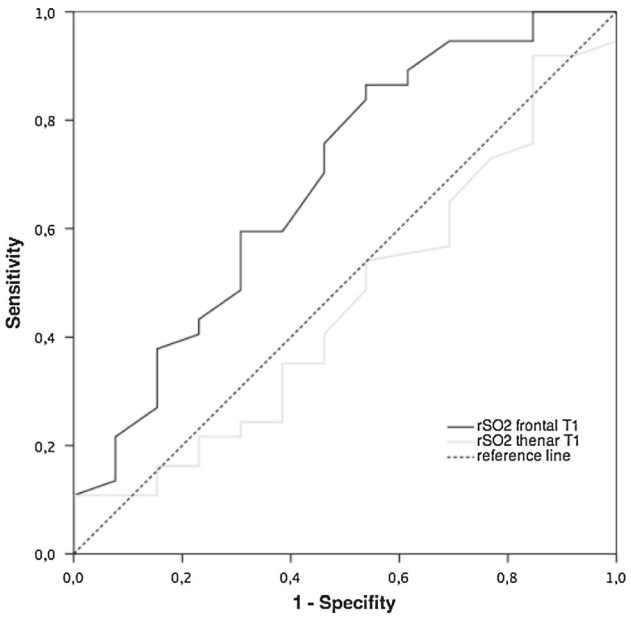

Fig. 1 Receiver operating characteristics for the prediction of $ScvO_2$ <70 % by rSO_2. ROC-Analysis for the prediction of $ScvO_2$ <70 by frontal rSO_2 at time T1 (n = 50) (*black line*). AUC 0.687 (95 % CI 0.511–0.863; $p = 0.047$). No significant prediction of $ScvO_2$ <70 by thenar rSO_2 at time T1 (n = 50) (*grey line*)

Nevertheless, there was no difference in rSO_2 levels according patient's outcome.

ROC analysis revealed the best prediction for mortality by APACHE II Score (0.777; 95 % CI 0.648–0.907; $p = 0.001$) and arterial lactate (T1) (0.748; 95 % CI

Table 5 Results of multivariate logistic regression analysis for the correlation of $ScvO_2$ with rSO_2, lactate, SaO_2, MAP and norepinephrine dose

	Odds ratio	95 % CI		*p*
Frontal rSO_2 T1	0.867	0.784	0.958	0.005
Thenar rSO_2 T1	1.052	0.986	1.123	0.126
Arterial Lactate T1	0.872	0.674	1.129	0.299
SaO_2 T1	0.878	0.763	1.011	0.070
MAP T1	1.004	0.942	1.070	0.897
Norepinephrine dose T1	3.228	0.129	80.643	0.475

SaO_2 oxygen saturation of arterial blood; *MAP* mean arterial pressure; *CI* confidential interval

0.612–0.883; $p = 0.003$). Also MAP (T1) (0.748; 95 % CI 0.610–0.886; $p = 0.003$), SAPS II Score (0.708; 95 % CI 0.565–0.852; $p = 0.012$), and $ScvO_2$ (T1) levels (0.683; 95 % CI 0.535–0.832; $p = 0.026$) were predictive for mortality. Measurements of frontal rSO_2 (T1) and SOFA Score did not serve for outcome prediction in this analysis (Table 7).

Referring the fact of increased mortality in patients with ScvO2 ≥70 % and lactate <2.5 mmol/l a four-field analysis for $ScvO_2$ and lactate levels with the cut-off values according to the clinical outcomes were performed. Combining the measurements of lactate level and $ScvO_2$, we detected the highest mortality (80 %) for patients with $ScvO_2$ ≥70 % and lactate levels ≥2.5 mmol/l (Table 6), which is confirmed by the Kaplan–Meier analysis (log rank test $p = 0.004$) (Fig. 2). Surprisingly, no person of the septic population with $ScvO_2$ <70 % and lactate levels <2.5 mmol/l died in this observation.

4 Discussion

In this prospective observational study, we performed repeated rSO_2 measurements in 50 surgical ICU patients with sepsis to investigate the correlation between rSO_2 and $ScvO_2$. A secondary aim was to evaluate the value of rSO_2, $ScvO_2$ and lactate for outcome prediction in sepsis. We revealed just a weak predictive value for $ScvO_2$ by frontal rSO_2 measurement. Surprisingly, septic patients with "normal" $ScvO_2$ ≥70 % and elevated lactate levels (≥ 2.5 mmol/l) showed the highest mortality.

In a primary preliminary analysis of 16 septic ICU patients we found that the frontal rSO_2 could be predictive for a depressed $ScvO_2$ <70 % (AUC = 0.844; $p = 0.045$).

Table 6 Explorative analysis of survivors and non-survivors at baseline

		Survivors	Non-survivors	*p*
APACHE II		22.04 ± 5.61	28.19 ± 6.46	0.001
SAPS II		44.79 ± 14.21	56.00 ± 14.24	0.008
SOFA		5.96 ± 2.37	6.85 ± 2.17	0.17
Septic Shock		11 (45.8)	17 (65.4)	0.16
rSO_2 frontal T1 (%)		61.13 ± 11.89	59.73 ± 10.52	0.66
rSO_2 thenar T1 (%)		49.21 ± 13.95	52.46 ± 15.36	0.44
$ScvO_2$ T1 (%)		71.10 ± 8.09	76.41 ± 8.37	0.027
$ScvO_2$ T1 < 70%		9 (37.5)	4 (15.4)	0.08
Lactate arterial T1 (mmol/l)		2.14 ± 2.16	5.86 ± 5.70	0.004
Lactate venous T1 (mmol/l)		2.24 ± 2.00	5.85 ± 5.55	0.004
Lactate T1 ≥ 2.5 mmol/l		5 (20.8)	16 (61.5)	0.004
SaO_2 T1 (%)		95.18 ± 7.11	96.89 ± 2.43	0.27
Horowitz Index T1		267.05 ± 116.02	208.55 ± 120.79	0.09
MAP T1 (mmHg)		84.50 ± 14.86	71.12 ± 11.55	0.001
Norepinephrine dose T1 (μg/kg/min)		0.18 ± 0.18	0.37 ± 0.40	0.04
Hemoglobine T1 (g/dl)		10.44 ± 1.61	9.82 ± 1.55	0.17
	n			0.004
$ScvO_2$<70 %. Lactate arterial < 2.5 mmol/l	7	7 (100)	0	
$ScvO_2$<70 %. Lactate arterial ≥ 2.5 mmol/l	6	2 (33.3)	4 (66.6)	
$ScvO_2$≥70 %. Lactate arterial < 2.5 mmol/l	22	12 (54.4)	10 (45.4)	
$ScvO_2$≥70 %. Lactate arterial ≥ 2.5 mmol/l	15	3 (20)	12 (80.0)	

ICU intensive care unit; *SSI* soft skin and tisue infections; *APACHE II* acute physiology and chronic health evaluation score; *SOFA* sequential organ failure assessment score; *SAPS II* simplified acute physiology score; *$ScvO_2$* central venous saturation; *SaO_2* oxygen saturation of arterial blood; *MAP* mean arterial pressure. Data are mean ± standard deviation

Table 7 Receiver operating characteristics for mortality prediction

	AUC	95 % CI		*p*
Frontal rSO_2 T1	0.434	0.274	0.595	0.426
$ScvO_2$ T1	0.683	0.535	0.832	0.026
Arterial Lactate T1	0.748	0.612	0.883	0.003
MAP T1	0.748	0.610	0.886	0.003
Norepinephrine dose T1	0.643	0.490	0.797	0.082
APACHE II	0.777	0.648	0.907	0.001
SOFA	0.614	0.457	0.771	0.168
SAPS II	0.708	0.565	0.852	0.012

SAPS II simplified acute physiology score; *APACHE II* acute physiology and chronic health evaluation score; *SOFA* sequential organ failure assessment score; *MAP* mean arterial pressure; *AUC* area under curve; *CI* confidence interval

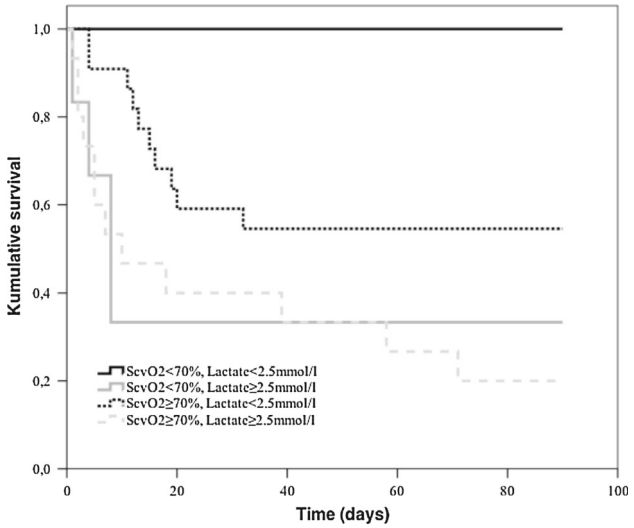

Fig. 2 Kaplan–Meier-analysis for in-hospital mortality depending on lactate and central venous saturation. Kaplan–Meier-analysis for in-hospital mortality depending on lactate (mmol/l) and central venous saturation ($ScvO_2$)(%) (*black line*: $ScvO_2$ <70 % und Lactat <2.5 mmol/l; *black broken line*: $ScvO_2$ <70 % und Lactate ≥2.5 mmol/l; *gray line*: $ScvO_2$ ≥70 % und Lactate <2.5 mmol/l; *gray broken line*: $ScvO_2$ ≥70 % und Lactate ≥2.5 mmol/l) (Log Rank $p = 0.004$)

A $ScvO_2$ <70 % was indicated by cerebral rSO_2 <56.5 with a sensitivity and a specificity of 75 and 100 %, respectively [18]. The data from this larger prospective study indicate a lower predictive value for $ScvO_2$ (AUC 0.617; 95 % CI 0.512–0.721; $p = 0.039$). Furthermore, patients representing $ScvO_2$ ≥70 % showed a trend towards a higher hospital mortality (59.5 % vs. 30.8 %, $p = 0.07$) compared to patients with $ScvO_2$ <70 %. Stratifying the study group for mortality, non-survivors represented significantly raised $ScvO_2$ values, higher APACHE II scores, SAPS II scores, and elevated lactate values, respectively. We observed a significant overall mortality in the study

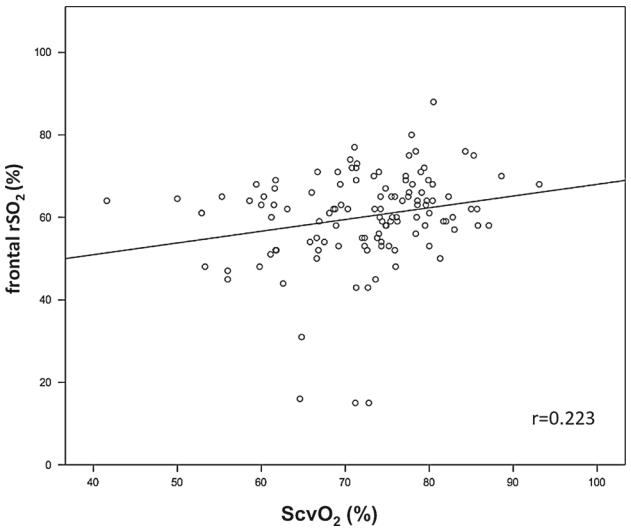

Fig. 3 Pearson correlation between frontal rSO_2 and $ScvO_2$. Pearson correlation between frontal rSO_2 (%) and $ScvO_2$ (%) using the pooled study data from each observation point (n = 110) (Pearson: $r = 0.223$; $p = 0.015$)

population (52 %) as predicted by high mean APACHE II and SAPS II scores whereas the observed mean SOFA score just predict a mortality of 15 %.

In our study we investigated patients with sepsis regarding three observation points at our surgical ICU. Patients were treated according to the guidelines of the Surviving Sepsis campaign including early resuscitation, source control and empirical anti-infective treatment [4]. Various studies already used NIRS in different settings to evaluate the severity of sepsis, for mortality prediction in sepsis and as a marker of local tissue oxygenation [18, 22–25]. Thereby, many studies focused on the vascular reactivity through changes during vascular occlusion maneuver and time or therapy related changes [23, 24, 26]. Sepsis is characterized by pathological changes in vasomotor reactivity and microcirculation leading to cellular hypoxia [27]. Early hemodynamic stabilization represents the main target of modern therapy in septic patients to achieve adequate supply of oxygen [5]. Guidelines also recommend the use of advanced hemodynamic monitoring in septic patients even though its benefit for mortality reduction is still not proved [4, 28]. $ScvO_2$ reflects global balance of oxygen supply and consumption in case of stabile respiratory conditions [29]. Further, lactate levels constitute a surrogate for impaired peripheral oxygen supply [30–32]. In order to this fact early hemodynamic stabilization in patients with sepsis should be proved by a decrease in lactate under a cut cut-off level of 2.5 mmol/l. Continuous measurement of therapeutic goals could be an opportunity to improve therapeutic efficiency but is also associated with higher costs. Moreover, continuous $ScvO_2$ measurement is not associated with outcome improvement [33]. NIRS

could be an additional monitoring tool for continuous, non-invasive assessment of tissue oxygenation in patients with impaired cardiac function [34–36].

In this prospective study we focused on rSO_2 baseline measurements and found a limited association between frontal rSO_2 and $ScvO_2$. However, patients with $ScvO_2$ <70 % did not have significantly lower rSO_2 values. Nevertheless, multivariate regression analysis revealed frontal rSO_2 at T1 as predictive for $ScvO_2$ ($p = 0.005$). According to previous studies in patients with severe sepsis and septic shock we also found only a weak correlation between thenar rSO_2 and $ScvO_2$ [14, 23, 37, 38]. Comparably, Mesquida et al. [39] showed the ability to predict $ScvO_2$ values in septic patients by the thenar rSO_2 and found a moderate correlation between both parameters (Pearson: $r = 0.39$; $p = 0.017$). Interestingly, Podbregar et al. [37] showed that thenar rSO_2 does not estimate SvO_2 in patients with severe left heart failure and additional severe sepsis or septic shock. But in patients with severe left heart failure without additional severe sepsis or septic shock, rSO_2 values could be used to provide estimation of SvO_2. That fact implicates that peripheral static measurements may not broadly present overall tissue oxygenation compared with frontal rSO_2 measurements in septic patients. That fact could be caused by local mismatch of oxygen supply and consumption. Also vasopressor therapy induces vasoconstriction in lower extremities and could influence diagnostic efficiency of thenar rSO_2 measurements.

Frontal rSO_2 measurement also shows some technical limitations. Because of the short effective measurement range of 2.5 cm NIRS cannot definitely reflect cerebral parenchyma in every single case. Magnetic resonance imaging showed that because of the limited penetration depth cerebral parenchyma in patients with cerebral atrophy could not be reached [40]. It was also shown that high total bilirubin concentrations were independently associated with artificial rSO_2 values below 50 % [41, 42].

In addition to the protocol of Rivers et al. [5] for an early goal directed therapy in sepsis, measurements of lactate levels as marker of tissue hypoxia are also recommended [4, 33]. It has also been demonstrated that a significant lag of lactate clearance is associated with increased mortality [9]. These data were confirmed by the findings of this prospective study. In addition, we investigated that septic patients representing increased lactate ≥2.5 mmol/l and $ScvO_2$ ≥70 % had significantly higher mortality ($p = 0.004$) than patients with normal lactate. Interestingly, at baseline $ScvO_2$ values of the non-survivors were significant increased compared to the survivors. In order to this fact patients representing increased lactate levels and increased $ScvO_2$ represented the highest mortality rate in the study group (80 %). Regarding these findings, the use of $ScvO_2$ as a goal in Rivers early hemodynamic treatment has to be scrutinized. The ProCESS trial revealed in a large randomized, controlled, multicenter study that protocol-based EGDT in patients with septic shock, diagnosed in the emergency department, did not improve outcome [43]. In his editorial, Lilly however claimed early recognition of sepsis, early administration of antibiotics, early adequate volume resuscitation, and clinical assessment of the adequacy of circulation to reduce mortality in patients with sepsis and septic shock [44]. These findings lead to the question if patients really benefit from reaching the target of $ScvO_2$ ≥70 % or if they simply benefit from early source control and treatment of impaired circulatory function in sepsis. Additionally, Asfar et al. [45] found that targeting a higher mean arterial pressure of 80 to 85 mmHg as compared to 65–70 mmHg in patients with septic shock undergoing resuscitation did not reduce mortality. But in a subgroup of patients with hypertension high MAP target decreased the risk of renal injury and the need for renal-replacement therapy [45]. In our study population patients with normal and decreased $ScvO_2$ did not differ according their mean MAP at T1 and reached a relatively high value of about 79 mmHg. However, non-survivor showed significantly lower MAPs than survivor.

The relationship between $ScvO_2$ and lactate has become goal of high interest as a marker of impaired tissue oxygenation. In case of impaired oxygen delivery or increased extraction, consumption becomes delivery dependent and tissues produce lactate according to their transition to anaerobic metabolism. Blood lactate level has been associated with the occurrence of shock and associated organ failure using several organ failure scales and is potentially a reliable marker of persistent occult hypoperfusion [46]. Even Jansen and colleagues claimed lactate as a marker of outcome after severe shock, especially in multiple organ dysfunction syndrome [47]. According to the analysis of Soga et al. [25] who revealed a significant correlation between NIRS-derived variables and the lactate concentration, we doubt that $ScvO_2$ should be the primary therapeutic goal during early resuscitation in sepsis. Even Perz et al. [48] detected that low and also supra-normal $ScvO_2$ values (>77.4 %) in patients undergoing cardiac surgery were associated with raised perioperative complications. In addition, the study revealed that increased lactate level were also associated with low and supra-normal $ScvO_2$ values. The authors concluded that high and low $ScvO_2$ could be under-recognized warning signs for impaired tissue oxygenation. Pope et al. [49] found that in patients with suspected sepsis in the emergency department both abnormally low and high $ScvO_2$ values were associated with increased mortality. Supra-normal $ScvO_2$ in sepsis or systemic inflammation may be a result of disrupted oxygen utilization caused by mitochondrial dysfunction [50, 51]. Nevertheless, even other mechanism

beside decreased tissue oxygenation could produce elevated lactate level [52]. Especially increased glycolysis may reflect an important cause of lactate rising. Even inotropic therapy with β-mimetics could cause significant lactate increments [53]. In order to these reasons this observational study may only provide limited mechanistic statements. Also, the power-analysis was performed for the primary aim, the correlation between $ScvO_2$ and rSO_2, but not for the value of lactate levels as surrogate for outcome prediction in sepsis. Non-survivor and survivor groups were similar in respiratory conditions, hemoglobin concentration and epinephrine doses. In consideration of these facts we would propose that septic patients representing raised lactate and supra-normal $ScvO_2$ are at high risk for tissue hypoxia and associated raised mortality.

5 Conclusion

In summary, our data revealed that frontal rSO_2 correlates with $ScvO_2$ but both frontal and thenar rSO_2 do not exactly discriminate between patients with high or low $ScvO_2$ in sepsis. The combination of elevated lactate >2.5 mmol/l and $ScvO_2$ >70 % is highly associated with poor outcome in ICU patients with sepsis, severe sepsis and septic shock.

Conflict of interest The authors declare that they have no conflict of interest. Authors did not receive funding or any other kind of financial support.

Ethical standard Ethical approval for this study (ethics proposal number AZ 57/12) was obtained from the Ethics Committee of the Faculty of Medicine at the Justus-Liebig-University Giessen, Giessen, Germany (Chairman Prof. H. Tillmanns) on 12 June 2012. Patients or their legal representative gave written informed consent before study inclusion.

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