Central Venous Oxygen Saturation above 75% on Day Three of Septic Shock is Associated with Tripled Mortality

Timo Sturm1,2, Jan Dertinger1,2, Michael Hagmann1,2, Manfred Thiel1,2 and Verena Schneider-Lindep1,2,3

1University Medical Centre Mannheim, Department of Anaesthesiology and Surgical Intensive Care Medicine, Mannheim, Germany
2TRACC-Group (Translational Research in Anaesthesiology and Critical Care), Canada
3Department of Community Health Sciences, University of Manitoba, Winnipeg, Canada

Abstract

Background: Central venous oxygen saturation (ScvO2) is commonly used to identify global oxygen uptake-delivery mismatches. A level above 70% was the declared goal in early resuscitation of septic shock for over a decade. Recent evidence leads to doubts and levels higher than 80% may represent harmful conditions. This study’s aim was to identify favourable ScvO2 levels in treatment of septic shock.

Methods: Electronic data of patients suffering from septic shock who have been admitted to the surgical intensive care unit of a university hospital were analysed surveying a period of six years with focus on the association of ScvO2 levels with in-hospital mortality.

Results: Data from 238 individuals were included. No difference was found comparing initially measured values of ScvO2 of survivors to non-survivors. Patients whose levels of ScvO2 never exceeded 70% (n=28) had a higher mortality rate (73.2% vs. 54.3%, p<0.05). On day three patients with values above 75% (n=32) had higher mortality rates (59.4% vs. 38.5%, p<0.05). A mortality rate of 100% was detected if ScvO2 levels exceeded 84% (n=6).

Conclusions: ScvO2 develops from a therapy guiding parameter to a prognostic marker. Reaching levels of at least 70% within the first 72 h of disease is favourable in regard to prognosis. Exceeding 75% after day two is associated with higher mortality. These findings require further confirmation. At this point it can be assumed that a varying, time-dependent ScvO2 approach might be required for clinical decision-making.

Keywords: Central venous; Saturation; Mortality; Septic shock; Prognosis

Introduction

Despite intensive efforts of improving therapy in treatment of septic shock mortality rates are still reported about 36.5% [1]. A number of 5.3 million deaths annually worldwide is estimated [2]. Treatment recommendations [3,4] focus on infection control and cardiorespiratory resuscitation to restore oxygen supply, optimize tissue perfusion, avoid hypoxia, and at least prevent organ failure [5]. Central venous oxygen saturation (ScvO2) and serum lactate concentration are commonly accepted indicators of oxygen supply and global oxygen balance [3,6,7] and have been suggested as goals of treatment for more than a decade. Serum lactate has traditionally been interpreted as a marker of tissue hypoxia due to inadequate oxygen delivery. Particularly during prolonged episodes of sepsis, however, high levels of serum lactate can also result from impaired hepatic clearance or increased pyruvate production which is irrespective to an optimized oxygen supply [8]. By now there are doubts concerning treatment strategies which are focused on serum lactate levels [9].

A level of ScvO2 above 70% has been a conventional goal in early septic shock therapy since first early goal directed therapy (EGDTh) studies have been released [10,11]. Recent trials failed to demonstrate a survival benefit for these classic treatment goals compared to usual care [12-15]. Particularly in later stages of disease, interpretation of ScvO2 is challenging for clinicians [7]. Reviews attest “no benefit of early resuscitation guided by venous oxygen saturation” [16] or suggest that a subset of patients could benefit [15]. Consequently, adjusting ScvO2 is no longer part of the current surviving sepsis campaign (SSC) guidelines [4]. In contrast, the SSC guidelines state that the use of the previous targets is still safe and may be considered as no harm was associated with the interventional strategies and clinicians still need guidance for approaching this group of patients with significant mortality and morbidity. This raises the question whether ScvO2 should still be measured in septic shock at all.

ScvO2 values are considered to reflect mixed venous oxygen saturation (SvO2) [11]. SvO2 is an indirect index of global oxygen supply-to-demand ratio [11]. In early septic shock with inadequate oxygen delivery, mostly due to anaemia, absolute or relative hypovolemia, or myocardial dysfunction, systemic extraction ratio rises and SvO2 decreases [17]. In prolonged septic shock oxygen utilization is compromised by oedema induced diffusion limitation and by toxic respiratory chain uncoupling [5,18,19]. As a result less oxygen is consumed and returned back to the central circulation as indicated by increasing SvO2 values. Increased risk of multiple organ dysfunction and death, hence, are likely reflected by both low and high ScvO2 values. This suggests there may be ranges or corridors of ScvO2.
values, which are associated with favourable patient outcome. Moreover, the significance of specific ScvO\textsubscript{2} values may vary in the course of septic shock and thus a single fixed goal or corridor may be inadequate for treatment guidance. Data supporting these hypotheses are scarce, retrospective analyses suggest reduced survival for patients with venous saturations below 70% and above 90% in the first 6 h [19], as well as above 80% up to day three of septic shock therapy [20]. Prognostic studies evaluating ScvO\textsubscript{2} with a time-dependent approach, however, are lacking.

The aim of this study therefore was to link the level of ScvO\textsubscript{2} with mortality rates and identify ScvO\textsubscript{2} levels in defined time corridors potentially beneficial for patient outcome from septic shock.

Materials and Methods

This investigation is single centre retrospective observational, using the patient data management system (PDMS) database (IntelliVue Clinical Information Portfolio, Phillips Healthcare, Netherlands) of a surgical intensive care unit (ICU). The study is designed corresponding to the declaration of Helsinki and ethical approval has been granted by a local committee (Medical Faculty of Mannheim, Germany, chairman Prof. JP Striebel, No. 2014-816R-MA). Design and reporting are according to the CONSORT statement recommendations (www.consort-statement.org).

Cohort inclusion and exclusion criteria

All patients admitted with septic shock between 1\textsuperscript{st} January 2007 and 31\textsuperscript{st} October 2013 were included (Figure 1). Septic shock was operationalized according to the SSC guidelines of 2012 focussing on sepsis-induced hypotension despite appropriate volume resuscitation [3].

![Figure 1: Flow-chart diagram of patient selection process. ICU: Intensive care unit; PDMS: Patient data management system; ICD: International statistical classification of diseases and related health problems; ScvO\textsubscript{2}: Central venous oxygen saturation.](image)

Note on clinical practice during the investigation

Moderate sedation, lung protective ventilator settings supporting spontaneous breathing, empirical antibiotics, early microbiological and radiological diagnostics as well as interventional and surgical focus control were ensured like recommended by the SSC [3]. For hemodynamic stabilization balanced crystalloid solutions, norepinephrine and dobutamine were preferred choices. A MAP of 65 mmHg, urine output of >0.5 ml/kg/h, ScvO\textsubscript{2}>70% and serum lactate concentration<2 mmol/l were declared as primary goals. If required, hemodynamic monitoring was augmented by echocardiography or pulse contour cardiac output (therapeutic aim: cardiac index (CI)>2.5 l/min/m\textsuperscript{2}) and to estimate volume status and contractility. ScvO\textsubscript{2} measurements were part of routine care, determined by a point-of-care blood gas analyzer (ABL800 Radiometer, Copenhagen, Denmark) and directly transmitted to the local PDMS.

Statistical analyses

Descriptive statistics were used to summarize demographic, clinical, hemodynamic and laboratory parameters of the cohort and also for survivors and non-survivors separately. Characteristics of the latter two groups were compared with two-tailed t-tests and chi-square tests. Survivors and non-survivors of the cohort were classified according to their ScvO\textsubscript{2}-level at each time interval. For each of the five time intervals, odds ratios (OR) with 95% confidence intervals (CI) for ScvO\textsubscript{2}-dependent mortality risk in those still alive at the beginning of the respective interval were obtained from logistic regression. ROC-curves were used to determine the maximum value for the sum of
sensitivity and 1-specificity of potential ScvO2 cut-off values for mortality prediction at the different time intervals. The probability of survival for different ScvO2 levels was depicted in Kaplan-Meier plots. For all analyses a p-value<0.05 (two-tailed) was considered statistically significant. SAS 9.4 (SAS Cooperation, Cary, North Carolina, USA) was used for data analysis.

Results

Of 16044 ICU admissions during the study period 466 potential shock patients fulfilled the inclusion criteria. After examination by an expert the final cohort of 238 patients with septic shock on admission was set (Figure 1). Overall hospital mortality of 57.6% and observed survival for shock patients (74%) and lower ones on day three (71.2% ± 7.7% vs. 73.1% ± 11.6%, p<0.05 for each interval). A trend to higher initial ScvO2 measurement values in survivors compared to non-survivors (mean ± SD: 75.7% ± 9.1% vs. 73.1% ± 10.1%, p=0.13; median: 77% vs. 76%) was detected (Figure 2).

Figure 2: Development of central venous saturation in septic shock. Graphical illustration of central venous saturation development of patients under ongoing septic shock treatment – survivors are displayed in blue, non-survivors in black; dots indicate mean value and error bars standard deviations; ScvO2: Central venous oxygen saturation.

| Hypertension (%) | 114 (48) | 49 (49) | 65 (47) | 0.87 |
| Impaired immunity (%) | 22 (9) | 10 (10) | 12 (9) | 0.76 |
| Malignancies (%) | 66 (28) | 18 (18) | 48 (35) | <0.01* |

Focus side:

Abdomen (%) 115 (48) 45 (45) 70 (51) 0.32
Lung (%) 82 (34) 37 (37) 45 (33) 0.54
Urogenital (%) 11 (5) 8 (8) 3 (2) <0.05*
Soft tissue (%) 10 (4) 3 (3) 7 (5) 0.42
Others or unknown (%) 20 (8) 8 (8) 12 (9) 0.82

Clinical data:

| SAPS 2 | 65.8 ± 14.6 | 61.4 ± 14.2 | 69.7 ± 13.9 | <0.001* |
| SOFA | 13.3 ± 2.5 | 12.5 ± 2.3 | 14.0 ± 2.5 | <0.0001* |
| Temperature (°C) | 36.9 ± 1.2 | 37.0 ± 1.0 | 36.8 ± 1.3 | 0.52 |
| CRP (mg/l) | 205 ± 108 | 196 ± 101 | 214 ± 113 | 0.44 |
| PCT (mg/l) | 22.5 ± 44.5 | 30.8 ± 55.9 | 16.8 ± 34.1 | 0.12 |
| Bilirubin (mg/dl) | 1.2 ± 1.2 | 1.2 ± 1.4 | 1.2 ± 1.0 | 0.85 |
| Creatinine (mg/dl) | 2.2 ± 2.2 | 2.2 ± 2.6 | 2.2 ± 1.8 | 0.91 |
| Haemoglobin (g/dl) | 10.3 ± 1.9 | 10.7 ± 1.9 | 9.9 ± 1.8 | <0.05* |
| MAP (mmHg) | 76 ± 14 | 77 ± 14 | 74 ± 13 | 0.37 |
| Heart rate (min) | 106 ± 21 | 105 ± 20 | 107 ± 22 | 0.52 |
| Cardiac index (l/min/m2) | 3.7 ± 1.3 | 4.1 ± 1.4 | 3.4 ± 1.2 | 0.22 |
| Fluid balance first day (l) | + 6.8 ± 5.0 | + 6.8 ± 4.9 | + 6.8 ± 5.0 | 0.93 |
| Norepinephrine (mg/kg/min) | 0.37 ± 0.43 | 0.33 ± 0.37 | 0.39 ± 0.48 | 0.41 |
| Lactate (mmol/l) | 3.7 ± 3.5 | 2.8 ± 2.5 | 4.4 ± 0.5 | <0.05* |
| SaO2 (%) | 95.2 ± 4.6 | 95.8 ± 3.4 | 94.9 ± 5.3 | 0.12 |
| ScvO2 (%) | 74.3 ± 9.8 | 75.7 ± 9.1 | 73.1 ± 10.1 | 0.13 |
| Mechanical ventilation (%) | 222 (93.3) | 93 (92.1) | 129 (94.2) | 0.53 |
| Renal replacement (%) | 46 (19.3) | 12 (11.9) | 34 (24.8) | <0.05* |
| ICU days | 14.1 ± 18.0 | 17.6 ± 18.6 | 11.3 ± 17.0 | <0.01* |
| Hospital days | 30.6 ± 45.5 | 49.0 ± 46.3 | 17.0 ± 39.7 | <0.0001* |

Table 1: Study population – basic characteristics. First six hours data are shown except for clinical scores (first day). Data are given as number and percentage or mean ± SD, respectively; SAPS: Simplified acute physiology score; SOFA: Sequential organ failure assessment score; CRP: C-reactive protein; PCT: Procalcitonin; MAP: Mean arterial pressure; SaO2: Arterial blood oxygen saturation; ScvO2: Central venous oxygen saturation.
Central venous oxygen saturation; *significant result by two-tailed t-test comparison.

The minimum value of ScvO₂ was 69.03% on average in all patients (range 35.2%-95.3%). While ScvO₂ minima did not differ in survivors and non-survivors, maximum ScvO₂ values, on average, were significantly higher in survivors compared to non-survivors (Figure 3a). Hospital mortality was higher if maximal ScvO₂ values recorded at any time within the first three days of therapy were below 70%, whereas no impact on outcome was detected for maximum values ≥ 80% (Figure 3b).

Figure 4 displays mortality rates in relation to increasing ScvO₂ cut-off values in the period of the first 72 h. In early phases of septic shock mortality was higher in patients having lower ScvO₂ values up to a cut-off of 80%. These differences were not statistically significant.

Figure 3: Minimal and maximal ScvO₂ values analyses. (a) Distribution of survivors' and non-survivors' minimal and maximal ScvO₂ values determined within the first 72 h of ICU stay; *significant result from a two-tailed t-test. (b) Mortality rates of septic shock patients classified by two different cut-off values for maximum ScvO₂ in the first 72 h: n=28 with maximum ScvO₂<70%; n=105 with maximum ScvO₂ ≥ 80%; *significant result from chi-square test. minScvO₂: Minimum central venous oxygen saturation; maxScvO₂: Maximum central venous oxygen saturation.

On day three ScvO₂ cut-offs above 70% distinguished well between survival until patient’s discharge from hospital and intra-hospital mortality (Figure 4). A ROC analysis detected an optimal cut-off at 76.0% for third day's ScvO₂ (70.4% sensitivity, 60.6% specificity; area under the curve: 0.662). ScvO₂ ≥ 84.0% (n=6) on day three identified non-survivors with a sensitivity of 100%.

Figure 4: In-hospital mortality in dependence of variable ScvO₂ cut-offs. Comparative representation of in-hospital mortality in dependence upon ScvO₂ cut-off values over time course of ICU stay–patients with ScvO₂ values below the respective limit are shown in deep blue, those above the limit in light blue; ScvO₂, central venous oxygen saturation; *Significant result from chi-square test.

Odds ratios for in-hospital mortality of patients classified in defined ScvO₂ corridors (66-75% and 71-80%) did not indicate any difference regarding mortality risk for patients with ScvO₂ values below or above these reference limits at the times of measuring within 48 h after ICU admission (Figure 5). Mortality was higher in patients with ScvO₂ values>75% (n=32) compared to those in the corridor of 66–75% (n=28) on day three with an odds ratio of 3.6 (95% confidence interval...
1.2 to 10.8, p=0.02). Kaplan-Meier analyses of both mentioned corridors on day three of septic shock treatment are presented as Figures 6a and 6b.

**Figure 5**: Forest plot of third days odds ration analyses. Forest plot of odds ratios for non-surviving in dependence upon ScvO\textsubscript{2} ranges and time intervals of ICU stay; ScvO\textsubscript{2}: Central venous oxygen saturation; *Significant result.

**Discussion**

Based on early EGDT studies [10,27] former treatment recommendations supported ScvO\textsubscript{2} correction above a value of 70% within the first 6 h of sepsis [3,15]. In accordance Pope et al. [19] reported mortality rates to be significantly elevated if septic patients in the emergency department indicated maximum ScvO\textsubscript{2} values below 70% (hypoxic range) compared to those being in normoxic range (ScvO\textsubscript{2}: 71-89%). Park et al. confirmed these findings for septic shock patients exhibiting oxygen extraction ratios higher than 0.3, being approximately equivalent to calculated ScvO\textsubscript{2} values lower than 70% [28] and Lee et al. also found reduced survival if ScvO\textsubscript{2} could not be raised above 70% and lactate remained abnormal [29]. In line with these observations, our data showed diminished survival rates if ScvO\textsubscript{2} values could not be increased above this threshold (<70%) during the first 72 h of ICU stay. About one third of our patients had ScvO\textsubscript{2} values below 70% and approximately in one fifth ScvO\textsubscript{2} was below 65% when first measured in ICU. These results are supported by findings of Boulain et al. who prospectively showed that ScvO\textsubscript{2} values<70% are frequent (27%) at ICU admission [30] and extended by van Beest et al. who demonstrated that even lower rates of ScvO\textsubscript{2} (<60%) were below 65% when first measured in ICU. These results are supported by findings of Boulin et al. who prospectively showed that ScvO\textsubscript{2} values<70% are frequent (27%) at ICU admission [30] and extended by van Beest et al. who demonstrated that even lower rates of ScvO\textsubscript{2} (<60%) are still occurring (6%) [25]. Initial mean ScvO\textsubscript{2} values (74% ± 11% [25] and 74 ± 10.4% [30]) were comparable to ours and there was also no difference detected between survivors and non-survivors [30].

On the other hand Park et al. [28] as well as Pope et al. [19] reported significantly elevated in-hospital mortality rates if ScvO\textsubscript{2} values and oxygen extraction rates were in the hyperoxic range, i.e., above 89% or lower than 20%, respectively, with the latter most likely indicating ScvO\textsubscript{2} values being above 80%. These observations were made within the first hour and after 6 h of ongoing goal directed therapy. The data reported on by Textoris et al. [20] confirmed and extended the period of increased mortality risk in septic patients by investigating maximum ScvO\textsubscript{2} values taken during 72 h of treatment, although this group gave no information on the exact time of ScvO\textsubscript{2} determination: Using a ScvO\textsubscript{2} cut-off value of 80%, a 1.5 fold higher mortality rate for patients with maximum values above 80% was shown compared to those with values below this threshold (48% vs. 30%, p<0.05).

Our analysis of mortality rates associated with ScvO\textsubscript{2} in the five time intervals using different cut-off values for ScvO\textsubscript{2} starting from 65% up to 85% revealed significantly higher mortality rates with ScvO\textsubscript{2} values above 75% on the third day. ROC analysis showed an optimal cut-off at 76.0% for third day’s ScvO\textsubscript{2} (70.4% sensitivity, 60.6%
unsuspicious. Moreover, mortality was significantly higher in patients with ScvO₂ >75% (n=32) compared to those in the corridor of 66-75% (n=28) on day three with an odds ratio of 3.6 (confidence interval 1.2 to 10.8, p=0.02) (Figure 5). Kaplan-Meier analysis of mentioned ScvO₂ corridor on day three confirmed lower survival rates for ScvO₂ values below and above the corridor of 66-75%, reaching the level of statistical significance for ScvO₂ values above 75% (Figure 6). Thus, patients whose ScvO₂ values were in the corridor of 66-75% on third day of septic shock had threefold higher odds of survival compared to those whose ScvO₂ was above 75%. This is a drastically lower limit than previously suggested (Pope et al. >90% [19], Textoris et al. >80% [20]) and within the previously recommended range of 70-80% [3,11].

Moreover, these recommendations have been extrapolated to nearly every kind of critical illness, perioperative situations [16,31] and decision-making concerning transfusion [32,33]. According to the present study ScvO₂ ranges above 75% have to be considered as potentially deleterious for patients in later stages of septic shock. This is supported by the observation of no single individual, whose ScvO₂ was above 85% on the third day of septic shock surviving. Unsurprisingly, specificity of ScvO₂ values ≥ 84.0% on day three regarding in-hospital mortality was 100%.

Overall the most important finding was a noticeably increased mortality risk even if ScvO₂ values were only slightly elevated (>75%) in later stages of septic shock, which until now have been considered as unsuspicious. They might be used as warning signs as recommended by some authors in the perioperative cardio surgical setting [24,34].

Limitations
This is a retrospective study. Therefore the observed associations may not be causal and the results have to be confirmed by adequately powered prospective studies. Because the data are from a single center, particularities of local practice may have had an impact on measurement frequency, but also magnitude of ScvO₂ values. In addition, ScvO₂ measurements were determined for routine care leading to factors of uncertainty such as mix-up of patients and documentation errors. Considering predefined time corridors retrospectively leads to data gaps in some patients because measurements are taken in irregular, clinically necessary and practical intervals. In contrast, for other patients only a fraction of available measurements was used. Incomplete data also result from patients dying during the observation period. Nonetheless we analysed numerous ScvO₂ values from septic patients with high mortality risk. In spite of these limitations, we consider it important to disseminate these results because they indicate that potentially harmful ScvO₂ levels are apparently very close to formerly recommended treatment goals. In future prospective studies ScvO₂ should ideally be measured regularly if not continuously in all patients irrespective of their clinical course. Specifically, in such studies the value of ScvO₂ for mortality prediction by U-shaped models should be addressed in a time course dependent fashion.

Conclusion
We strengthened the hypothesis that ScvO₂ is of potential value in predicting unfavourable outcome in septic shock. If ScvO₂ values of at least 70% have not been achieved within 72 h of therapy, in-hospital mortality significantly increased. On the other hand ScvO₂ values above 75% on day three were associated with a threefold mortality rate compared to values in a ScvO₂ range of 66-75%. High values in early septic shock seem to be unsuspicious as well as lower ones in later stages. Further investigations have to confirm these findings in before they can be implemented in clinical decision-making.

Acknowledgements
The authors would like to thank Mr. Christoph Clauss for critical reading and editing the manuscript.

Funding
This work and the purchase of equipment and software were supported by the Department of Anaesthesiology and Surgical Intensive Care Medicine, University Medical Centre Mannheim, Germany and in part by the foundation Klaus Tschira Stiftung, Germany.

Competing Interests
The authors declare that they have no competing interests.

References
1. Gu WJ, Wang F, Bakker J, Tang L, Liu JC (2014) The effect of goal-directed therapy on mortality in patients with sepsis - earlier is better: a meta-analysis of randomized controlled trials. 18: 570.
2. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, et al. (2016) Assessment of Global Incidence and Mortality of Hospital-treated Sepsis - Current Estimates and Limitations. Am J Respir Crit Care Med 193: 259-272.
3. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, et al. (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. 2012. Crit Care Med 41: 580-637.
4. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, et al. (2017) Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 43: 304-377.
5. Angus DC, van der Poll T (2013) Severe sepsis and septic shock. N Engl J Med 369: 840-851.
6. He H, Long Y, Liu D, Wang X, Zhou X (2015) Clinical classification of tissue perfusion based on the central venous oxygen saturation and the peripheral perfusion index. Crit Care 19: 330.
7. van Beest P, Wietasch G, Scheeren T, Spronk P, Kuiper M (2011) Clinical review: use of venous oxygen saturations as a goal—a yet unfinished puzzle. Crit Care 15: 232.
8. Suetrong B, Walley KR (2016) Lactic acidosis in sepsis: It’s not all anaerobic. Implications for diagnosis and management. Chest 149: 252-261.
9. Marik PE (2014) Early management of severe sepsis: concepts and controversies. Chest 145: 1407-1418.
10. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, et al. (2011) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345: 1368-1377.
11. Hartog C, Bloos F (2014) Venous oxygen saturation. Best Pract Res Clin Anaesthesiol 28: 419-428.
12. Yealy DM, Kellum JA, Huang DT, Barnato AE (2014) A Randomized Trial of Protocol-Based Care for Early Septic Shock. N Engl J Med 370: 1683-1693.
13. Peake SL, Delaney A, Bailey M (2014) Goal-directed resuscitation for patients with early septic shock. N Engl J Med 371: 1496-1506.
14. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, et al. (2015) Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 372: 1301-1311.
15. Gupta RG, Hartigan SM, Kashiouris MG, Sessler CN, Bearman GM (2015) Early goal-directed resuscitation of patients with septic shock: current evidence and future directions. Crit Care 19: 286.
16. Chemtob RA, Eskesen TG, Moeller-Soerensen H, Perner A, Ravn HB (2016) Systematic review of the association of venous oxygenation and outcome in adult hospitalized patients. Acta Anaesthesiol Scand 60: 1367-1378.

17. Rivers EP, Yataco AC, Jaehne AK, Gill J, Disselkamp M (2015) Oxygen extraction and perfusion markers in severe sepsis and septic shock: diagnostic, therapeutic and outcome implications. Curr Opin Crit Care 21: 381-387.

18. Galley HF (2011) Oxidative stress and mitochondrial dysfunction in sepsis. Br J Anaesth 107: 57-64.

19. Pope JV, Jones AE, Giaeski DF, Arnold RC, Trzeciak S, et al. (2010) Multicenter study of central venous oxygen saturation (ScvO2) as a predictor of mortality in patients with sepsis. Ann Emerg Med 55: 40-46.

20. Textoris J, Fouche L, Wiramus S, Antonini F, Tho S, et al. (2011) High central venous oxygen saturation in the latter stages of septic shock is associated with increased mortality. Crit Care 15: R176.

21. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, et al. (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22: 707-710.

22. Le Gall JR, Lemeshow S, Saultier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270: 2957-2963.

23. Hosking C, Wilander R, Goosen J, Jacobson H, Moeng M, et al. (2011) Low central venous oxygen saturation in haemodynamically stabilized trauma patients is associated with poor outcome. Acta anaesthesiologica Scandinavica 55: 713-721.

24. Balzer F, Sander M, Simon M, Spies C, Habicher M, et al. (2015) High central venous saturation after cardiac surgery is associated with increased organ failure and long-term mortality: an observational cross-sectional study. Crit Care 19: 168.

25. van Beest FA, Hofsstra JJ, Schultz MJ, Boerma EC, Sprook PE, et al. (2008) The incidence of low venous oxygen saturation on admission to the intensive care unit: a multi-center observational study in The Netherlands. Crit Care 12: R33.

26. Jones AE, Shapiro NJ, Trzeciak S, Arnold RC, Claremont HA, et al. (2010) Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA 303: 739-746.

27. Puskarich MA, Marchick MR, Kline JA, Steuerwald MT, Jones AE (2009) One year mortality of patients treated with an emergency department based early goal directed therapy protocol for severe sepsis and septic shock: a before and after study. Crit Care 13: R167.

28. Park JS, Kim SJ, Lee SW, Lee EJ, Han KS, et al. (2015) Initial Low Oxygen Extraction Ratio Is Related to Severe Organ Dysfunction and High In-Hospital Mortality in Severe Sepsis and Septic Shock Patients. J Emerg Med 49: 261-267.

29. Lee YK, Hwang SY, Shin TG, Jo IJ, Suh GY, et al. (2016) Prognostic Value of Lactate and Central Venous Oxygen Saturation after Early Resuscitation in Sepsis Patients. PLoS One 11: e0153305.

30. Boulain T, Garot D, Vignon P, Lascarrou JB, Desachy A, et al. (2004) Prevalence of low central venous oxygen saturation in the first hours of intensive care unit admission and associated mortality in septic shock patients: a prospective multicentre study. Crit Care 18: 609.

31. Shepherd SJ, Pearse RM (2009) Role of central and mixed venous oxygen saturation measurement in perioperative care. Anesthesiology 111: 649-656.

32. Vallet B, Adamczyk S, Barreau O, Lebuffe G (2009) Physiologic transfusion triggers. Best Pract Res Clin Anaesthesiol 21: 173-181.

33. Meybohm P, Shander A, Zacharowski K (2015) Should we restrict erythrocyte transfusion in early goal directed protocols? BMC anesthesiology 15: 75.

34. Perz S, Uhlig T, Kohl M, Bredle DL, Reinhart K, et al. (2011) Low and "supranormal" central venous oxygen saturation and markers of tissue hypoxia in cardiac surgery patients: a prospective observational study. Intensive Care Med 37: 52-59.