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# Agreement of noninvasive cerebral oxygenation with mixed venous oxygen saturation in patients undergoing ECMO-therapy

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**Abstract**

**Purpose:** Approximately 1% of patients require temporary circulatory support due to cardiogenic shock following cardiac surgery. These patients are at risk of a mismatch between oxygen delivery and demand and carry a substantial mortality and morbidity risk. Mixed venous oxygen saturation ($SvO_2$) is the still the "gold standard" for the determination of the ratio between systemic oxygen delivery and consumption ($DO_2/VO_2$ ratio) in cardiac surgery patients. A noninvasive technique is thought to be cerebral near-infrared spectroscopy determining cerebral oxygen saturation ($ScO_2$). The present analysis aims to compare $ScO_2$ and $SvO_2$ in adult patients undergoing ECMO therapy for postoperative cardiogenic shock.
**Methods:** Data were collected hourly for the first 24 hours postoperatively. Each patient was equipped with a pulmonary artery catheter (PAC) connected to a Vigilance II® monitor (Edwards Lifesciences, Irvine, USA) for continuous determination of $SvO_2$ and an INVOS 5100 monitoring system (Somanetics, Troy, USA) to determine $ScO_2$. Data were analyzed by parametric testing and Bland-Altman analysis.
**Results:** 10 consecutive patients were included in this prospective, observational study. $SvO_2$ and $ScO_2$ did not differ significantly throughout the observation period. Bland-Altman analysis showed a mean difference (bias) of 2,37 % and limits of agreement of 13,72 % to -8,99 %
**Conclusions:** These data suggest that $ScO_2$ does not differ significantly from $SvO_2$ in patients undergoing ECMO therapy for postoperative cardiogenic shock and may thus be a noninvasive alternative to monitor the $DO_2/VO_2$ ratio during this condition.

**Key words:** cardiac surgery, near-infrared spectroscopy, pulmonary artery catheter, mixed venous oxygen saturation, cerebral oxygen saturation.

## Introduction

Approximately 1% of all patients undergoing cardiac surgery require prolonged postoperative circulatory support due to refractory cardiac and/or pulmonary dysfunction. Because of their inability to be managed with standard medical therapy, these patients are at very high risk for subsequent morbidity and mortality, presenting a therapeutic challenge for cardiac surgeons and intensivists as well. To secure hemodynamic stability, extracorporeal membrane oxygenation (ECMO) is one treatment modality for temporary bridging in this critical early postoperative phase [1].

As maintenance of adequate tissue oxygenation is essential in critical ill patients, goal-directed hemodynamic optimization targeting a mixed venous oxygen saturation ($SvO_2$) greater than 70% has been shown to reduce postoperative organ dysfunction and length of hospital stay in patients after cardiac surgery [2]. Therefore, $SvO_2$ guided therapy has received a *"grade A recommendation"* in the German S3 guideline for the postoperative hemodynamic treatment of these patients [3].

Because very recent publications have clearly shown that central venous oxygen saturation cannot be used as a substitute for mixed venous oxygen saturation ($SvO_2$) in this setting [4,5,6], the use of a pulmonary artery catheter (PAC) for determination of $SvO_2$ may still be regarded as a "gold standard". However, the insertion of a PAC in patients undergoing veno-arterial ECMO – i.e. right atrial cannulation – is technically demanding. Additionally, the prolonged use of a PAC is not without risk [7]. Thus a noninvasive but continuous technique would be desirable for early detection of deterioration of the global oxygen balance.

One such technique is near-infrared spectroscopy (NIRS) [8,9]. Cerebral oximetry was first described more than 25 years ago and has recently been investigated in the context of severe traumatic brain injury [10,11], high-risk cardiac surgery [12], and cardiac surgery [13]. This technology is similar to pulse oximetry in that it uses differences in light absorption between oxygenated and desoxygenated hemoglobin to measure regional oxygen saturation. As the blood in the brain microvasculature is approximately 70% venous, 25% arterial and 5% capillary the measurement reflects the regional balance between oxygen delivery and consumption. However, several lines of evidence [13,14] are suggestive that cerebral oxygen saturation readings also reflect the systemic ratio between oxygen delivery and demand and may thus be related to mixed-venous oxygen saturation.

Thus, the aim of this observational study was to evaluate whether $ScO_2$ determined by NIRS may be used as a substitute of $SvO_2$ in adult patients requiring temporary circulatory support due to cardiogenic shock following cardiac surgery in an intensive care setting.

## Materials and methods

### Study protocol

Following approval by the local ethical committee and written informed consent of the patient or his legal representative, cerebral oxygen saturation readings and hemodynamics of 1178 patients undergoing cardiac or thoracic vascular surgery at the Department of Cardiac and Thoracic Vascular Surgery (University of Lübeck) were prospectively studied intra- and postoperatively in 2008 [15]. For this specific analysis we focused on patients requiring temporary circulatory support due to refractory cardiogenic shock following cardiac surgery.

### Patient monitoring

All patients were already equipped intraoperatively with a pulmonary artery catheter (CCOmbo 744HF75), connected to a Vigilance II® monitor (Edwards Lifesciences, Irvine, USA) for semi-continuous monitoring of cardiac output (CCO) and continuous monitoring of $SvO_2$.

At admission to the ICU, two $ScO_2$ sensors of an INVOS 5100 monitoring system (Somanetics, Troy, USA) were positioned on the right and left side of the patient's forehead. To avoid interference from the sagittal sinus, the light emitter was placed 2 cm above the supraorbital ridge and 2 cm lateral to the midsagittal plane. To secure obtaining signals from the frontoparietal brain tissue, the detector was placed laterally from the emitter and on a line parallel to that between the supraorbital ridge and the outer ear canal. The probes were secured to the head by their self-adhesive layer and by an additional self-adhesive bandage. Additionally, immediately after ICU-admission and following pressure guided verification of the catheter position, in-vivo calibration of the Vigilance-II® monitor was performed according to the instructions of the manufacturer.

### ECMO management and patient interventions

Arterial cannulation was performed with a 15–21F cannula inserted directly into the ascending aorta and venous drainage was achieved with a 21–28F cannula inserted directly into the right atrium. ECMO flow was gradually increased to 4.5 L/min and thereafter adjusted to achieve a normal arterial blood pressure while not completely unloading the pulmonary circulation and the left heart. Inotropes (dobutamine and milrinone) and vasopressors (noradrenaline) were adjusted accordingly. The optimal ECMO blood flow was determined by monitoring mixed venous oxygen saturation (SvO2), with the goal being an $SvO_2$ of >70%.

Oxygen flow ($FiO_2$) was adjusted to maintain a postoxygenator partial oxygen pressure of 300mmHg or greater. By adjusting ECMO gas flow, carbon dioxid was kept within the normal range (37-42 mmHg). Mechanical ventilation was continued during ECMO therapy with biphasic positive airway pressure. Respirator settings were most commonly set at a tidal volume of 6-7 mL/kg body weight, rate of 10 breaths/min, positive end expiratory pressure of 7 cm $H_2O$, maximum ventilation pressure of 25 cm $H_2O$ and an inspiratory $O_2$ concentration of 40%. Analgosedation was maintained within the first 24h hours with a continuous infusion of remifentanil (0.2 mg * kg *min) and propofol (3 mg * kg * h). An external convective warming system with overbody blanket (Bairhugger®, Arizant Healthcare, Eden Prairie, MN) was used to actively warm the patients to 36°C core temperature measured by urine bladder temperature.

During ECMO-therapy routine clinical targets include isotonic fluid as well as parenteral/enteral nutrition administration at maintenance rate, a mean arterial blood pressure between 60 and 80mmHg and a central venous pressure between 12 to 14 mmHg.

### Data collection

Comparative measurements of $SvO_2$ and averaged $ScO_2$ levels from the left and right forehead values were performed hourly for the first 24 hours after ICU-admission.

### Statistical analyses

Data entry and data analyses were conducted by using MedCalc 10 for Windows. Measurements were reported as mean ± standard deviation. Following analysis for normal distribution by the Kolmogorov-Smirnov test, data were analyzed parametrically by Student's t-test for paired samples. Additionally, Bland-Altman statistics for repeated measures (16) were calculated on the raw and relative data. With respect to the clinical relevance to detect $SvO_2$ levels below 70%, Bland-Altman analyses were additionally performed for average $SvO_2$ levels lower and equal or higher than 70%. Level of statistical significance was set at $p < 0.05$ for all tests.

## Results

A total of 10 patients requiring temporary circulatory support due to cardiogenic shock following cardiac surgery were enclosed. Mean duration of ECMO support was 116 hours (48 to 265 hours). Patient's basic demographic data are shown in table 1. All SvO2 values were in a range between 47 to 86 %.

*Table 1: Basic Demographic Data*

| Demographic | Value |
|---|---|
| No.<br>male (%)<br>female (%) | 10<br>7 (70)<br>3 (30) |
| Age, yr | 69 ± 15 |
| Height, cm | 175 ± 10.2 |
| Weight, kg | 86.3 ± 12.8 |
| BSA, cm² | 1.86 ± 0.29 |
| Euroscore, % | 12.5 ± 3.1 |
| Procedure type, (%)<br>CABG operations<br>Valve operations<br>Others | <br>6 (60)<br>3 (30)<br>1 (10) |

Bland-Altman analyses for repeated measures of the collected oxygenation data (n = 10 patients with 25 measures each) revealed a bias of 2,37 % (mean 95 % CI: 0,58 to 4,15) and limits of agreement (1,96 standard deviation) of 13,72 % to -8,99 % (upper 95 % CI: 21,06 to -1,65; lower 95 % CI 6,39 to -16,33) for the raw data of the whole group (figure 1).

Bland-Altman analyses of average $SvO_2$ values below 70 % (n = 5 patients with 25 measures each) showed a bias of 2,96 % (mean 95 % CI: -0,11 to 6,04) and limits of agreement (1,96 standard deviation) of 16,79 % to -10,86 % (upper 95 % CI: 32,94 to 5,29; lower 95 % CI -0,64 to -27,01).

Bland-Altman analyses of average $SvO_2$ values equal or higher than 70% (n = 5 patients with 25 measures each) revealed a bias of 1,77% (mean 95 % CI: 1,51 to 5,05) and limits of agreement (1,96 standard deviation) of 10,10 % to -6,56 % (upper 95 % CI: 19,83 to 3,17; lower 95 % CI 0,37 to -16,30).

In addition to the Bland-Altman analyses described above, t-test for paired samples were conducted to see whether $SvO_2$ and $ScO_2$ mean values differ significantly from each other. In 9 out of 25 pairs we could find a statistically significant difference with $p < 0,05$ (mean differences ranging from 1,10 – 3,20)

Interestingly, despite $SvO_2$ values > 70 %, we noticed 19 events in 4 patients with $ScO_2$ values less than 50 % for more than 5min. All events had been associated with arterial $pCO_2$ levels below 30 mmHg, whereas no other changes in hemodynamic or oxygenation parameters could be determined.

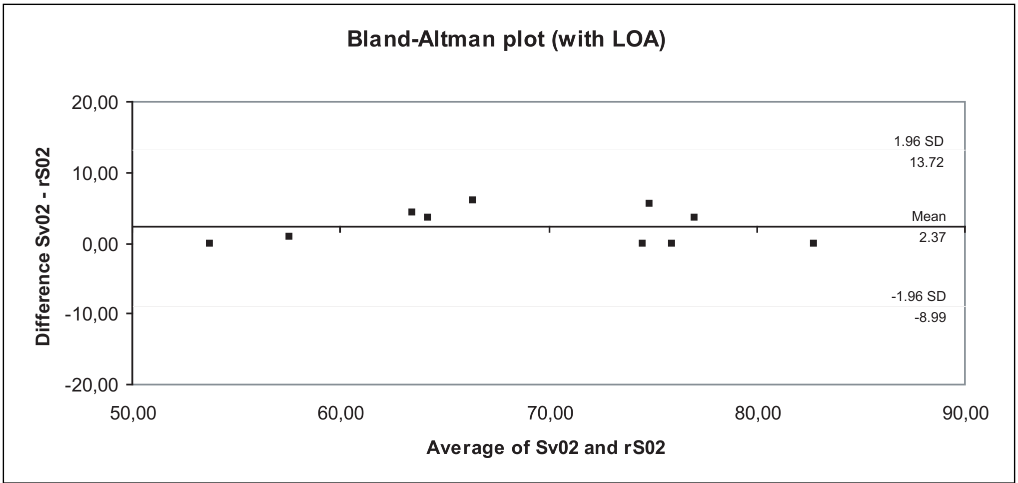


*Figure 1: Bland-Altman plot of relative $SvO_2$ and $ScO_2$ data from patients requiring temporary circulatory support obtained by continuous mixed venous oximetry ($SvO_2$ monitor) or by near-infrared spectroscopy.*

## Discussion

The present prospective observational pilot study was designed to determine if cerebral oxygen saturation monitoring may be used as noninvasive alternative for monitoring systemic oxygen balance in adult cardiac surgery patients requiring ECMO therapy. The main finding was an excellent agreement of $ScO_2$ and $SvO_2$ as a measure of the systemic oxygen to delivery ratio in a range of $SvO_2$ values between 47% and 86%.

Variable results on the comparability of $ScO_2$, $SvO_2$, and $ScvO_2$ have been obtained in other populations. Dullenkopf et al. [14] observed only a poor correlation ($r = 0.3$) between $SvO_2$ and $ScO_2$ in adult patients after cardiac surgery, but an acceptable sensitivity to detect changes in mixed-venous oxygen saturation in patients after cardiac surgery. Nagdyman et al. [17], Tortoriello et al. [18], and Bhutta et al. [19] reported moderate to good correlations ($r = 0.5$ to $r = 0.7$) between cerebral oxygen saturation and $ScvO_2$ either in postoperative pediatric cardiac surgery patients and spontaneously breathing children undergoing endomyocardial biopsy after heart transplantation. These discrepancies may, at least in part, be caused by different patient populations in the above mentioned studies, but also by variations in clinical management, i.e. the effects of sedation and ventilator therapy [20].

Beyond these direct comparison studies, indirect evidence from observational and interventional studies supports that $ScO_2$ is an index of systemic oxygen balance. We have recently shown that the preoperative cerebral oxygen saturation determined by NIRS is reflective of the severity of cardiopulmonary dysfunction, associated with mortality and morbidity in cardiac surgery patients [15], and that patients showing an intraoperative $ScO_2$ below 50% have a higher complication rate and a prolonged length of intensive care unit and hospital stay [21]. Murkin et al. demonstrated a lower incidence of major organ morbidity and mortality when cerebral saturations were maintained above 75% of baseline intraoperatively [13]. Similarly, Casati and colleagues demonstrated a shorter hospital and recovery room stay when cerebral saturations were maintained at 75% of baseline by following a present algorithm [12]. Taken together, these data underline that cerebral oximetry may be capable of detecting ischemic events, guiding therapeutic interventions and possibly reducing the incidence of neurological and systemic insults during the perioperative phase of patients undergoing cardiac surgery.

Following the argumentation of Critchley and Critchley a difference of less than 30% for relative data is clinically acceptable [22]. It may be debatable, if the Critchley and Critchley criteria – developed for the comparison of cardiac output monitors – can also be applied for the comparison of venous oximetry data. However, keeping in mind the imprecision of different blood gas analyzers in measuring venous oxygen saturations [23] and the differences between intermittent and continuous mixed venous oxygen saturation monitoring [24] some degree of uncertainty is unavoidable when using venous oximetry for guiding treatment.

The limits of agreement found in our data were much smaller than 30%, while at the same time an excellent correlation between $ScO_2$ and $SvO_2$ values was observed (ranging from $r = 0,87$ to $r = 0,98$; $p < 0,01$). This suggests that $SvO_2$ and $ScO_2$ are clinically interchangeable values for monitoring global oxygenation in patients undergoing ECMO therapy.

## Limitations

This study has several limitations:
First of all, the value of the NIRS technology to detect changes in cerebral oxygenation has been questioned in the past. Especially the contribution of extracerebral tissue to the NIRS reading is controversial [25,26]. After cardiac surgery and especially after prolonged procedures, patients tend to be vasoconstricted and mildly hypothermic when ad-

mitted to the intensive care unit. Increasing peripheral perfusion because of decreasing peripheral vasoconstriction in patients being rewarmed may result in higher $ScO_2$ values after rewarming without any changes in $SvO_2$ [27].

Second, one has to keep in mind that the NIRS technology used in the present study has mainly developed for *monitoring regional impairment in cerebral perfusion or oxygenation* in patients undergoing carotid and aortic arch surgery. In this context, most data published so far aimed at detecting regional oxygenation disturbances and brain desaturation episodes during major surgery [27]. With bilateral cerebral oximetry, a unilateral decrease in NIRS parameters would indicate a severe regional perfusion disturbance. However, this study was designed to determine global oxygenation especially as assessed by $SvO_2$ because cerebral tissue blood mainly consists of the venous compartment. Therefore we used the mean value of $ScO_2$ being aware that on the one hand discrepancies between both sides in $ScO_2$ were obscured and on the other hand low $ScO_2$ values due to unilateral desaturation could be obtained although $SvO_2$ values could be still unchanged.

Third, one explanation of the poor correlation between $ScO_2$ values and venous oxygenation in previous studies may be based on the fact, that cerebral oximetry mostly represents the venous perfusion portion of the anterior brain section, but cerebral perfusion is more closely controlled with various physiologic reflex mechanisms than in the thoracoabdominal part of the body. In particular, vascular tonus in the brain is strongly influenced by $pCO_2$ [20] compared to the rest of the body. Comparable observations have been made for the difference between $SvO_2$ and $ScvO_2$ since the difference between both variables increases if oxygen extraction (mainly from the lower part of the body) is increased [28]. Nevertheless, we found in this exclusive patient population an excellent agreement between $ScO_2$ and $SvO_2$ and additionally detected four patients at risk for cerebral hypoxia.

In summary this pilot study suggests that $ScO_2$ may be used for estimation of $SvO_2$ in patients undergoing ECMO therapy due to refractory cardiac dysfunction and that $ScO_2$ may be a noninvasive alternative to monitor global tissue oxygenation under this condition, if normocapnia is maintained. A multicenter study is being implemented to expand our patient experience and determine whether the results of this study can be confirmed.

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