

RESEARCH ARTICLE

Accuracy and precision of $S_{cv}O_2$ measured with the CeVOX-device: A prospective study in patients with a wide variation of $S_{cv}O_2$ -values

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Abstract

Introduction

Central-venous oxygen saturation ($S_{cv}O_2$) is a key parameter of hemodynamic monitoring and has been suggested as therapeutic goal for resuscitation. Several devices offer continuous monitoring features. The CeVOX-device (Pulsion Medical Systems) uses a fibre-optic probe inserted through a conventional central-venous catheter (CVC) to obtain continuous $S_{cv}O_2$.

Objectives

Since there is a lack of studies validating the CeVOX, we prospectively analyzed data from 24 patients with CeVOX-monitoring. To increase the yield of lower $S_{cv}O_2$ -values, 12 patients were equipped with a *femoral* CVC.

Methods

During the 8h study period $S_{cv}O_2$ _CeVOX was documented immediately before withdrawal of blood to measure $S_{cv}O_2$ by blood gas analysis ($S_{cv}O_2$ _BGA) 6min, 1h, 4h, 5h and 8h after the initial calibration. No further calibrations were performed.

Results

In patients with *jugular* CVC (primary endpoint; 60 measurements), bias, lower and upper limits of agreement (LLOA; ULOA) and percentage error (PE) of the estimate of $S_{cv}O_2$ ($S_{cv}O_2$ _CeVOX_jug) were acceptable with 0.45%, -13.0%, 13.9% and 16.6%, respectively.

As supposed, $S_{cv}O_2$ was lower in the *femoral* compared to the *jugular* measurements (69.5 ± 10.7 vs. 79.4 ± 5.8 ; $p < 0.001$). While the bias (0.64%) was still acceptable, LLOA (-23.8%), ULOA (25.0%) and PE (34.5%) were substantially higher for *femoral* assessment of $S_{cv}O_2$ by the CeVOX ($S_{cv}O_2$ _CeVOX_fem).

Analysis of the entire data-pool with *jugular* as well as *femoral* CVCs allowed for a multivariate analysis which demonstrated that the position of the CVC per se was not

Competing interests: Wolfgang Huber is member of the Medical Advisory Board of Pulsion Medical Systems SE, Feldkirchen, Germany. This does not alter our adherence to PLOS ONE policies on sharing data and materials. All other authors have declared that no competing interests exist.

independently associated with the bias $S_{cv}O_2_{CeVOX} - S_{cv}O_2_{BGA}$. The amount of the bias $|S_{cv}O_2_{CeVOX} - S_{cv}O_2_{BGA}|$ was independently associated with the amount of the change of $S_{cv}O_2_{CeVOX}$ compared to the initial calibration to $S_{cv}O_2_{BGA_baseline}$ ($|S_{cv}O_2_{CeVOX} - S_{cv}O_2_{BGA_baseline}|$) as well as with low values of $S_{cv}O_2_{BGA_baseline}$. Furthermore, increasing time to the initial calibration was associated to the amount of the bias with borderline significance.

A statistical model based on $|S_{cv}O_2_{CeVOX} - S_{cv}O_2_{BGA_baseline}|$ and “time to last calibration” derived from an evaluation dataset (80 of 120 datasets, 16 of 24) provided a ROC-AUC of 0.903 to predict an amount of the bias $|S_{cv}O_2_{CeVOX} - S_{cv}O_2_{BGA}| \geq 5\%$ in an independent validation group (40 datasets of 8 patients).

Conclusion

These findings suggest that the CeVOX device is capable to detect stability or instability of $S_{cv}O_2_{BGA}$. $S_{cv}O_2_{CeVOX}$ accurately estimates $S_{cv}O_2_{BGA}$ in case of stable values. However, intermittent measurement of $S_{cv}O_2_{BGA}$ and re-calibration should be performed in case of substantial changes in $S_{cv}O_2_{CeVOX}$ compared to baseline. Therefore, continuous measurement of $S_{cv}O_2$ with the CeVOX cannot replace $S_{cv}O_2_{BGA}$ in instable patients. On the other hand, CeVOX might be useful for the monitoring of stable patients as a pre-test tool for more differentiated monitoring in case of changes in $S_{cv}O_2_{CeVOX}$.

Introduction

In case of stable values for hemoglobin and the arterial oxygen saturation S_aO_2 the oxygen saturation of blood returning to the right heart necessarily depends on cardiac output (CO) and oxygen consumption VO_2 . The oxygen saturation of blood drawn from a central venous catheter (CVC) or via a pulmonary arterial catheter (PAC) has been termed central-venous oxygen saturation $S_{cv}O_2$ and mixed-venous oxygen saturation $S_{mv}O_2$, respectively. Both parameters reflect the relation of oxygen delivery and consumption. Normally, only about 25% of the delivered oxygen is withdrawn by the oxygen consuming tissues. Therefore, normal values for $S_{cv}O_2$ and $S_{mv}O_2$ are about 65–75%. In case of increased oxygen consumption and/or reduced delivery, $S_{cv}O_2$ and $S_{mv}O_2$ decrease. Consequently, decreasing values of $S_{cv}O_2$ and $S_{mv}O_2$ are used as warning signs indicating that mechanisms to compensate an impaired balance between oxygen consumption and delivery have been activated. While smaller decreases in $S_{cv}O_2$ and $S_{mv}O_2$ can be considered as physiological compensatory mechanism, more pronounced and prolonged decreases frequently precede anaerobic metabolism and hyperlactatemia.

Based on this pathophysiological rationale, $S_{cv}O_2$ and $S_{mv}O_2$ have been suggested as therapeutic goals for resuscitation and as key targets of hemodynamic monitoring to avoid tissue hypoxia despite normal macro-circulatory parameters such as MAP and CVP [1,2,3,4,5]. Furthermore, $S_{cv}O_2$ has been suggested as therapeutic goal for resuscitation and as a basic parameter of haemodynamic monitoring [3,6].

Several approaches have been established to facilitate these concepts:

Since the use of a PAC has certain risks and it is costly and limited in time, $S_{mv}O_2$ has largely been replaced by $S_{cv}O_2$ which can easily be determined via a CVC [1,2,3].

Since repeated measurements are cumbersome and costly in long term critically ill patients, several devices *continuously* deriving $S_{cv}O_2$ have been introduced. In addition to economic advantages, continuous monitoring offers the potential to increase the yield of pathological

$S_{cv}O_2$ measurements. Therefore, continuous monitoring is in particular attractive in stable patients at risk of sudden circulatory instability to provide a sensitive pre-test tool for more differentiated monitoring.

Several devices offer continuous monitoring features, including the CeVOX (Pulsion Medical Systems SE, Feldkirchen, Germany). Usually, continuous measurement is based on infrared oximetry which detects transmitted light of different wavelengths reflected by red blood cells varying with different concentrations of oxyhemoglobin and hemoglobin [1].

While some devices have integrated the infrared probe into special catheters, the use of the CeVOX is even further facilitated, since the probe can be introduced into a catheter already in place. Despite its use for more than a decade, there are only few studies available that prove validity and clinical usefulness [7,8,9,10,11]. Some validation studies suggest that accuracy and precision might depend on the absolute value of $S_{cv}O_2$ with lower values resulting in imprecision compared to the gold-standard of blood gas analysis (BGA; Table 1).

Therefore, we performed a validation study in 24 patients equipped with the CeVOX device. To increase the yield of lower $S_{cv}O_2$ -values, we included 12 patients equipped with a femoral CVC.

Materials and methods

The study was approved by the institutional review board (Ethikkommission Technische Universität München; Fakultät für Medizin; No. 5384/12). Written informed consent was obtained by all patients or their legal representatives. All patients were treated in a 14-bed university hospital general ICU with predominantly medical patients. Informed consent was obtained by all patients or their legal representatives. Between July and October 2016 we included 24 patients with hemodynamic monitoring comprising transpulmonary thermodilution (TPTD; PiCCO; Pulsion Medical Systems SE, Feldkirchen, Germany), central venous catheter and measurement of $S_{cv}O_2$ irrespective of the study. For indicator injections for TPTD, blood

Table 1. Experimental and clinical studies on the use of CeVOX.

Reference	Setting	No. of patients	No. of measurements	Mean and/or range $S_{cv}O_2$ _BGA	Bias CeVOX-BGA	LLOA; ULOA	Comment
Huber D et al. [10]	In vitro	n.a.	2*40 (2 different CeVOX-catheters)	~60%; 9%-100%	+0.957%-0.175%	-7.69%; +9.61%-11.20%; +10.85%	In vitro using ECMO-device; underestimation of high $S_{cv}O_2$, overestimation of low $S_{cv}O_2$
Baulig W et al. [7]	In vitro	n.a.	n = 66	~55%;5.5–100%	+2.4%	-11.8%; +16.6%	In vitro using paediatric cardio-pulmonary bypass. Underestimation of high $S_{cv}O_2$, overestimation of low $S_{cv}O_2$
Baulig W et al. [8]	Cardiac surgery; ICU	n = 20	n = 84 surgery;	~70% (45%-89%)	-0.9%	-7.9%; +6.1%	Intra- and peri-operative measurements. Underestimation of high $S_{cv}O_2$, overestimation of low $S_{cv}O_2$. Underestimation in case of high cardiac index.
			n = 106 ICU	~75% (43%-90%)	-1.2%	-10.5%; +8.1%	
Müller M et al. [9]	Paediatric cardiac surgery	n = 3	n = 12	~60%; ~33–82%	-4.38%	-7.86%; -0.90%	4 measurements per patient
Molnar Z et al. [11]	Critically ill patients	n = 53	n = 526	72.3±9.9; ~30–95%	+0.3%	-12.5%; +13.2%	Multi-centric trial
This study: jugular CVC	Critically ill patients	n = 12	n = 60	79.4±5.7; 66–90%	+0.45%	-13.0% +13.9%	
This study: femoral CVC	Critically ill patients	n = 12	n = 60	69.5±10.7; 33–86%	+0.64%	-23.8% +25.0%	Only study reporting on femoral CVC

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withdrawal for blood gas analysis including $S_{cv}O_2$ and insertion of the CeVOX-probe (PV2022-37; Pulsion Medical Systems SE, Feldkirchen, Germany) a 5-lumen CVC (Multicath 5, Vygon; Aachen, Germany) with a maximum intravascular length of 20 cm and a diameter of 3.15 mm (9.5 Fr) was used. The position of the tip was controlled (and corrected) according to X-ray in case of jugular, but not in case of femoral venous catheter access. The vascular part of the femoral venous catheter was completely inserted under ultrasound guidance. The CeVOX was inserted into the medial lumen of the CVC ending at the tip of the catheter according to the manufacturer's recommendations with the aim to protrude the distal end of the catheter by 2 cm. For insertion a sterile Y-adapter was used which enables insertion of the probe through one lumen and withdrawal of blood for BGA through the other lumen of adapter. This provides withdrawal of blood at the most distal lumen of the CVC in close proximity to the fiber probe. For blood gas analysis a Siemens RapidPoint 500 (Siemens Healthcare, Erlangen, Germany) analyzer was used. Baseline BGA was performed to calibrate the CeVOX subunit of a PiCCO-2 or Pulsioflex monitor (Pulsion Medical Systems SE, Feldkirchen, Germany). No further calibrations of the CeVOX were performed during the study period. To investigate a potential impact of cardiac index (CI) on the accuracy of the estimate of $S_{cv}O_2$ provided by the CeVOX ($S_{cv}O_2$ _CeVOX) a triplicate TPTD was performed immediately before the baseline BGA. The registration of the arterial TPTD curve was performed as previously described [12,13].

During the 8h study period $S_{cv}O_2$ _CeVOX was documented immediately before withdrawal of blood to measure $S_{cv}O_2$ by BGA ($S_{cv}O_2$ _BGA) 6min, 1h, 4h, 5h and 8h after the initial calibration.

Statistical analyses

Raw data were examined for input data error. Continuous variables were expressed as mean \pm standard deviation. Categorical variables are expressed as percentages. Spearman's coefficient of correlation was calculated to analyze the correlation of two parameters. To compare continuous variables we used Wilcoxon-test for paired samples.

Bland-Altman analysis was used to analyze the bias between $S_{cv}O_2$ _CeVOX and $S_{cv}O_2$ _BGA as well as to compute limits of agreement and percentage error. Bland-Altman analyses were corrected for repeated measurements allowing variability of true values within each subject [14].

With regard to clinical importance and comparability with previous studies Bland-Altman-analysis of the data derived from jugular BGA measurements was the primary endpoint of the study.

Prediction of the amount of the bias $|S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA| was a major secondary endpoint. The amount of the bias is the absolute **non-negative** value of the bias without regard to its **sign**. To optimize the yield of our dataset, we used a three step approach: In a first step, we tried to assess the overall potential to derive a formula predicting unacceptable bias of $S_{cv}O_2$ _CeVOX. Therefore, we performed multivariate analysis regarding the amount of the bias $|S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA| in the total dataset ($n = 120$) including variables with a p -value < 0.2 in univariate analysis regarding this endpoint.

With regard to practical application only those variables were included in the regression analysis that would be available during continuous use of CeVOX after a single initial calibration.

In a second step, we randomly allocated the 24 patients in a 2:1 ratio to an evaluation group ($n = 16$ patients with 80 measurements) and to an independent validation group ($n = 8$ patients with 40 measurements). This was done to derive a prediction formula from two thirds

of the datasets and to test its “robustness” in 40 “independent” measurements of the validation group that did not contribute to the derivation of the prediction formula (third step).

A similar approach has been described previously to derive and validate different models predicting inaccuracy of transpulmonary thermodilution with room temperature instead of ice-cold saline injectate [15].

Receiver operating characteristics (ROC)-analyses were performed to assess the discriminative ability of predictors regarding categorical endpoints.

Sample size was chosen according to the recommendation of Bland (<https://www-user.york.ac.uk/~mb55/meas/sizemeth.htm>). This publication suggests a number of $n = 100$ pairs in order to achieve an appropriate precision for the Bland-Altman analyses. Also accounting for potential drop-outs, incomplete datasets and pre-defined subgroup analyses we choose a number of $n = 120$.

All statistical analyses were performed using the IBM SPSS Statistics software version 23 (SPSS Inc., Chicago, IL, USA).

Results

Patients characteristics

Table 2 shows the patients baseline characteristics.

All patients were critically with a mean APACHE-II score of 21. Half of the patients suffered from ARDS, another 33% of sepsis. Consequently, 75% were under mechanical ventilation and vasopressors were necessary during 67% of the measurements. The baseline cardiac index derived from TPTD with the PiCCO-device was 4 ± 1.6 L/min/m².

Comparison of $S_{cv}O_2$ _CeVOX_jug and $S_{cv}O_2$ _BGA_jug in patients with jugular CVC (primary endpoint)

In patients with jugular CVC (primary endpoint) $S_{cv}O_2$ _BGA_jug and $S_{cv}O_2$ _CeVOX_jug were significantly correlated ($r = 0.567$; $p < 0.001$).

$S_{cv}O_2$ _CeVOX_jug and $S_{cv}O_2$ _BGA_jug were not significantly different (79.9 ± 8.2 vs. $79.4 \pm 5.7\%$; $p = 0.337$) with a mean bias of $0.45 \pm 6.8\%$. Lower and upper limits of agreement

Table 2. Patients characteristics.

Based on datasets (n = 24)	
Sex (male:female; n (%))	13:11 (54%:46%)
Age (years±SD)	65±15
Underlying disease (n (%))	
- Sepsis	8 (33%)
- ARDS	12 (50%)
- Severe pancreatitis	2 (8%)
- Liver cirrhosis	2 (8%)
Height (cm ± SD)	173±9
Weight (kg ± SD)	81±20
APACHE-II score (n ± SD)	21±8
Measurements under vasopressors	16 (67%)
Measurements under mechanical ventilation	18 (75%)
Measurements under controlled ventilation (CV)	13 (54%)
Measurements under sinus rhythm (SR)	23 (96%)
Measurements under SR and CV	12 (50%)

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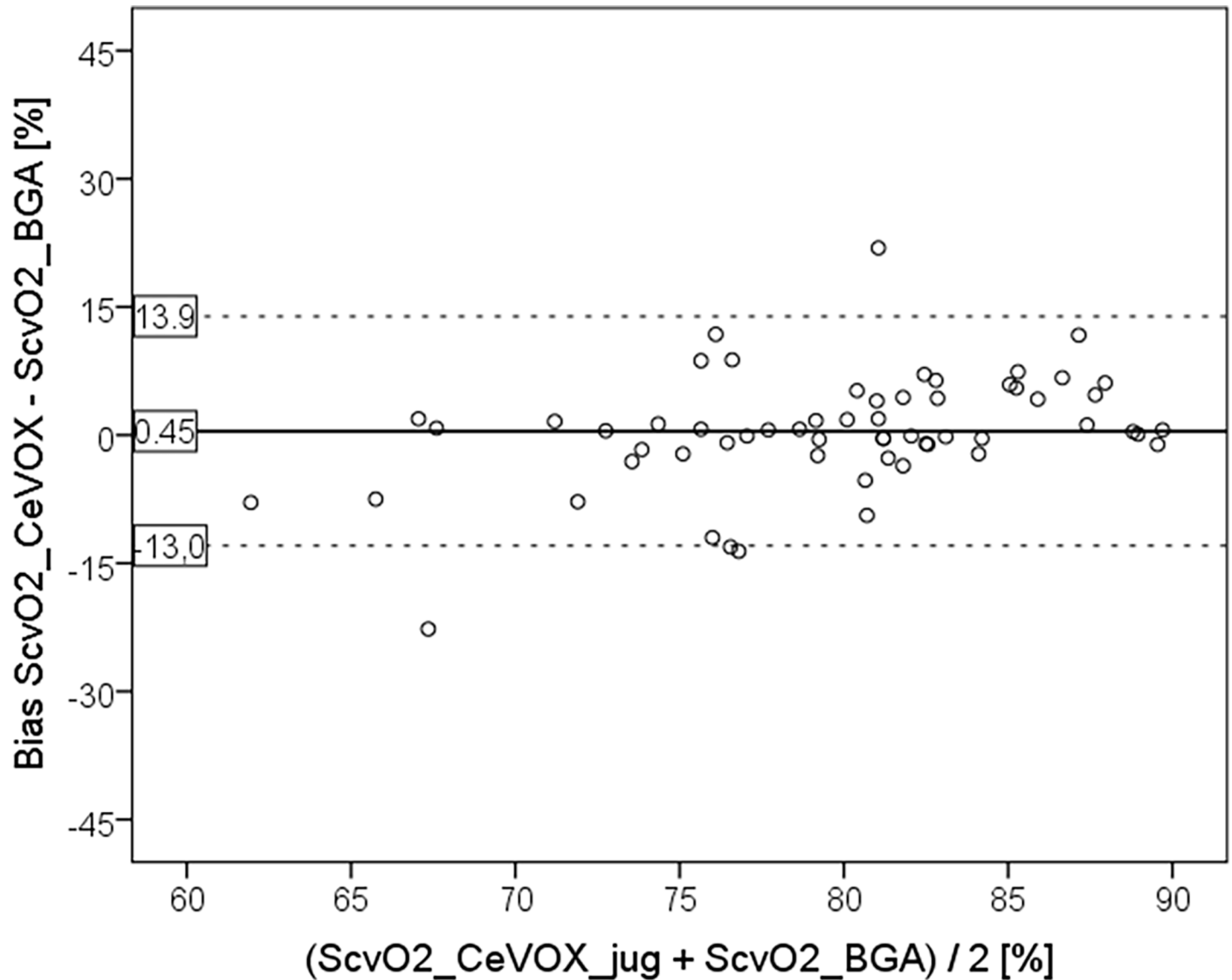


Fig 1. Bland Altman plot comparing $S_{cv}O_2$ _CeVOX_jug to $S_{cv}O_2$ _BGA derived from measurements with jugular CVC. $S_{cv}O_2$ _CeVOX_jug: Central venous oxygen saturation derived from the CeVOX-device. $S_{cv}O_2$ _BGA: Central venous oxygen saturation derived from blood gas analysis. CVC: Central venous catheter.

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(LLOA; ULOA) and percentage error (PE) were acceptable with -13.0%, 13.9% and 16.6% respectively (Fig 1).

Comparison of $S_{cv}O_2$ _CeVOX_fem and $S_{cv}O_2$ _BGA_fem in patients with femoral CVC

As supposed, $S_{cv}O_2$ _BGA was lower in femoral compared to jugular measurements (69.5 ± 10.7 vs. $79.4 \pm 5.8\%$; $p < 0.001$).

Similar to jugular measurements $S_{cv}O_2$ _BGA_fem and $S_{cv}O_2$ _CeVOX_fem significantly correlated ($r = 0.488$; $p < 0.001$) for measurements with femoral vein CVC access. Mean values of $S_{cv}O_2$ _CeVOX_fem and $S_{cv}O_2$ _BGA_fem were comparable (70.1 ± 13.1 vs. $69.5 \pm 10.7\%$; $p = 0.496$) with a mean bias of 0.64%.

While the bias was still acceptable, LLOA (-23.8%), ULOA (25.0%) and PE (34.5%) were substantially higher for femoral assessment of $S_{cv}O_2$ by the CeVOX ($S_{cv}O_2$ _CeVOX_fem; Fig 2) compared to $S_{cv}O_2$ _CeVOX_jug.

Analyses with jugular and femoral CVC

To further analyze the potential impact of catheter position (jugular or femoral), the amount of $S_{cv}O_2$ _BGA, time to calibration of the CeVOX-device and other variables on accuracy and precision of $S_{cv}O_2$ _CeVOX we analyzed the total dataset including jugular as well as femoral catheter positions.

$S_{cv}O_2$ _BGA and $S_{cv}O_2$ _CeVOX significantly correlated ($r = 0.607$; $p < 0.001$). Mean values of $S_{cv}O_2$ _CeVOX and $S_{cv}O_2$ _BGA were comparable (75.0 ± 11.9 vs. $74.5 \pm 9.9\%$; $p = 0.262$) with a mean bias of 0.55%, LLOA of -18.9%, ULOA of 20.0% and a PE of 25.9% (Fig 3).

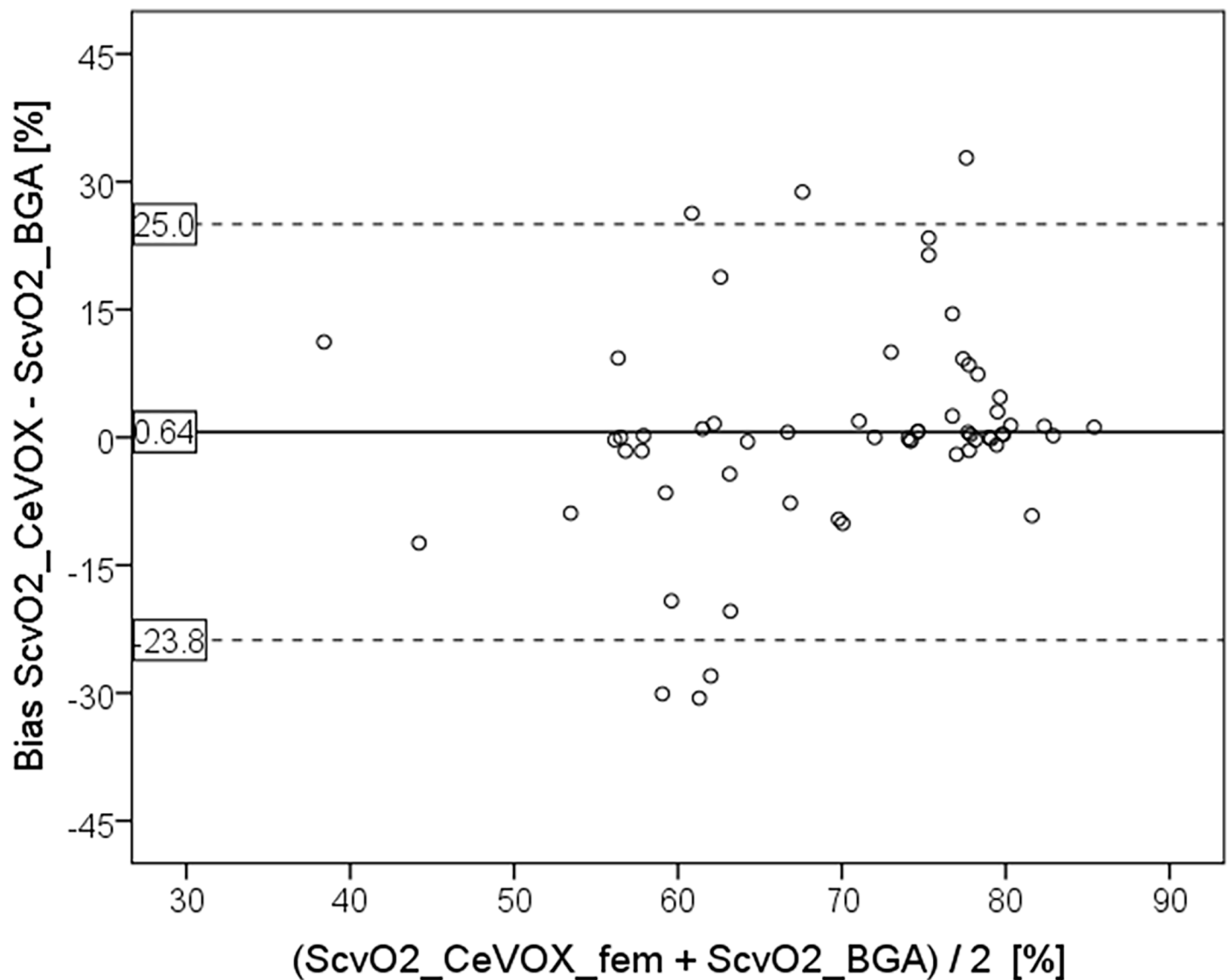


Fig 2. Bland Altman plot comparing $S_{cv}O_2$ _CeVOX_fem to $S_{cv}O_2$ _BGA derived from measurements with femoral CVC. $S_{cv}O_2$ _CeVOX_fem: Central venous oxygen saturation derived from the CeVOX-device. $S_{cv}O_2$ _BGA: Central venous oxygen saturation derived from blood gas analysis. CVC: Central venous catheter.

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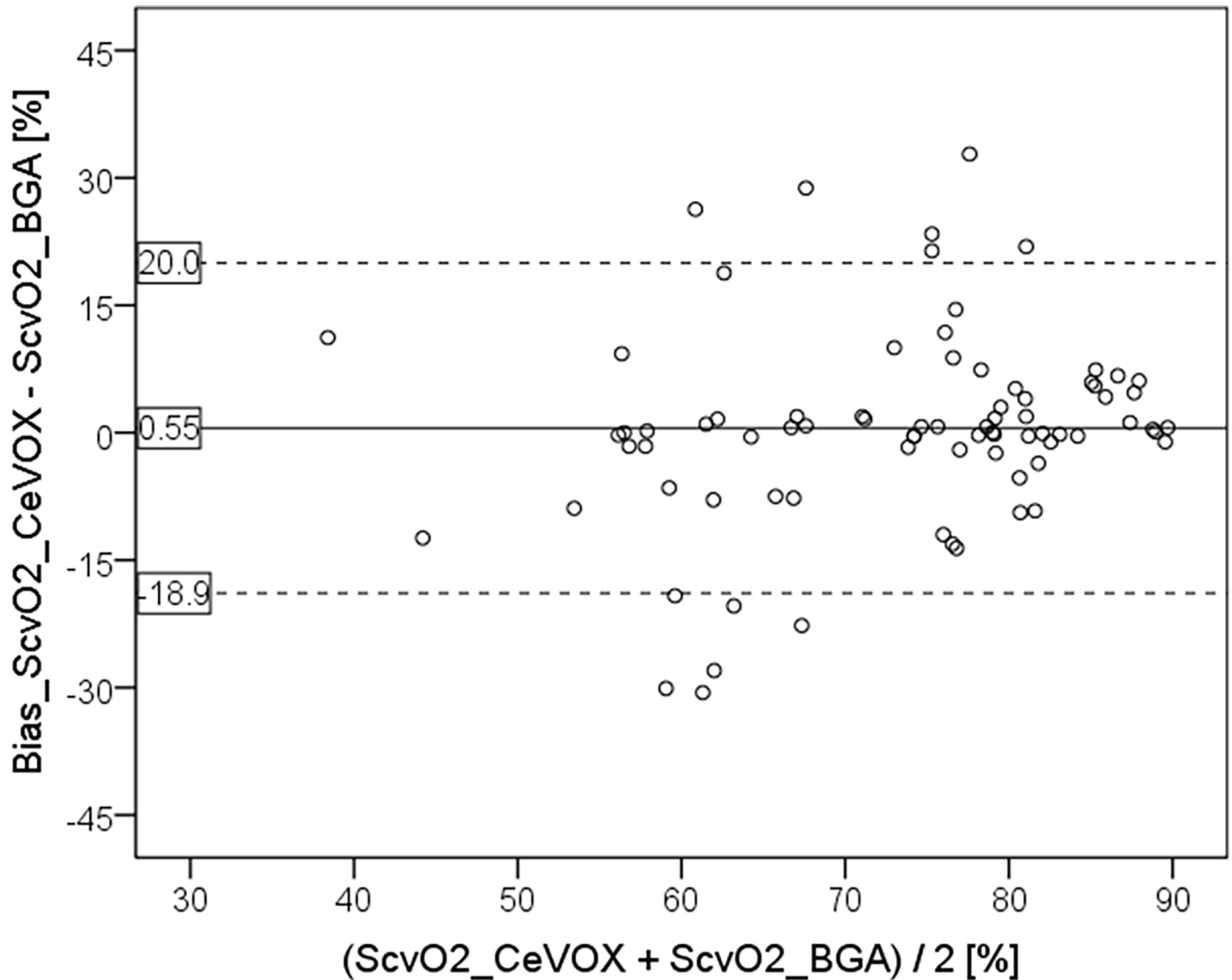


Fig 3. Bland Altman plot comparing $S_{cv}O_2$ _CeVOX to $S_{cv}O_2$ _BGA derived from all measurements (jugular or femoral CVC). $S_{cv}O_2$ _CeVOX: Central venous oxygen saturation derived from the CeVOX-device. $S_{cv}O_2$ _BGA: Central venous oxygen saturation derived from blood gas analysis. CVC: Central venous catheter.

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Predictors of imprecision of $S_{cv}O_2$ _CeVOX in all patients with jugular or femoral CVC

Table 3 shows the univariate correlations (Spearman) of several variables to the bias $S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ and to the amount of the bias $|S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA|. The bias and its amount were neither correlated with femoral position of the CVC nor with the base CI derived from TPTD.

In univariate analysis bias $S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA was significantly associated with changes in $S_{cv}O_2$ compared to baseline $S_{cv}O_2$ _BGA.

The bias $S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA was associated with high values of $S_{cv}O_2$ _CeVOX ($r = 0.556$; $p < 0.001$), high values of $\Delta S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA_baseline ($r = 0.790$; $p < 0.001$) and lower values of $\Delta S_{cv}O_2$ _BGA- $S_{cv}O_2$ _BGA_baseline ($r = -0.323$; $p < 0.001$).

Table 3. Univariate association of different variables to $S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ and the amount $|S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ |.

Variable	Association to bias $S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA		Association to the amount $ S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA	
	r-value	p-value	r-value	p-value
CVC_femoral	r = -0.008	p = 0.931	r = 0.041	p = 0.659
Time after calibration	r = 0.018	p = 0.846	r = 0.561	p < 0.001
$S_{cv}O_2$ _BGA	r = -0.160	p = 0.082	r = -0.243	p = 0.008
$S_{cv}O_2$ _CeVOX	r = 0.556	p < 0.001	r = -0.086	p = 0.355
BGA_baseline	r = -0.056	p = 0.545	r = -0.226	p = 0.014
CI_td_baseline	r = -0.140	p = 0.147	r = -0.045	p = 0.640
PEEP_base	r = -0.280	p = 0.006	r = 0.029	p = 0.780
PIP_base	r = 0.056	p = 0.593	r = 0.046	p = 0.662
F_iO_2 _base	r = -0.120	p = 0.250	r = 0.149	p = 0.151
pH	r = -0.096	p = 0.300	r = 0.102	p = 0.272
pCO ₂	r = 0.262	p = 0.004	r = -0.157	p = 0.088
pO ₂	r = -0.141	p = 0.129	r = -0.249	p = 0.007
HCO ₃ ⁻	r = 0.113	p = 0.220	r = -0.013	p = 0.884
Tricuspid regurgitation [grade]	r = 0.067	p = 0.499	r = 0.02	r = 0.799
Δ _ $S_{cv}O_2$ _BGA- $S_{cv}O_2$ _BGA_baseline	r = -0.323	p < 0.001	r = -0.257	p = 0.005
Δ _ $S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA_baseline	r = 0.790	p < 0.001	r = 0.028	p = 0.763
$ (\Delta$ _ $S_{cv}O_2$ _BGA- $S_{cv}O_2$ _BGA_baseline)	r = 0.076	p = 0.410	r = 0.532	p < 0.001
$ (\Delta$ _ $S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA_baseline)	r = 0.038	p = 0.685	r = 0.773	p < 0.001

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Furthermore, the bias $S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA was associated with lower PEEP (r = -0.280; p = 0.006) and higher central-venous pCO₂ (r = 0.262; p = 0.004) with a low degree of correlation.

The amount of the bias $|S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA| was univariately associated with increasing time after calibration (r = 0.561; p < 0.001), lower values of $S_{cv}O_2$ _BGA (r = -0.242; p = 0.008), lower values of $S_{cv}O_2$ _BGA_baseline (r = -0.226; p = 0.014) and of Δ _ $S_{cv}O_2$ _BGA- $S_{cv}O_2$ _BGA_baseline (r = -0.257; p = 0.005). A particular strong association of the amount of the bias $|S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA| was found for the absolute changes in $S_{cv}O_2$ _BGA and $S_{cv}O_2$ _Cevox compared to $S_{cv}O_2$ _BGA_baseline (r = 0.773; p < 0.001 for $|(\Delta$ _ $S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA_baseline)| and r = 0.532; p < 0.001 for $|(\Delta$ _ $S_{cv}O_2$ _BGA- $S_{cv}O_2$ _BGA_baseline)|. This suggests that the amount of the bias increases with increasing changes of $S_{cv}O_2$ (measured by BGA or by CeVOX) compared to baseline.

Furthermore, the bias $|S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA| was weakly associated with a lower central-venous pO₂ (r = -0.249; p = 0.007).

Close association of one or more parameters to (the amount of) the bias $S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA could be of interest for practical use, e.g. to provide an internal control for the device suggesting recalibration by measurement of $S_{cv}O_2$ _BGA as a kind of recalibration-alarm.

Therefore, we performed multivariate analysis regarding the amount of the bias $|S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA|. With regard to practical application only those variables were included in the regression analysis that would be available during continuous use of CeVOX after a single initial calibration.

For this major secondary endpoint we used a three-step-approach:

In a first step we performed a multiple regression analysis in the total dataset (n = 120) regarding the amount of the bias $|S_{cv}O_2$ _CeVOX- $S_{cv}O_2$ _BGA|.

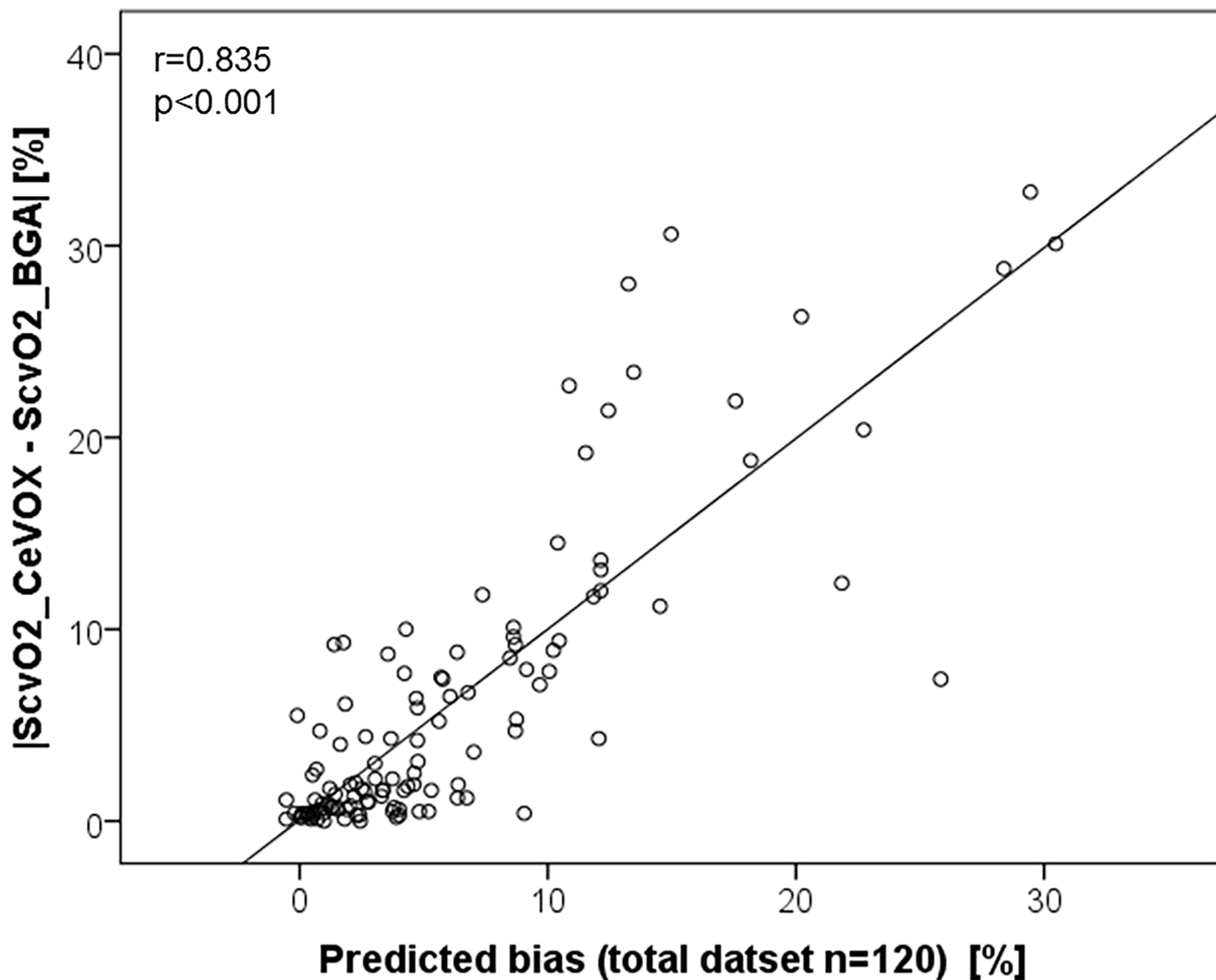


Fig 4. Correlation of the amount of the bias $|S_{cv}O_2_{CeVOX}-S_{cv}O_2_{BGA}|$ with a prediction formula derived from the total dataset (n = 120). $S_{cv}O_2_{CeVOX}$: Central venous oxygen saturation derived from the CeVOX-device. $S_{cv}O_2_{BGA}$: Central venous oxygen saturation derived from blood gas analysis.

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The final model ($R = 0.835$; $R^2 = 0.697$; Fig 4) included $|S_{cv}O_2_{CeVOX}-S_{cv}O_2_{BGA}_{baseline}|$ ($p < 0.001$; t -value 14.959), $S_{cv}O_2_{BGA}_{baseline}$ ($p = 0.007$; $t = -2.770$) and—with borderline significance— $S_{cv}O_2_{CeVOX}$ ($p = 0.083$; t -value = 1.751, whereas time after initial calibration and CVC-site were not independently associated to the amount of the bias $|S_{cv}O_2_{CeVOX}-S_{cv}O_2_{BGA}|$.

In a second step, we randomly divided the 120 datasets in 80 evaluation datasets and 40 independent validation datasets.

The final model derived from the 80 evaluation datasets included $|S_{cv}O_2_{CeVOX}-S_{cv}O_2_{BGA}_{baseline}|$ ($p < 0.001$; t -value 11.610) as outstanding predictor of $|S_{cv}O_2_{CeVOX}-S_{cv}O_2_{BGA}|$. Furthermore, “time to last calibration” was independently associated with $|S_{cv}O_2_{CeVOX}-S_{cv}O_2_{BGA}|$ with borderline significance ($p = 0.065$; t -value 1.875) in this model. The predictive capabilities of this model were high ($R = 0.830$; $R^2 = 0.689$).

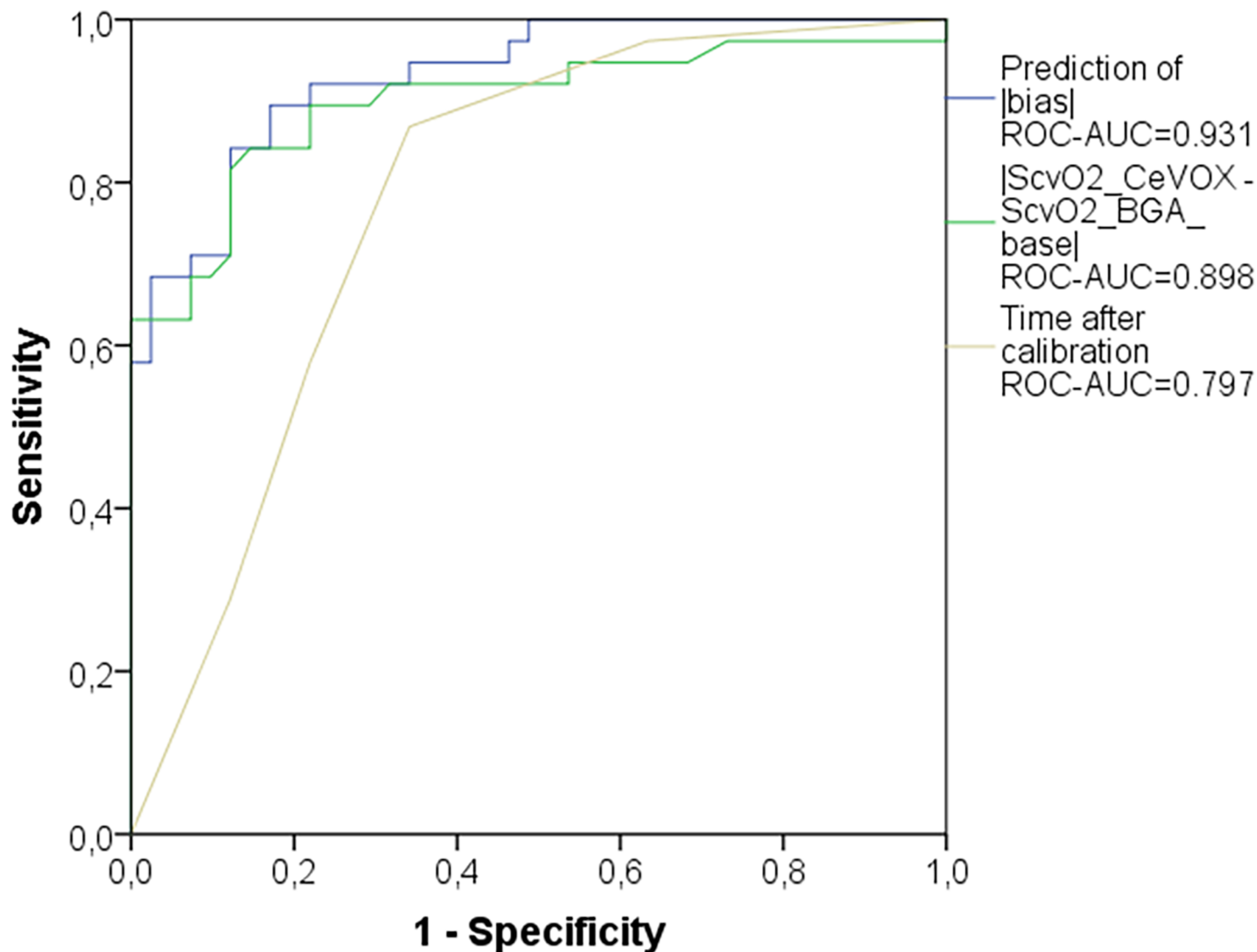


Fig 5. ROC curve comparing different predictors of $|S_{cv}O_2_{CeVOX} - S_{cv}O_2_{BGA}| \geq 5\%$ in the evaluation group (n = 80). “Prediction of |bias|”: model predicting $|S_{cv}O_2_{CeVOX} - S_{cv}O_2_{BGA}|$ which was derived from multiple regression analysis within the evaluation group. ROC: receiver operating characteristic. AUC: area under the curve. $S_{cv}O_2_{CeVOX}$: Central venous oxygen saturation derived from the CeVOX-device. $S_{cv}O_2_{BGA}$: Central venous oxygen saturation derived from blood gas analysis.

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A prediction model derived from these two parameters provided a ROC-AUC of 0.931 ($p < 0.001$) in the evaluation group to predict an amount of the bias $|S_{cv}O_2_{CeVOX} - S_{cv}O_2_{BGA}| \geq 5\%$. The ROC-AUC for this model was slightly higher than that for $|S_{cv}O_2_{CeVOX} - S_{cv}O_2_{BGA_baseline}|$ (AUC = 0.898; $p < 0.001$) and substantially higher than for time to last calibration (AUC = 0.779; $p < 0.001$; Fig 5).

In a third step, the prediction model derived from the evaluation group provided a ROC-AUC of 0.903 ($p < 0.001$) in the validation group to predict an amount of the bias $|S_{cv}O_2_{CeVOX} - S_{cv}O_2_{BGA}| \geq 5\%$. This was in the same range as for $|S_{cv}O_2_{CeVOX} - S_{cv}O_2_{BGA_baseline}|$ (AUC = 0.905; $p < 0.001$), but substantially higher than for “time after last calibration” (AUC = 0.758; $p = 0.020$; Fig 6).

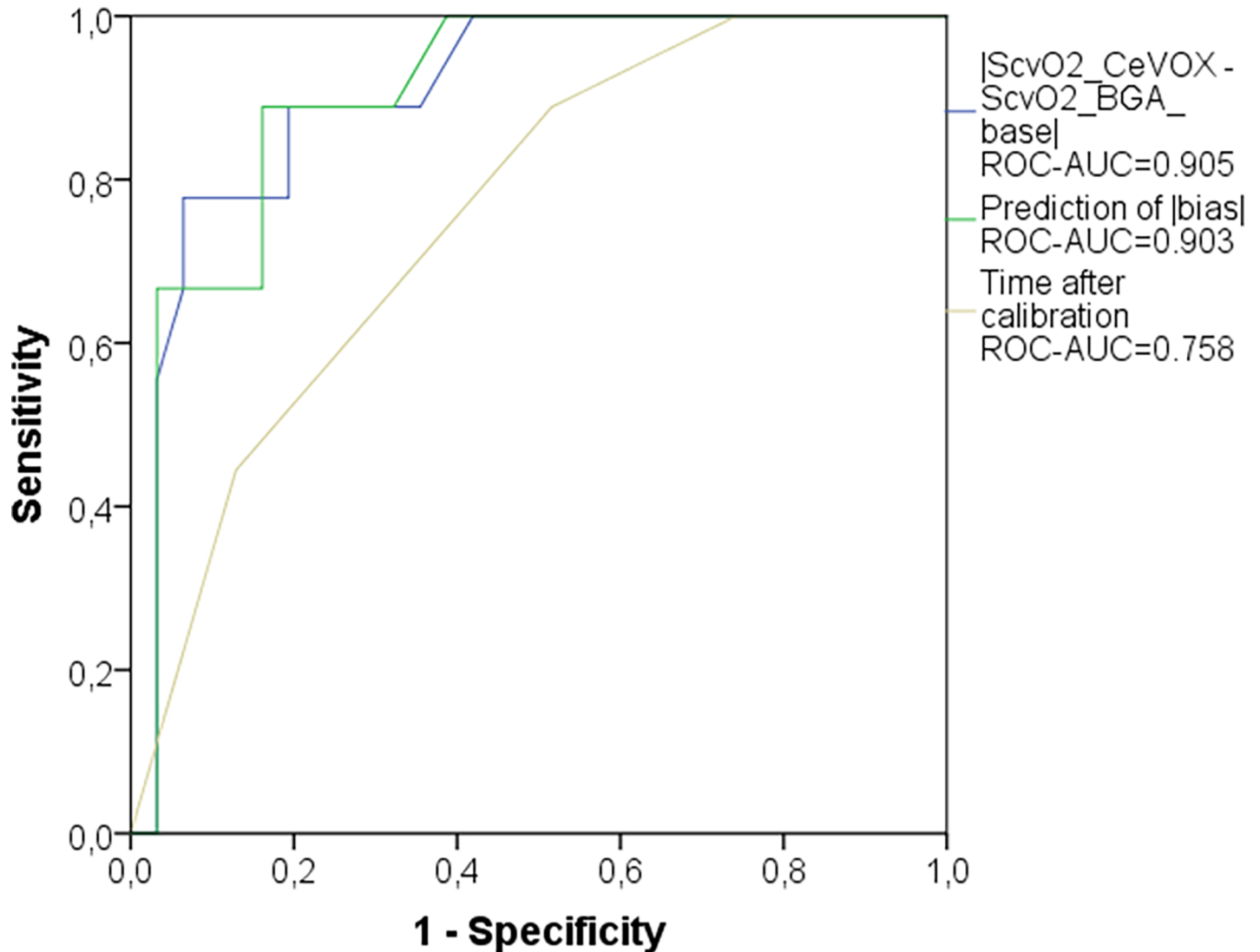


Fig 6. ROC curve comparing different predictors of $|S_{cv}O_2_{CeVOX} - S_{cv}O_2_{BGA}| \geq 5\%$ in the independent validation group (n = 40). Prediction of |bias|: model predicting $|S_{cv}O_2_{CeVOX} - S_{cv}O_2_{BGA}|$ which was derived from multiple regression analysis within the evaluation group. ROC: receiver operating characteristic. AUC: area under the curve. $S_{cv}O_2_{CeVOX}$: Central venous oxygen saturation derived from the CeVOX-device. $S_{cv}O_2_{BGA}$: Central venous oxygen saturation derived from blood gas analysis.

<https://doi.org/10.1371/journal.pone.0192073.g006>

Discussion

$S_{cv}O_2$ has been used to guide resuscitation with [3] and without success [16,17,18]. Most of the patients in the intervention group in these studies were equipped with a CVC with continuous $S_{cv}O_2$ monitoring capability. Despite the use of continuous measurement of $S_{cv}O_2$ and $S_{mv}O_2$ for several decades, there are only few studies available that prove their accuracy, precision and clinical usefulness.

This also applies to the CeVOX-device. Our observational study compared $S_{cv}O_2_{CeVOX}$ to $S_{cv}O_2_{BGA}$ during an 8-hours period without recalibration, but repeated withdrawal of blood to determine $S_{cv}O_2_{BGA}$. We deliberately included patients with a femoral CVC to increase the yield in lower values of $S_{cv}O_2$, since in critically ill patients with (analgo)-sedation $S_{cv}O_2$ in vena cava inferior usually is lower than in vena cava superior.

Using this approach the following main results were found:

1. For higher values of $S_{cv}O_2_BGA$ derived from jugular CVCs (primary endpoint) the $S_{cv}O_2_CeVOX_jug$ provided acceptable bias, percentage error and limits of agreement.
2. By contrast, for lower values of $S_{cv}O_2$ predominantly withdrawn from femoral CVCs, $S_{cv}O_2_CeVOX_fem$ provided an acceptable bias, but inappropriately high values for the percentage error and the limits of agreement as well as a poor correlation to $S_{cv}O_2_BGA$ ($r = 0.488$).
3. Analysis of the entire data-pool with *jugular* as well as *femoral* CVCs allowed for the multivariate analysis which demonstrated that the position of the CVC per se was not independently associated with the bias $S_{cv}O_2_CeVOX - S_{cv}O_2_BGA$. The amount of the bias was independently associated with the amount of the change of $S_{cv}O_2_CeVOX$ compared to the initial calibration to $S_{cv}O_2_BGA_baseline$ as well as to low values of $S_{cv}O_2_BGA_baseline$. Furthermore, increasing time to the initial calibration was associated to the amount of the bias with borderline significance.
4. A statistical model based on $|S_{cv}O_2_CeVOX - S_{cv}O_2_BGA_baseline|$ and “time to last calibration” derived from an evaluation dataset (80 of 120 datasets, 16 of 24) provided a ROC-AUC of 0.903 to predict an amount of the bias $|S_{cv}O_2_CeVOX - S_{cv}O_2_BGA| \geq 5\%$ in an independent validation group (40 datasets of 8 patients).

As for most of the few previously published studies the bias for $S_{cv}O_2_CeVOX$ was acceptable and clearly within a range between -1% and +1%, irrespective of jugular (+0.45%) or femoral (+0.63%) position of the CVC [7,8,9,10,11].

In case of *jugular* CVC, lower and upper limits of agreement (-13.0%; +13.9%) for $S_{cv}O_2_CeVOX_jug$ were in the range of the two previous in vitro and of three in vivo studies with nearly identical values as for the study by Molnar and colleagues including patients from the same ICU as this study (-12.5; +13.2%; see Table 1).

However, for lower $S_{cv}O_2_CeVOX_fem$ derived from a *femoral* CVC LLOA (-23.8%) and ULOA (+25.0%) were not in the acceptable range. Consequently, percentage error values were acceptable for jugular measurements (16.6%), “borderline” for the totality of measurements (25.9%) and out of the acceptable range for femoral measurements (34.5%). At first glance, even the percentage error for femoral measurements seems in the same range as given by Molnar et al. (35.5%). However, a closer look at this study demonstrates that the percentage error was calculated by dividing the difference between ULOA and LLOA by the mean of $S_{cv}O_2_CeVOX$ and $S_{cv}O_2_BGA$. This is an unusual method to calculate the percentage error which results in values twice as high as suggested by Critchley and colleagues [19]. Consequently, the percentage error according the Critchley-method would have been 17.8% in the Molnar-study which is the range of our findings for jugular measurements.

Our findings of a lower precision of $S_{cv}O_2_CeVOX_fem$ in case of lower $S_{cv}O_2_BGA$ derived from femoral measurements raise the key question, if imprecision is related to femoral measurement, to lower values of $S_{cv}O_2_BGA$ or to any other variables. With a wide range of $S_{cv}O_2_BGA$ between 33% and 90%, jugular as well as femoral measurements, different standardized intervals between measurements and concomitant TPTD measurement of CI our data allowed for *univariate* as well as *multivariate* analyses of different potential confounders of $S_{cv}O_2_CeVOX$.

Several previous studies (see Table 1) suggested a *systematic* imprecision resulting in an underestimation of high and an *overestimation* of high values of $S_{cv}O_2_BGA$ [7,8,10]. By

contrast, in our study there was a better agreement for higher values of $S_{cv}O_2$ in general without a hint for a systematic *underestimation*.

One of five previous studies demonstrated an underestimation of $S_{cv}O_2$ _BGA by the CeVOX-device in case of high cardiac index [8]. These findings were neither confirmed by our univariate nor by multivariate analyses. However, the study by Baulig et al. was performed in patients undergoing cardiac surgery with a markedly lower mean CI of 2.6 (range 1.0–4.5 L/min/m²) compared to our study (mean CI 4.3±1.6; range 2.1–7.4 L/min/m²).

On the contrary, our results with increasing imprecision of CeVOX with lower values of $S_{cv}O_2$ _BGA are in line with the statement of Molnar et al. that “the scatter increases as $S_{cv}O_2$ goes below 65%” [11].

Although our study suggests that imprecision of the CeVOX is associated rather to low values of $S_{cv}O_2$ than to *femoral* measurement per se, a potential impact of femoral measurement has to be discussed: Kissoon and co-workers demonstrated in an animal experiment simulating various hemodynamic conditions that oximetry-based estimates of $S_{cv}O_2$ derived with a different catheter were more imprecise for measurements in the inferior vena cava than in the superior vena cava. They concluded that “the oximetry catheter is capable of identifying changes in $S_{cv}O_2$ under physiological conditions usually encountered in clinical medicine but was less accurate at the extremes of physiology and when placed in the inferior vena cava catheter especially during hypovolaemia and hypoxia” [20].

Finally, “drifts over time” have been reported [10], suggesting decreasing precision over time. These findings are supported by our study showing uni- and multivariate association of the amount of the bias to the time to last calibration. This clearly suggests the need for regular re-calibration of continuous oximetry catheters estimating $S_{cv}O_2$.

According to our analyses of the total data pool as well as of separate evaluation and validation groups changes in $S_{cv}O_2$ _CeVOX compared to the baseline calibration were—by far—the strongest predictors of imprecision of the $S_{cv}O_2$ _CeVOX.

Practical implications

Derivation of a formula—based on changes in $S_{cv}O_2$ _CeVOX compared to calibration and on time to last calibration—predicting inappropriate precision of $S_{cv}O_2$ _CeVOX might have practical implications. Since the usefulness of this formula was confirmed in an independent validation group of patients, this formula could be implemented as a kind of automated quality control suggesting re-calibration. A similar “calibration-index” has been suggested for re-calibration of continuous pulse contour analysis derived cardiac index by transpulmonary thermodilution [21]. A modification of the suggested formula has been included in the latest software of the PiCCO-2-device as a kind of decision support to optimize re-calibration and to improve the yield of relevant findings by thermodilution.

Strengths and limitations

Heterogeneity of the patients, also investigating measurements derived from femoral CVCs increasing the yield of low values of $S_{cv}O_2$, availability of TPTD to measure CI can be considered as strengths of the study. These characteristics also allowed for the multivariate analyses. Furthermore, the number of patients and measurements was sufficient to validate findings within an *evaluation* group in an independent *validation* group.

Finally, the findings of the study might have practical implications with regard to the above-mentioned “calibration-index” as a kind of automated quality control which might improve patient care and safe personal as well as material resources.

Nevertheless, this single-center study is based on a limited number of patients and measurements over a short period.

Conclusions

Continuous estimation of $S_{cv}O_2$ by the CeVOX is accurate and precise, if the values are close to those at baseline. However, re-calibration should be performed in case of substantial changes compared to baseline. Furthermore, low values of $S_{cv}O_2$ and longer time to calibration were associated with imprecision of the CeVOX-device. The integration of a calibration.index indicating the need for recalibration might help to improve the precision of the CeVOX device.

Finally, continuous measurement of $S_{cv}O_2$ with the CeVOX cannot replace $S_{cv}O_2$ -BGA in instable patients. On the other hand, CeVOX might be useful for monitoring of stable patients as a pre-test tool for more differentiated monitoring in case of changes in $S_{cv}O_2$ -CeVOX. Improved continuous assessment of $S_{cv}O_2$ including automated quality control might be useful also during anaesthesia in high risk surgery and during the stabilization phase in certain patients in an accident and emergency department.

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Visualization: Alexander Herner, Ulrich Mayr, Sebastian Rasch, Wolfgang Huber.

Writing – original draft: Alexander Herner, Wolfgang Huber.

Writing – review & editing: Alexander Herner, Bernhard Haller, Ulrich Mayr, Sebastian Rasch, Lea Offman, Roland Schmid, Wolfgang Huber.

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