



Non-invasive capnodynamic mixed venous oxygen saturation during major changes in oxygen delivery

Anders Svedmyr^{1,2} · Mark Konrad³ · Mats Wallin^{1,3} · Magnus Hallbäck³ · Per-Arne Lönnqvist^{1,2} · Jacob Karlsson^{1,2}

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Abstract

Mixed venous oxygen saturation (SvO₂) is an important variable in anesthesia and intensive care but currently requires pulmonary artery catheterization. Recently, non-invasive determination of SvO₂ (Capno-SvO₂) using capnodynamics has shown good agreement against CO-oximetry in an animal model of modest hemodynamic changes. The purpose of the current study was to validate Capno-SvO₂ against CO-oximetry during major alterations in oxygen delivery. Furthermore, evaluating fiberoptic SvO₂ for its response to the same challenges. Eleven mechanically ventilated pigs were exposed to oxygen delivery changes: increased inhaled oxygen concentration, hemorrhage, crystalloid and blood transfusion, preload reduction and dobutamine infusion. Capno-SvO₂ and fiberoptic SvO₂ recordings were made in parallel with CO-oximetry. Respiratory quotient, needed for capnodynamic SvO₂, was measured by analysis of mixed expired gases. Agreement of absolute values between CO-oximetry and Capno-SvO₂ and fiberoptic SvO₂ respectively, was assessed using Bland–Altman plots. Ability of Capno-SvO₂ and fiberoptic SvO₂ to detect change compared to CO-oximetry was assessed using concordance analysis. The interventions caused significant hemodynamic variations. Bias between Capno-SvO₂ and CO-oximetry was +3% points (95% limits of agreements –7 to +13). Bias between fiberoptic SvO₂ and CO-oximetry was +1% point, (95% limits of agreements –7 to +9). Concordance rate for Capno-SvO₂ and fiberoptic SvO₂ vs. CO-oximetry was 98% and 93%, respectively. Capno-SvO₂ generates absolute values close to CO-oximetry. The performance of Capno-SvO₂ vs. CO-oximetry was comparable to the performance of fiberoptic SvO₂ vs. CO-oximetry. Capno-SvO₂ appears to be a promising tool for non-invasive SvO₂ monitoring.

Keywords Hemodynamic monitoring · Carbon dioxide · Cardiac output · Pulmonary artery · Oxygen · Oximetry

1 Introduction

Mixed venous oxygen saturation (SvO₂) is a clinically useful monitoring parameter that provide important information regarding the whole-body oxygen delivery/consumption

balance and is of particular interest in the setting of anaesthesia and intensive care [1]. The use of SvO₂ as a routine monitoring parameter has so far been hampered by the fact that intermittent blood sampling from the pulmonary artery (CO-oximetry; representing “gold standard”) as well as continuous assessment by fibreoptic spectrophotometry both require invasive catheterization of the pulmonary artery, which is associated with certain risks as well as increased nursing care demands and cost [2, 3].

During our development of a modern version of capnodynamic assessment of cardiac output (Effective Pulmonary Blood Flow, CO_{EPBF}), which we have found to produce similar results when compared to accepted reference methods, we have come to realize that combining CO_{EPBF} with the respiratory quotient (RQ) results in the possibility to determine SvO₂ noninvasively [4–7]. In a recent proof-of-concept study we have found that this new non-invasive and

✉ Jacob Karlsson
jacob.karlsson.1@ki.se

¹ Karolinska Institute Department of Physiology and Pharmacology (FYFA), C3, Per-Arne Lönnqvist Group - Section of Anesthesiology and Intensive Care, Anestesi- och Intensivvårdsavdelningen, 171 76 Stockholm, PA, Sweden

² Pediatric Perioperative Medicine and Intensive Care, Karolinska University Hospital, Eugenivägen 23, 171 64 Stockholm, Sweden

³ Maquet Critical Care AB, Röntgenvägen 2, 171 06 Solna, Sweden

continuous methodology of monitoring SvO₂ (Capno-SvO₂) show promising results when compared to CO-oximetry determinations of SvO₂ in a porcine model, during modest hemodynamic challenges [8].

The aim of the present study was to validate Capno-SvO₂ against the gold standard CO-oximetry for agreement of absolute values and ability to detect change during profound variations in oxygen delivery while measuring RQ, using our previously well-established porcine model. A comparison between CO-oximetry and another continuous SvO₂ methodology, i.e., fiberoptic SvO₂, was also included for comparison.

2 Materials and methods

2.1 Animal preparations

The study was performed at the Hedenstierna Laboratory, Uppsala University, Uppsala Sweden. Authorization was granted from Uppsala Animal Ethics Committee (Uppsala, Sweden case number C75/16, chairperson Erik Göransson on August 26, 2016).

The animals were handled in accordance with the animal experimentation guidelines of the Uppsala Animal Ethics Committee and Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines.

Eleven domestic-breed pigs of both sexes (median weight 29.6 kg, range 27.1–31.7 kg, 6–8 weeks of age), from the same breeding colony (Mångsbo Farm, Uppsala, Sweden) were used. The animals were kept in a light- and temperature-controlled environment, with unlimited access to tap water and food on a standardized schedule. The experiments were done during daytime hours.

The pigs were anaesthetized as previously described and mechanically ventilated in a volume-controlled mode (Servo-I; Maquet, Solna, Sweden), with tidal volume of 10 mL kg⁻¹ and fraction of inspired oxygen (FiO₂) 0.3 [9]. Positive end-expiratory pressure (PEEP) was kept at 5 cm H₂O after an initial 2-min period of lung expansion using PEEP 10 cm H₂O as previously described [8]. After the lung expansion manoeuvre, an air test using FiO₂ 0.21 was performed and repeated if necessary, aiming for sustained pulse oximetry saturation > 97% as indicative of open lung conditions [10]. The animals were given a bolus of Ringers' acetate solution 20 mL kg⁻¹ after induction and thereafter kept on maintenance infusion of glucose 25 mg mL⁻¹ 8 mL kg⁻¹ h⁻¹ and Ringer's acetate solution 10 mL kg⁻¹ h⁻¹. Exhaled CO₂ was measured by a mainstream infrared CO₂ sensor (Capnostat-3; Respironics Inc, Wallingford, CT), and ventilation airflow was registered through the regular flow sensor of the servo-I ventilator. Volumetric capnography was

utilised for calculating the CO₂ elimination rate (VCO₂), as described in previous studies [11].

Adequate anesthetic depth and analgesic level were tested regularly during the experiment according to standard procedures of the laboratory. The animals were fitted with monitoring devices described in detail in previous studies [9]. In addition a 7.5 F pulmonary artery catheter with fiberoptic SvO₂ monitoring (Swan-Gantz pulmonary artery catheter, model 774F75; Edwards Lifesciences, Irvine CA; USA) and a 5 F femoral artery cannula for transpulmonary thermodilution cardiac output monitoring (PICCO2™, Pulsion Medical Systems, Munich, Germany), were also included as well as an additional 7.5 F pulmonary artery introducer sheath for rapid fluid administration.

A 12 F balloon tipped catheter (Mediq Sverige AB, Uppsala, Sweden) was surgically introduced through the left femoral vein, to a depth of 30 cm corresponding to the inferior vena cava (IVC). The catheter was fitted with a 10 mL balloon allowing partial IVC occlusion when inflated with NaCl 0.9%. The animals were given a bolus dose of intravenous heparin 5000 U (LEO pharma) to minimize the risk of clotting due to the extensive intravascular monitoring setup.

SvO₂ through blood samples were analysed by a CO-oximeter calibrated for porcine hemoglobin (OSM3; Radiometer Medical AbS, Brønshøj, Denmark). This also provided the hemoglobin level, necessary for the calculations of CO_{EPBF} and Capno-SvO₂ as well as for calibrations of fiberoptic SvO₂.

2.2 Assessment of Capno-SvO₂

The principle behind continuous Capno-SvO₂ method has been described in detail in previous work by our research team [8]. The Capno-SvO₂ method is based on the differential Fick principle and utilizes a combination of continuous estimation of CO_{EPBF} and oxygen consumption (VO₂) incorporated in a rearranged Fick's equation [12]. CO_{EPBF} is estimated by applying a special breathing pattern of variations in I:E relationships (six breaths with normal I:E relations followed by three breaths with an approximately 2 s expiratory pause). This breathing pattern causes small fluctuations in alveolar CO₂ concentration and VCO₂, related to the pulmonary blood flow participating in gas exchange which allows for estimation of CO_{EPBF} [5, 7, 13]. VO₂ can be estimated using continuous volumetric capnography measurement of VCO₂ combined with RQ:

$$VO_2 = \frac{VCO_2}{RQ} \quad (1)$$

where VO₂ is the oxygen consumption (mL min⁻¹), VCO₂ is the CO₂ production rate (mL min⁻¹), RQ is the respiratory quotient.

VCO₂ applied in Eq. 1 is determined as a moving mean value of measured CO₂ elimination made over a period of 20 min in order to produce stable VCO₂ values with the intent to reflect an assumed stable metabolism.

Using Fick’s equation for oxygen, the content of oxygen in mixed venous blood (CvO₂) can be derived:

$$CO_{EPBF} = \frac{VO_2}{CcO_2 - CvO_2} \tag{2}$$

where CO_{EPBF} is the effective pulmonary blood flow (L min⁻¹), VO₂ is the oxygen consumption (mL min⁻¹), CcO₂ is the pulmonary end capillary oxygen content (mL L⁻¹), CvO₂ is the pulmonary mixed venous oxygen content (mL L⁻¹).

Equation 2 can be further rearranged to derive CvO₂:

$$CvO_2 = CcO_2 - \frac{VO_2}{CO_{EPBF}} \tag{3}$$

where CO_{EPBF} is the effective pulmonary blood flow (L min⁻¹), VO₂ is the oxygen consumption (mL min⁻¹), CcO₂ is the pulmonary end capillary oxygen content (mL L⁻¹), CvO₂ is the pulmonary mixed venous oxygen content (mL L⁻¹).

CvO₂ from Eq. 3 can then be used to calculate SvO₂ by using the solubility constant for oxygen in blood plasma, Hüfner’s constant and the hemoglobin value as previously described thereby generating breath-by-breath estimations of SvO₂ [8].

2.3 RQ-measurements

The RQ was determined immediately before the start of the first challenge (morning) and immediately before the start of the last challenge (afternoon), approximately 4 h apart (shown in Fig. 1). Measurements were performed in all animals, by analysis of mixed expired gas collected in a Douglas bag. Each RQ measurement was conducted in the following way:

- Ventilator bias flow during expiration phase ((normally 2 L min⁻¹ in Servo-I ventilator (Maquet, Solna, Sweden))

was turned off to avoid diluting the gas in the bag with inspiration gas.

- FiO₂ was changed from 0.30 to 0.21 (i.e., room air), which was done for two reasons; it gives the best conditions for the RQ calculation (as shown in Eq. 1 below) and the inspired gas concentration is well-defined without relying on accurate gas mixing by the ventilator.
- To reach a stable state of nitrogen (N₂), 20 min wash-in of N₂ was allowed after the change of FiO₂ and before the bag was connected to the ventilator exhaust port.
- Gas was collected for about 10 min; roughly 70 L of expiratory gas was collected.
- The content of the bag was analyzed using the side-stream gas analyzer of a Flow-i anesthesia system (Maquet, Solna, Sweden). Gas was alternatingly sampled from the bag or from the room air.

Gas concentrations of FiO₂ (room air), FemixO₂ (bag) and FemixCO₂ (bag) were measured at ATPD state (Ambient temperature and pressure, dry). RQ was calculated using the following formula, which is based on the Haldane transformation to account for the imbalance between inspiration and expiration volumes:

$$RQ = \frac{(1 - FiO_2) \cdot FemixCO_2}{(1 - FemixCO_2) \cdot FiO_2 - FemixO_2}$$

RQ is the respiratory quotient, FiO₂ is the fraction of inspired oxygen, FemixCO₂ is the carbon dioxide concentration in the Douglas bag, FemixO₂ is the oxygen concentration in the Douglas bag.

A detailed derivation of the RQ-equation can be found in Supplemental Description Content 1.

2.4 Study protocol

After preparation, the animals were allowed a 20-minute stabilizing period. Following this, an arterial blood sample was taken for calibration of the fiberoptic (Hb and CO-oximetry SvO₂ as per the manufacturers recommendation) and the capnodynamic monitoring system (Hb). Subsequently, five paired baseline measurement of all three methods were performed, 1 min apart, for calculation of

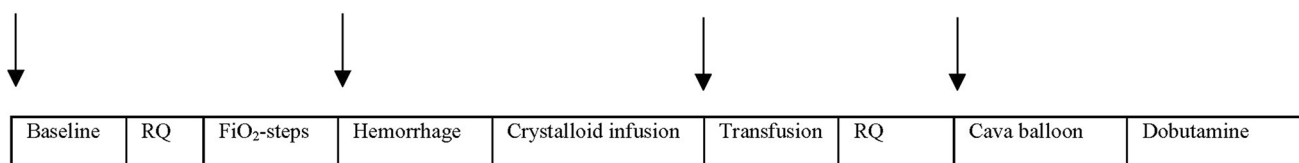


Fig. 1 Scheme of the study protocol. RQ respiratory quotient; (FiO₂), FiO₂ steps. Black arrows indicate calibration points were fiberoptic SvO₂ was calibrated against CO-oximetry and hemoglobin and Capno-SvO₂ against current hemoglobin

inherent precisions. After this, the animals were subjected to six different hemodynamic challenges anticipated to affect SvO₂ (Fig. 1):

1. Stepwise increase in FiO₂: (0.21–0.4–0.75–1.0). Each FiO₂ level was applied for 3 min and simultaneous SvO₂ recordings were made at the end of each FiO₂ level. After this, FiO₂ was returned to baseline 0.3 and an air test was performed to ensure open lung conditions after FiO₂ 1.0 and lungs expanded as described if needed as described above.
2. Hemorrhage: 15 mL kg⁻¹ of blood were drawn under 5–10 min and kept in a plastic bag intended for donor blood, containing 5000 U of Heparin (LEO pharma). SvO₂ values were recorded just before and 5 min after the hemorrhage.
3. Crystalloid bolus: 15 mL kg⁻¹ of Ringer's acetate solution was given centrally in the 7.5 F PA introducer sheath to simulate crystalloid resuscitation of acute hypovolemia, over 5 min, 6 simultaneous SvO₂ measurements were obtained: before crystalloid infusion and 0, 5, 10, 15 and 20 min after completions of infusion where 0 is just after completed infusion.
4. Blood transfusion: blood drawn under step 2 was transfused back over 5–10 min and SvO₂ data were recorded before transfusion and 0, 5, 10, 15 and 20 min after completion of the transfusion where 0 is just after completed infusion.
5. Cava balloon: the cava balloon was inflated (reducing cardiac output by 30–50%). SvO₂ data was collected prior to inflating the balloon, 2 min after inflation, and 3 min after deflation.
6. Dobutamine: a central infusion of dobutamine (Hameln pharma gmbh, Hameln, Germany) 10 mcg kg⁻¹ min⁻¹ was started immediately after the 3-min recording after cava balloon deflation. SvO₂ was then recorded 5, 10 and 15 min after starting the dobutamine infusion.

The fiberoptic SvO₂ measurement was calibrated with Hb-level and CO-oximetry SvO₂ values as per manufacturer's instructions. This was performed totally 4 times during the experiment as marked in Fig. 1 to ensure continuous optimal performance during the experiment. At the same time points, the capnodynamic method was calibrated with the corresponding Hb-level. Throughout the study protocol, Capno-SvO₂ and fiberoptic SvO₂, were recorded just before the blood samples for CO-oximetry were drawn. Due to previous experiences from caval occlusion causing extensive hemodynamic strain on the animals, no baseline recordings were made before the dobutamine step. Instead, dobutamine was started immediately after the last recording of step 5 as described above. The 3-minute recordings after cava balloon deflation, i.e., just before start of the dobutamine infusion,

was used as comparison point for concordance analysis for the dobutamine step.

The animals were euthanized at the end of the experiment, according to the laboratory's routines.

2.5 Statistical analysis

Raw data for absolute values of all three SvO₂ methods (CO-oximetry, Capno-SvO₂ and fiberoptic SvO₂), as well as paired differences between Capno-SvO₂ and CO-oximetry and between fiberoptic SvO₂ and CO-oximetry, were controlled for normal distribution by D'Agostino and Pearson test and visual inspection of the corresponding histograms. Values are presented as mean and 95% confidence interval (CI).

The first five measurements, during hemodynamically stable baseline conditions, were used for calculation of inherent precision for each SvO₂ method respectively. Inherent precision was defined as 2 times the coefficient of variation (CV = SD/mean) and was in turn used to quantify the least significant change (LSC) for the reference method CO-oximetry [14]. The LSC reflects the minimum change measured and recognized as a true change [14]. LSC was then used to determine the exclusion zone in the concordance analysis as previously described [8].

Bland–Altman analysis corrected for repeated measurements was used to assess agreement of absolute values between paired recording of CO-oximetry and Capno-SvO₂ as well as between CO-oximetry and fiberoptic SvO₂. Bias was defined as the mean difference between the tested methods and the reference method [15, 16]. Limits of agreement (bias ± [1.96 × SD]) were used when presenting the spread of included data points and are shown with the corresponding 95% CI. Mean percentage error (PE) was calculated as 1.96 × SD of the differences, divided by the mean of the reference method [17]. A predefined PE of < 30% was defined a priori to indicate a clinically useful agreement. The predefined maximum allowed difference for agreement between the tested methods and the reference method was set to 15% points (based on previous published performance of fiberoptic SvO₂ devices and Capno-SvO₂) [8, 18–20]. Based on our previous study, given the maximally allowed difference between the tested method and the reference method, a minimum of approximately 250 paired data points (corresponding to 10 animals with 25 paired recording per animal) was required to show that the 95% confidence interval of the limits of agreement would fall within the pre-defined maximal allowed difference thus showing that the methods are in agreement (80% power, 0.05 significance level) [8, 15, 21]. The ability of Capno-SvO₂ and fiberoptic SvO₂ to track changes in SvO₂ compared to the reference method, was assessed by calculating the concordance rate, i.e., the percentage

of data points moving in the same direction when comparing two different techniques [22]. Recorded changes between baseline measurements before each hemodynamic intervention, and the value corresponding to the highest change from baseline within that intervention, were used for calculation of the concordance rate. The LSC for CO-oximetry was found to be 9.5%. Based on this, changes in SvO₂ of less than 9.5% (rounded up to 10%) of the mean of all SvO₂ CO-oximetry recordings (corresponding to a minimal change in CO-oximetry SvO₂ of 5% points) were not regarded as true changes and excluded from the concordance analysis [14].

Due to the increasingly unreliable performance of CO-oximetry method for low SvO₂ levels, i.e., for values under 30%, CO-oximetry SvO₂ values under 30% and its associated Capno-SvO₂ and fibreoptic SvO₂ values were excluded in the analysis [23, 24].

GraphPad Prism (version 9.0.0 for Windows, GraphPad Software, San Diego, CA, USA) and Medcalc Statistical Software version 16.8.4 (MedCalc Software, Ostend, Belgium) was used for statistical calculations and Microsoft Excel for Mac 2020 version 16.41 for data handling.

3 Results

All animals survived the experiment. SvO₂ data for step 1–3 in the protocol was excluded from one animal due malposition of the PA-catheter which was then repositioned correctly for step 4–6. The dobutamine step was

introduced after the first animal and thus includes only 10 animals.

3.1 Calculated inherent precision

The inherent precision was found to be $\pm 7\%$ for CO-oximetry SvO₂ and $\pm 8\%$ and $\pm 6\%$ for Capno-SvO₂ and fiberoptic SvO₂, respectively which is in line with previous publications [8, 19].

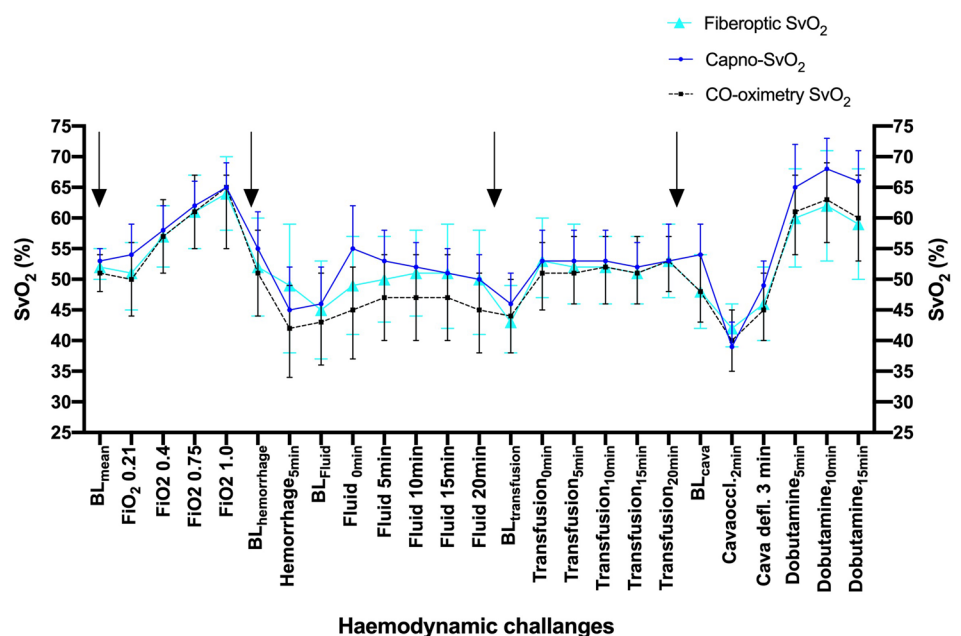
3.2 RQ

The mean RQ for morning and afternoon recordings for all eleven animals, i.e., in total 22 RQ values, was found to be 0.97 (range 0.88–1.06) and RQ 0.97 was then used for all SvO₂-capno calculations.

3.3 Response to hemodynamic interventions

All animals displayed SvO₂ reactions in an anticipated manner when exposed to the various hemodynamic interventions. Both Capno-SvO₂ and fiberoptic SvO₂ showed parallel changes when compared to the reference method CO-oximetry with increase in SvO₂ in response to increased FiO₂, crystalloid infusion, blood transfusion and dobutamine administration. Correspondingly, hemorrhage and partial cava occlusion led to decreases in SvO₂ for all methods. The changes in SvO₂ for each hemodynamic intervention for all three SvO₂ methods are shown in the event plot in Fig. 2.

Fig. 2 Event plot showing SvO₂ responses to the various hemodynamic challenges for all three SvO₂ monitoring methods. Values are mean (95% CI). N=11. Arrows indicate recalibration points for SvO₂-capno and fiberoptic SvO₂. *BL* Baseline, *BL_{mean}* mean of precision recordings, *FiO₂* fraction inspired oxygen; *BL_{cava}* Baseline cava occlusion step, *Cavaoccl.2 min* 2 min after cava occlusion, *Cava defl. 3 min* 3 min after cava balloon deflation



3.4 Agreement of absolute values

Bland–Altman analysis for all paired data showed a bias between Capno-SvO₂ and CO-oximetry of +3% points with 95% limits agreement of -7 (CI -10 to -4) to +13 (CI 11 to 17) percentage points and a mean percentage error of 18%. Correspondingly, the bias between fiberoptic SvO₂ and CO-oximetry was found to be +1% point with 95% limits of agreement of -7 (CI -8 to -6) to +9 (CI 8 to 11) percentage points and PE 16%. Bland Altman plots for Capno-SvO₂ vs. CO-oximetry and fiberoptic SvO₂ vs. CO-oximetry are shown in Fig. 3. Table 1 shows the agreement of absolute values between the reference method and the tested methods for each hemodynamic intervention.

3.5 Trending ability

The trending ability for Capno-SvO₂ and fiberoptic SvO₂, compared to CO-oximetry, are presented as four-quadrant plot illustrations in Fig. 4.

For Capno-SvO₂, a total of 45 data points were found to lie outside the predefined 10% exclusion zone. 44 out of 45 values changed in the same direction as the reference method CO-oximetry which generates a concordance rate of 98%. The corresponding data for fiberoptic SvO₂ was 46 data points outside the exclusion zone with 43 data points moving in the same direction as the reference method i.e., a concordance rate of 93%.

Fig. 3 Bland–Altman plots for pooled recordings for Capno-SvO₂ vs. CO-oximetry (A) and fiberoptic SvO₂ vs. CO-oximetry (B). Dotted line represents bias, blue dotted lines represent upper and lower limits of agreement and black broken lines represents the corresponding CI for the limits of agreements. N = 11. A 271 paired data points, B 272 paired data points

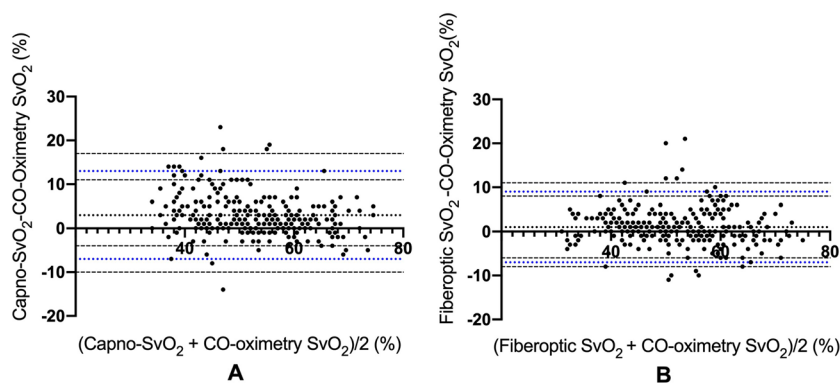
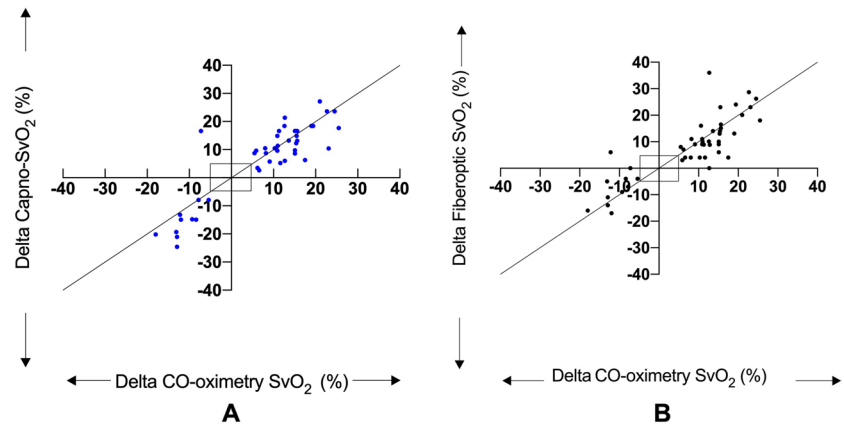


Table 1 Bias and limits of agreement between Capno-SvO₂ and CO-oximetry SvO₂ as well as between fiberoptic and CO-oximetry SvO₂ for the various hemodynamic challenges

Hemodynamic intervention	Compared methods	Bias (percentage points)	ULOA (CI) (percentage points)	LLOA (CI) (percentage points)
Baseline precision	Capno vs. CO-oxi	2	10 (7 to 16)	-6 (-12 to -3)
	Fiber vs. CO-oxi	2	10 (7 to 15)	-6 (-12 to -4)
FiO ₂	Capno vs. CO-oxi	1	11 (8 to 18)	-8 (-15 to -5)
	Fiber vs. CO-oxi	0	7 (7 to 11)	-7 (-12 to -5)
Hemorrhage	Capno vs. CO-oxi	3	14 (10 to 23)	-8 (-17 to -4)
	Fiber vs. CO-oxi	2	13 (9 to 20)	-8 (-15 to -4)
Crystalloid infusion	Capno vs. CO-oxi	6	17 (14 to 23)	-6 (-12 to -3)
	Fiber vs. CO-oxi	3	10 (8 to 15)	-3 (-8 to -1)
Transfusion	Capno vs. CO-oxi	1	7 (5 to 11)	-5 (-8 to -3)
	Fiber vs. CO-oxi	1	9 (7 to 14)	-8 (-13 to -6)
Cava balloon	Capno vs. CO-oxi	5	13 (10 to 19)	-4 (-10 to -1)
	Fiber vs. CO-oxi	1	6 (4 to 9)	-6 (-8 to -3)
Dobutamine infusion	Capno vs. CO-oxi	5	11 (8 to 17)	-2 (-7 to 1)
	Fiber vs. CO-oxi	-1	8 (4 to 16)	-10 (-18 to -6)

ULOA upper limits of agreement, LLOA lower limits of agreement, CI 95% confidence interval, Capno Capno-SvO₂, CO-oxi CO-oximetry SvO₂, Fiber fiberoptic SvO₂

Fig. 4 Four quadrant plots presenting the concordance between Capno-SvO₂ and CO-oximetry SvO₂ (A) and between fiberoptic SvO₂ and CO-oximetry SvO₂ (B). **A** 44 paired delta values, **B** 46 paired delta values. The central boxed area illustrates the 10% exclusion zone. Dotted line is line of identity. N = 11



4 Discussion

The main finding of the current study was that Capno-SvO₂ generates absolute values close to the gold standard CO-oximetry during major hemodynamic provocations. The agreement between Capno-SvO₂ and CO-oximetry was comparable to that found for fiberoptic SvO₂ vs. CO-oximetry. Furthermore, Capno-SvO₂ demonstrated a slightly more accurate ability to detect change in SvO₂ than fiberoptic SvO₂.

4.1 Agreement of absolute values between CO-oximetry and the tested methods

Reliability in consistency during repeated measures and the ability to generate absolute values that corresponds acceptably with the gold standard can be considered absolute prerequisites for any new monitoring technique. During stable baseline conditions, Capno-SvO₂ displayed an inherent precision matching those of both CO-oximetry and fiberoptic SvO₂, thus, indicating a reliable monitoring system. During the following hemodynamic interventions Capno-SvO₂ generated values close to the gold standard method and the overall agreement between Capno-SvO₂ and CO-oximetry was within the predefined 95% limits of agreement of 15% points and well below the a priori determined limit for a PE of < 30%. There was an overall tendency for Capno-SvO₂ to display slightly higher SvO₂ values compared to CO-oximetry even if this difference was relatively small and within clinically acceptable limits. Fiberoptic SvO₂ showed a smaller bias and narrower limits of agreement against CO-oximetry than that recorded for Capno-SvO₂. Even if the difference in agreement against gold standard was relatively similar for both methods, the fact that fiberoptic SvO₂ showed slightly better agreement is not entirely surprising since this value is generated from direct estimation of SvO₂ in the actual pulmonary artery whereas the Capno-SvO₂ is

a figure derived from mathematical analysis of an induced variability exhaled CO₂.

Both Capno-SvO₂ and fiberoptic SvO₂ showed variable levels of agreement against CO-oximetry depending on the type of hemodynamic intervention. During stable baseline conditions, both Capno-SvO₂ and fiberoptic SvO₂ showed near enough equal agreement against gold standard. This pattern was repeated for the FiO₂ step which is reassuring since increased FiO₂ is a common method of augmenting oxygen delivery in the clinical setting.

Differences between Capno-SvO₂ and CO-oximetry can be attributed to mainly two factors. Firstly, issues related to CO_{EPBF} calculations i.e., disturbances in the prerequisites for the capnodynamic method, mainly the assumption of stable or slowly varying mixed venous CO₂ content and the use of updated Hb levels. Secondly the incorporated RQ value will affect the Capno-SvO₂ and thus its level of agreement against CO-oximetry.

The relatively high bias and limits of agreements seen during the fluid resuscitation (especially data points 0 and 5 min) and cava occlusion step is most likely due to initial disturbances in the mixed venous CO₂ content and Hb level.

4.2 Ability to track changes in SvO₂ for Capno-SvO₂ and fiberoptic SvO₂

Agreement of absolute values is central, but in the clinical context trending ability may be even more important [25]. In this study, Capno-SvO₂ showed a very good concordance rate when compared to the gold standard, detecting 98% of the changes, which is well in line with the established fiberoptic method. In addition, the agreement between CO-oximetry and Capno-SvO₂ during stable baseline conditions was very good. Appropriate agreement during stable conditions in combination with a high concordance rate against CO-oximetry, makes Capno-SvO₂ potentially interesting as an early warning sign of not only more major hemodynamic

deteriorations but also minor hemodynamic changes (as shown in our previous publication) [8].

4.3 Limitations

Even if the Capno-SvO₂ technique showed potentially promising performance in the current study, like most monitoring methods it has inherent limitations that needs to be considered and further investigated, particularly if applied in a clinical setting.

4.3.1 Issues related to calibration of the fiberoptic method

The fiberoptic SvO₂ method was recalibrated against CO-oximetry four times during the protocol to optimize its performance as shown in Fig. 1. Normally, the fiberoptic system is intended to be calibrated once daily and not frequently recalibrated [26]. As a consequence of these frequent recalibrations, not corresponding to normal clinical routine, the subsequent fiberoptic SvO₂ values will have affected the performance of the fiberoptic catheter in a positive way. The Capno-SvO₂ was recalibrated at the same time points as the fiberoptic system but only against the current Hb level since the Capno-SvO₂ method is independent from repeated alignment against gold standard CO-oximetry obtained mixed venous saturations (as is the case for fiberoptic SvO₂).

4.3.2 Influence of respiratory quotient

The RQ value is an important determinant in estimating Capno-SvO₂ and will affect the agreement between Capno-SvO₂ and CO-oximetry. Mathematically, choosing a higher RQ will elevate the Capno-SvO₂ and vice versa. Statistically this affects accuracy, but not precision – i.e., bias will shift and will subsequently move upper and lower limit of agreements equally in parallel [14]. It will, however, not have an impact on the trending ability, maybe the most important feature of a monitoring method, as discussed above.

In this study the RQ was directly measured, and the mean value of all measurements was used for calculations of Capno-SvO₂. In the clinical setting it is more likely that RQ will be taken from tabulated values since a direct measurement is impractical with currently available methods. Furthermore, RQ depends on fasting time and the nutritional substrate given and this needs to be taken into consideration when evaluating the recorded RQ [27, 28]. In the current study, the animals were fasted and kept on a low-level glucose maintenance infusion, a common practice during anaesthesia. The scenario may have been different if nutritional status and/or infusions had been altered regarding glucose concentration or type of substrate, something that can be of importance in the intensive care setting [27]. Despite

this, using the mean RQ for the whole group still resulted in acceptable agreement and trending ability.

4.4 Clinical applicability

In its current form, the Capno-SvO₂ method requires controlled mechanical ventilation [7, 29]. However, most of the patients that would benefit from continuous non-invasive assessment of SvO₂ will already be subjected to controlled mechanical ventilation both in the operating room and in the intensive care unit. Still, the fact that the method requires controlled ventilation will exclude patients that are spontaneously breathing or are treated with various modes of patient triggered ventilation.

Although Capno-SvO₂ has the potential to considerably expand the ability to continuously monitor SvO₂ compared to today, it is important to emphasize that Capno-SvO₂ is not a substitute for the proper use of a pulmonary artery catheter since it does not provide information regarding relevant pressure and resistance parameters. However, it could potentially provide real time SvO₂ monitoring in situations where a pulmonary artery catheter is neither practical or justifiable due to its invasive nature, associated risks, and cost. Thus, the potential role of Capno-SvO₂ deserves further translational studies to define its place in monitoring of patients that are cared for in the operating room or in intensive care.

In conclusion, the current study shows that the Capno-SvO₂ method is in close agreement with the gold standard CO-oximetry and displays good trending ability even during major changes in oxygen delivery. These features of the Capno-SvO₂ method, in combination with its non-invasive nature, may offer a novel real time option for SvO₂-monitoring. Even if a pulmonary artery catheter is of seminal importance for complete hemodynamic assessment, the Capno-SvO₂ method could facilitate more advanced hemodynamic surveillance when a pulmonary artery catheter is not warranted, technically possible (such as in pediatric practice) or even contraindicated, thereby acting as a useful adjunct to more traditional hemodynamic monitoring.

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Data availability Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest Per-Arne Lönnqvist received an unrestricted research grant from Maquet Critical Care AB. Mats Wallin and Mark Konrad was employed by Maquet Critical Care AB at the time of the study. Magnus Hallböck is employed at Maquet Critical Care AB. Anders Svedmyr and Jacob Karlsson report no conflicts of interest.

Ethical approval Authorization was granted from Uppsala Animal Ethics Committee (Uppsala, Sweden case number C75/16, chairperson Erik Göransson on August 26, 2016). The animals were handled in accordance with the animal experimentation guidelines of the Uppsala Animal Ethics Committee and Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

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