Clinical predictors of a low central venous oxygen saturation after major surgery: a prospective prevalence study

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Summary

Optimising perioperative haemodynamic status may reduce postoperative complications. In this prospective prevalence study, we investigated the associations between standard haemodynamic parameters and a low central venous oxygen saturation ($ScvO_2$) in patients after major surgery. A total of 201 patients requiring continuous arterial and central venous pressure monitoring after major surgery were recruited. Simultaneous arterial and central venous blood gases, haemodynamic and biochemical data and perfusion index were obtained from patients at a single time-point within 24 hours of surgery. A low $ScvO_2$ (<70%) was observed in 109 patients (54%). Use of mechanical ventilation, mean arterial pressure, central venous pressure, haemoglobin concentrations, arterial pH and lactate concentrations, arterial oxygen (PaO_2) and carbon dioxide tensions ($PaCO_2$) were all associated with a low $ScvO_2$ in the univariate analyses. In the multivariate analysis, only a higher perfusion index (odds ratio [OR] 0.87, 95% confidence interval [CI] 0.78 to 0.98), PaO_2 (OR 0.98 per mmHg increment, 95% CI 0.97 to 0.99) and $PaCO_2$ (OR 0.88 per mmHg increment, 95% CI 0.82 to 0.95) and a lower central venous pressure (OR 1.14 per mmHg increment, 95% CI 1.04 to 1.25) were significantly associated with a reduced risk of a low $ScvO_2$, all in a linear fashion. In conclusion, PaO_2, $PaCO_2$, perfusion index and central venous pressure were significant predictors of a low $ScvO_2$ in patients after major surgery including cardiac surgery, suggesting that $ScvO_2$ should always be interpreted with the arterial blood gases and that liberal perioperative fluid therapy aiming at a high central venous pressure may be detrimental in optimising $ScvO_2$.

Key Words: central venous oxygen saturation, haemodynamic targets, oxygenation, prediction, perioperative period

Postoperative complications are the strongest determinant of short- and long-term morbidity and mortality in patients undergoing anaesthesia and surgery[1,2]. Optimising perioperative haemodynamic status through goal-directed therapy may reduce postoperative complications[3–5]. However, the most important variables to monitor and what parameters to target remain uncertain. Recent evidence suggests that optimising cardiac output during the perioperative period is beneficial in reducing perioperative complications[6,7]. Central venous oxygen saturation ($ScvO_2$) reflects the balance between oxygen delivery (DO_2) and consumption and has been reported as an independent predictor of perioperative complications. Previous studies have demonstrated that patients with a low $ScvO_2$ (<70%) during the perioperative period had a higher incidence of complications and prolonged duration of mechanical ventilation, intensive care unit and hospital stay[8–12]. Furthermore, $ScvO_2$ did not have to reach a very low level (64.4%) in order to differentiate between patients with and without complications after surgery[8].

The incorporation of $ScvO_2$ monitoring into perioperative management requires either frequent central venous blood sampling or a specialised central venous catheter capable of measuring $ScvO_2$ continuously, which substantially limits its general applicability as a routine perioperative haemodynamic target. As $ScvO_2$ reflects the balance between DO_2 and oxygen consumption, it is likely that $ScvO_2$ can be predicted using commonly measured haemodynamic and biochemical parameters that relate to the balance between DO_2 and oxygen consumption. We hypothesised that $ScvO_2$ can be predicted by standard haemodynamic and biochemical variables and hence continuous monitoring of the $ScvO_2$ may not be necessary in most patients after major surgery. In the present study, we sought to identify the prevalence and predictors of a low $ScvO_2$ in patients after major surgery.

Recent studies show that two relatively new and promising haemodynamic parameters, perfusion index (PI) and plethysmographic variability index ([PVI] >12% to 19%), may be more useful than some invasive haemodynamic targets, such as central venous pressure (CVP), in predicting preload status and fluid responsiveness, especially when the PI is over 4%[13]. PVI is similar to pulse pressure variation, while the PI is a ratio of the pulsatile to non-pulsatile component of the saturation

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trace and is a measure of peripheral perfusion akin to capillary refill. As such, in this study we also assessed whether PVI and PI were useful in predicting a low $ScvO_2$ in patients after major surgery.

Methods

After obtaining ethics approval for the study from the Royal Perth Hospital Human Research Ethics Committee (2011/039), we planned to recruit a total of 200 patients (100 mechanically ventilated, 100 spontaneously breathing) who had major surgery requiring either intensive care or high dependency unit admission, in this single-centre, prospective, prevalence study. Patients who had both an arterial pressure catheter and a central venous catheter in either the internal jugular or subclavian vein within 24 hours after major surgery were eligible for recruitment. As atrial fibrillation or other persistent irregular cardiac rhythms (e.g. bigeminy) may affect the accuracy and reliability of some haemodynamic parameters (e.g. heart rate, PVI), only patients with regular cardiac rhythms were included in this study. Royal Perth Hospital is a tertiary university teaching hospital admitting patients in all medical and surgical specialties including trauma and cardiothoracic surgery. Goal-directed fluid therapy or restrictive fluid therapy for patients undergoing surgery was not a routine practice in this study centre during the study period.

After obtaining informed consent from the patients or their next of kin, haemodynamic and biochemical data were collected from each patient at a single time-point within the first 24 hours after major surgery. In brief, the following data was obtained: personal demographics (including surgical procedure), Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores, heart rate, mean arterial blood pressure, CVP, urine output in the hour prior to study enrolment, ventilator settings (when applicable) and fraction of inspired oxygen, vasoactive infusions, PI and PVI (Radical-7, Masimo Corporation, Irvine, CA, USA), serum haemoglobin concentration and simultaneous arterial and central venous blood gases (ABL800 FLEX, Radiometer, Copenhagen, Denmark). Attending clinicians were blinded to the $ScvO_2$, PVI and PI data in this study.

Sample size estimation

The planned sample size of this study had the ability to assess eight predictors for a low $ScvO_2$ (<70%) after major surgery, if we assumed the prevalence of low $ScvO_2$ was 40%[8] and limited the multivariate analysis to a maximum of one predictor per ten outcomes of interest (or patient with a low $ScvO_2$).

Statistical analytic techniques

The associations between a low $ScvO_2$ (<70%) and commonly measured haemodynamic parameters, including heart rate, CVP, mean arterial pressure, hourly urine output, PI, PVI, haemoglobin concentration, arterial oxygen (PaO_2) and carbon dioxide tension ($PaCO_2$), were tested with univariate logistic regression analyses, followed by multivariate logistic regression analyses. Multicollinearity between continuous predictors (e.g. pH and lactate concentration) was excluded by a Pearson's correlation coefficient of <0.8 before they were entered into the multivariate analyses. In the multivariate logistic analysis, a 3-knot restricted cubic spline function was used for all continuous predictors to allow a non-linear association between continuous predictors and a low $ScvO_2$[14,15]. Because the accuracy of PVI and CVP in predicting preload status of the patients could be affected by mechanical ventilation[13], interaction terms between mechanical ventilation and PVI or CVP were also entered into the multivariate analyses. During the multivariate modelling process, predictors with a *P*-value >0.25 were removed to improve the precision of the final multivariate model. The relative impor-

Table 1

Characteristics and demographic factors of the included patients (n=201)

	Number (%, unless stated otherwise)
Median age, years (IQR)	62 (50–71)
Male gender	141 (71)
Body Mass Index (IQR)	28 (24–32)
Surgery type	
Cardiothoracic*	157 (78)
General	21 (10)
Orthopaedic	9 (4)
Vascular	6 (3)
Neurosurgical	3 (2)
Other	5 (3)
Emergency surgery	40 (20)
Core body temperature, ºC	36.5 (36–37)
Median APACHE score (IQR)	10 (8–14)
Median SOFA score (IQR)	4 (2–5)
Noradrenaline infusion	99 (49)
Dobutamine infusion	30 (15)
Either on noradrenaline or dobutamine infusion	105 (52)
Ejection fraction, % (IQR)**	60 (48–65)
Mechanically ventilated	101 (50)
Median hospital length of stay, days (IQR)	11 (7–20)
Survival to hospital discharge	199 (99)

*Seven patients had off-pump cardiac surgery, 44 patients had valvular surgery, eight patients had atrial septal defect repair, one patient had ventricular septal defect repair, eight patients had ascending aortic graft replacement, three patients had lung transplantation, two patients had pericardial surgery, one patient had pulmonary thromboembolectomy, 11 patients had combined coronary artery bypass and valvular surgery and 72 patients had on-pump coronary artery bypass surgery. **Only 107 patients had ejection fraction documented in the preoperative echocardiography. IQR=interquartile range, APACHE=Acute Physiology and Chronic Health Evaluation, SOFA=Sequential Organ Failure Assessment.

tance of each predictor in explaining a low $ScvO_2$ (<70%) was assessed using the chi-square statistic minus the degrees of freedom[14,15]. In this study, a *P*-value <0.05 was taken as statistically significant. All tests were two-tailed and performed by using SPSS for Windows, version 19.0 (IBM, Chicago, IL, USA) and S-PLUS, version 8.0 (Insightful Corp., Seattle, WA, USA).

Results

Of the 201 patients recruited between December 2011 and September 2013, 101 were mechanically ventilated and 100 were spontaneously breathing at the time of study enrolment. The median age and Acute Physiology and Chronic Health Evaluation II score of the patients were 62 years (interquartile range 50 to 71) and 10 (interquartile range 8 to 14), respectively. The most common types of surgery were cardiothoracic and general surgery. Further patient details are summarised in Table 1.

The median $ScvO_2$ of all patients was 68% (interquartile range 62% to 75%) and a low $ScvO_2$ (<70%) was observed in 109 patients (54%, 95% confidence interval [CI] 47% to 61%). In the univariate analyses, a low $ScvO_2$ was significantly associated with the use of mechanical ventilation, the interaction term between mechanical ventilation and PVI, CVP, serum haemoglobin concentration, arterial lactate concentration, PaO_2, $PaCO_2$, and arterial pH. The results of univariate analyses are described in Table 2.

Table 2

Univariate logistic regression analysis

	Low $S_{cv}O_2$ (<70%) (n=109)	Normal $S_{cv}O_2$ (≥70%) (n=92)	Odds ratio (95% confidence interval)	*P*-value
CVP, mmHg	11 (8–13)	8 (7–12)	1.16 (1.07–1.26) (per mmHg increment)	0.001
HR, /min	88 (75–95)	86 (77–91)	1.00 (0.98–1.02) (per beat/min increment)	0.887
MAP, mmHg	75 (70–84)	78 (72–86)	0.98 (0.95–1.01)(per mmHg increment)	0.103
Urine output, ml/hr	53 (36–98)	50 (35–89)	1.00 (0.99–1.01)(per ml/hr increment)	0.478
Use of noradrenaline, number (%)	53 (49)	46 (50)	1.06 (0.61–1.84)	0.846
Arterial lactate concentration, mmol/l	1.6 (1.1–2.2)	1.3 (0.9–1.9)	1.59 (1.09–2.32) (per mmol/l increment)	0.015
Arterial pH	7.38 (7.35–7.41)	7.37 (7.34–7.40)	2.05 (1.09–3.85) (per 0.1 increment)	0.025
Arterial CO_2 tension, mmHg	38 (34–41)	40 (37–44)	0.89 (0.84–0.95) (per mmHg increment)	0.001
Arterial O_2 tension, mmHg	98 (82–127)	121 (98–140)	0.99 (0.98–0.99) (per mmHg increment)	0.001
Haemoglobin, g/l	102 (91–112)	106 (94–122)	0.98 (0.97–1.00) (per g/l increment)	0.036
Cardiac index, l/min/m^2	2.5 (2.3–2.8)	2.5 (2.3–2.9)	0.78 (0.27–2.23) (per l/min/m^2 increment)	0.641
PVI	15 (10–20)	14 (9–19)	1.01 (0.97–1.05) (per index increment)	0.587
PI	2.7 (1.3–5.3)	3.3 (1.5–7.1)	0.92 (0.85–1.00) (per index increment)	0.067
Mechanically ventilated, number (%)	47 (43)	54 (59)	0.53 (0.30–0.94)	0.028
Interaction term between mechanical ventilation & PVI	0 (0–9.8)	7.5 (0–14)	1.04 (1.01–1.07)	0.008
Interaction term between mechanical ventilation & CVP	0 (0–10)	7 (0–11)	0.96 (0.91–1.01)	0.086

Analysis shows the associations between standard clinical haemodynamic or biochemical variables and occurrence of a low central venous oxygen saturation (<70%) after surgery. All raw haemodynamic or biochemical data are presented in median and interquartile range unless stated otherwise. $S_{cv}O_2$=central venous oxygen saturation, CVP=central venous pressure, HR=heart rate, MAP=mean arterial pressure, PVI=plethysmographic variability index, PI=perfusion index.

In the final multivariate model, only four variables remained significantly associated with a low $ScvO_2$ (Table 3), including CVP (odds ratio [OR] 1.14, 95% CI 1.04 to 1.25), PI (OR 0.87, 95% CI 0.78 to 0.98), $PaCO_2$ (OR 0.88, 95% CI 0.82 to 0.95) and PaO_2 (OR 0.98, 95% CI 0.97 to 0.99). There was a suggestion that a higher arterial lactate concentration (OR 1.51, *P*=0.051) and a lower mean arterial pressure (OR 0.97, *P*=0.064) were also associated with an increased risk of a low $ScvO_2$, but these did not reach statistical significance. The Hosmer-Lemeshow chi-square, Nagelkerke R-squared and the area under the receiver operating characteristic curve of the final model in predicting a low $ScvO_2$ were 7.0 (*P*=0.535), 0.299 and 0.77 (95% CI 0.70 to 0.83), respectively.

Of the six variables retained in the final model, PaO_2 was most important, explaining about 50% of the variability in the risk of having a low $ScvO_2$, and had a linear inverse relationship with the risk of a low $ScvO_2$ (Figures 1 and 2). Conversely, increasing CVP was associated with an increased risk of a low $ScvO_2$ (Figure 3). The associations between a low $ScvO_2$and the other four continuous predictors also appeared to be relatively linear and are described in Figures A to D in the online Appendix.

Table 3
Final multivariate logistic regression analysis

	β coefficient	Odds ratio (95% confidence interval)	*P*-value
CVP (per mmHg increment)	0.133	1.14 (1.04–1.25)	0.005
MAP (per mmHg increment)	-0.029	0.97 (0.94–1.00)	0.064
Arterial lactate concentration (per mmol/l increment)	0.411	1.51 (1.00–2.28)	0.051
Arterial CO_2 tension (per mmHg increment)	-0.125	0.88 (0.82–0.95)	0.001
Arterial O_2 tension (per mmHg increment)	-0.017	0.98 (0.97–0.99)	0.001
PI (per index increment)	-0.135	0.87 (0.78–0.98)	0.018

Analysis shows the associations between standard haemodynamic or biochemical variables and occurrence of a low central venous oxygen saturation (<70%) after surgery. All variables included in the univariate analyses were initially entered into the multivariate analysis and were removed in a stepwise fashion, beginning with the variable associated with the largest *P*-value. Only predictors with a *P*-value <0.25 were retained in the final multivariate model. The Hosmer-Lemeshow chi-square and Nagelkerke R-squared of the final model were 7.0 (*P*=0.535) and 0.299, respectively, and the area under the receiver operating characteristic curve for prediction of a low $ScvO_2$ was 0.77 (95% confidence interval: 0.70–0.83). CVP=central venous pressure, MAP=mean arterial pressure, PI=perfusion index, $ScvO_2$=central venous oxygen saturation.

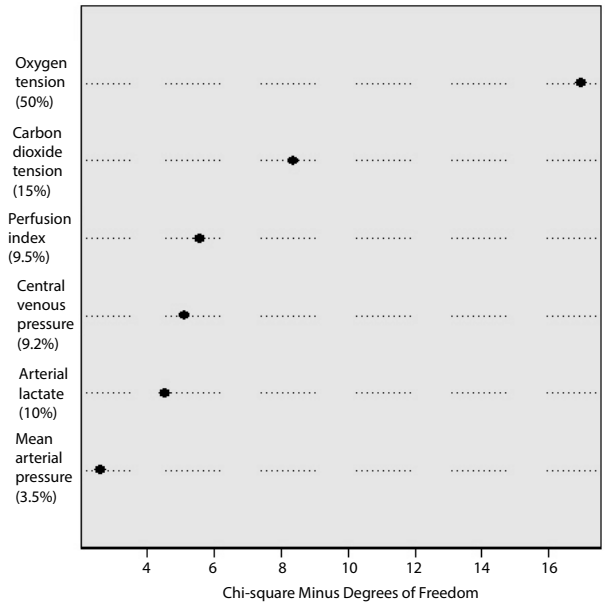

Figure 1: The relative contribution of each predictor in explaining the variability of central venous oxygen saturation.

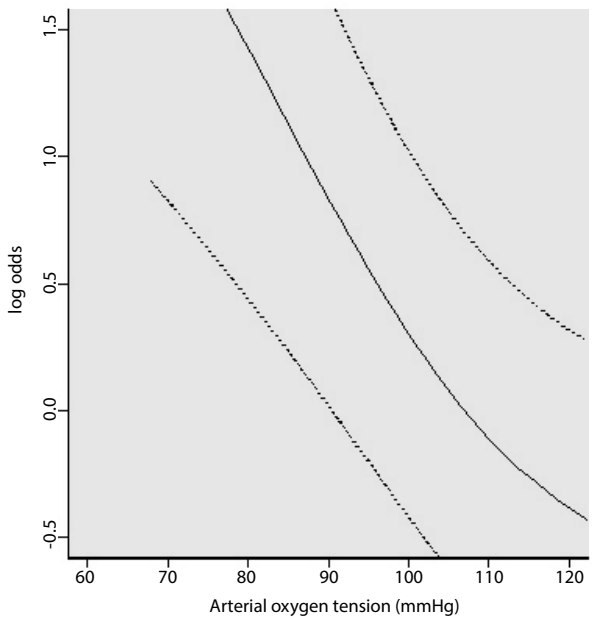

Figure 2: A linear inverse relationship between arterial oxygen tension and risk of a low central venous oxygen saturation, allowing non-linearity with a 3-knot restricted cubic spline function and adjusted for perfusion index, central venous pressure, mean arterial pressure, arterial lactate concentrations, arterial carbon dioxide tension. Note that log odds 0=1 and dotted lines indicate 95% confidence interval.

Discussion

Previous studies have shown that the occurrence of a low $ScvO_2$ in the perioperative period is associated with an increased risk of morbidity and mortality[8–12] and ensuring an adequate cardiac output and $ScvO_2$ perioperatively may improve outcomes[6,7,16,17]. In this prospective prevalence study of patients who required continuous haemodynamic monitoring after major surgery, we showed that a low $ScvO_2$ was common (54%) and that a high CVP and lower PI, PaO_2 and $PaCO_2$ were associated with an increased risk of a low $ScvO_2$ (<70%), all in a linear fashion. However, even by combining six haemodynamic and biochemical parameters, a low $ScvO_2$ could not be accurately predicted (area under the receiver operating characteristic curve=0.77). These results are clinically relevant and require further consideration.

Firstly, we could not confirm our original hypothesis. Even by combining six commonly measured haemodynamic and biochemical parameters, the model only had a modest ability in predicting the occurrence of a low $ScvO_2$ in patients after major surgery. Nevertheless, we observed a significant novel finding in the relationship between CVP and $ScvO_2$. Although CVP has been used as a marker of preload for many years, there is increasing evidence to suggest that CVP is not a reliable marker of preload in the perioperative and critical care settings[18–20]. The inverse relationship between CVP and $ScvO_2$ we observed is consistent with the findings reported by Vellinga et al[21], whose study showed that microcirculatory flow and mixed venous oxygen saturation were lower in patients with severe sepsis or septic shock who had an elevated CVP. A high CVP may reduce venous return, regional organ perfusion and microcirculatory bloodflow[22–24], resulting in an increased risk of postoperative complications[25–27]. Our findings support the emerging evidence that a high CVP due to excessive fluid administration may indeed be harmful in patients after major surgery[28–30].

Secondly, we observed a positive linear association between $ScvO_2$ and PaO_2 or $PaCO_2$. Traditional physiology teaching assumes that arterial oxygen and carbon dioxide tension are not important in determining DO_2 and, hence, they should not affect $ScvO_2$ in a substantial fashion. Our findings in this study challenge this traditional dogma. Indeed, our recent work on patients with circulatory failure requiring vasopressors showed that PaO_2 could increase $ScvO_2$ and mixed venous oxygen saturation in a very substantial fashion (up to 10% in some patients)—more than the effect associated with changes in cardiac output[31]. Mathematical modelling also supports the fact that $ScvO_2$ could be affected by PaO_2 in a substantial fashion[32]. This novel concept is important because any increases in $ScvO_2$ due to an increase in PaO_2 would confound its associations with the cardiac output status of patients, rendering a 'good' $ScvO_2$ uninterpretable as a marker of adequate cardiac output or oxygen delivery[33]. As for the association between $ScvO_2$ and $PaCO_2$, this is likely related to the haemodynamic effects of moderate hypercapnia, including tachycardia, decreased systemic vascular resistance and increased cardiac index[34], which would improve DO_2 and thus possibly also $ScvO_2$. Given arterial oxygen and carbon dioxide tension are the most important determinants of $ScvO_2$, our results may, at least in part, explain why targeting a certain $ScvO_2$ without considering the effects of arterial blood gases on $ScvO_2$ did not improve outcomes of patients with severe sepsis[35].

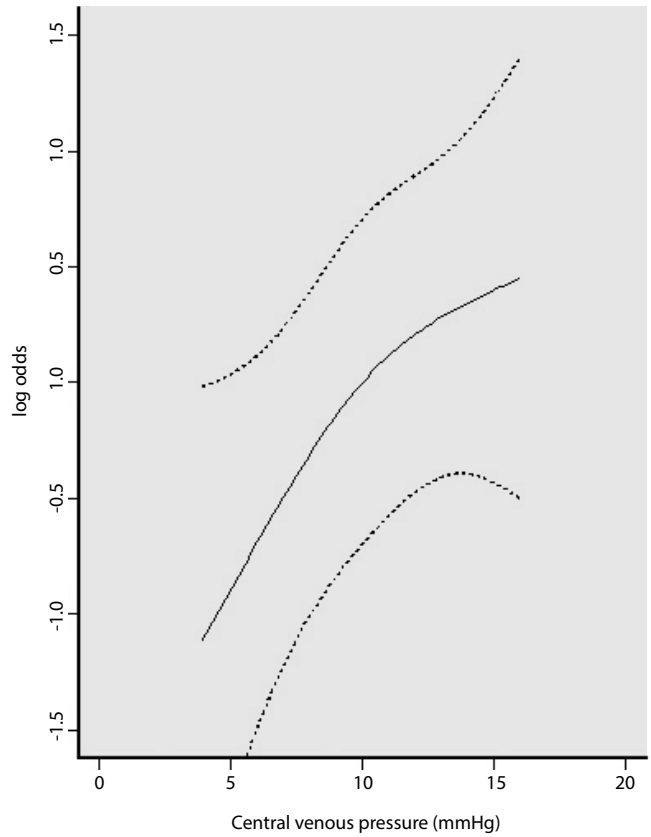

Figure 3: A linear relationship between central venous pressure and risk of a low central venous oxygen saturation, allowing non-linearity with a 3-knot restricted cubic spline function and adjusted for pressure index, mean arterial pressure, arterial lactate concentrations, arterial oxygen and carbon dioxide tension. Note that log odds 0=1 and dotted lines indicate a 95% confidence interval.

Thirdly, although PVI appears promising as a predictor of fluid responsiveness in perioperative patients[13], we could not confirm its association with $ScvO_2$ in either patients who were mechanically ventilated or spontaneously breathing in this study. This may have been due to the fact that over 50% of our patients were receiving vasopressors, which are known to affect the accuracy of PVI[36–38]. It is also possible that the relationship between fluid responsiveness and $ScvO_2$ is weak and heavily dependent on the underlying cardiac function of the patient. Nevertheless, we did demonstrate that PI (which is used to estimate PVI by calculating the changes in PI with respiratory variations) may still be useful in reflecting adequacy of peripheral perfusion and, hence, the $ScvO_2$.

This study has some limitations. Firstly, it included predominantly elective postoperative patients. Whether the predictors of a low $ScvO_2$ remain consistent in populations with markedly different haemodynamic patterns, such as the hyperdynamic circulation associated with sepsis, remains uncertain. Secondly, we could not confirm the association between serum haemoglobin concentration and $ScvO_2$ in the multivariate analysis, likely related to the low prevalence of anaemia in our patients or that haemoglobin may not be as important as other factors in determining $ScvO_2$ in the perioperative setting. Thirdly, we only measured $ScvO_2$ and all other biochemical and haemodynamic parameters at a single time-point within 24 hours after surgery. It is possible that both $ScvO_2$, and the factors associated with it, may change significantly with time after surgery. Finally, emerging evidence suggests that optimising cardiac output using a restrictive fluid strategy could improve DO_2 and patient-centred outcomes compared to liberal fluid therapy[28]. This strategy appears promising, but was not assessed in this study.

In conclusion, a low $ScvO_2$ (<70%) was prevalent in patients after major surgery. A low $ScvO_2$ could not be accurately predicted by commonly measured haemodynamic and biochemical parameters. Interpreting a low $ScvO_2$ as a marker of inadequate cardiac output or systemic oxygen delivery could be confounded by a high PaO_2. A high CVP appeared to have an adverse association with $ScvO_2$ and this provides support to the emerging evidence that CVP is not a useful haemodynamic target and that excessive perioperative fluid therapy may be potentially detrimental to tissue oxygenation.

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