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Central venous oxygen saturation during cardiopulmonary bypass predicts 3-year survival

Staffan Svenmarker[a,*], Sören Häggmark[a], Margareta Östman[b], Anders Holmgren[c] and Ulf Näslund[d]

[a] Department of Surgical and Perioperative Science, Heart Centre, Umeå University, Umeå, Sweden
[b] Department of Surgical and Perioperative Science, Thoracic Anaesthesia, Heart Centre, Umeå University, Umeå, Sweden
[c] Department of Surgical and Perioperative Science, Thoracic Surgery, Heart Centre, Umeå University, Umeå, Sweden
[d] Department of Surgical and Perioperative Science, Cardiology, Heart Centre, Umeå University, Umeå, Sweden

* Corresponding author. Heart Centre, Umeå University Hospital, 901 85 Umeå, Sweden. Tel: +46-907853650; fax: +46-907863601; e-mail: staffan.svenmarker@vll.se (S. Svenmarker).

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Abstract

OBJECTIVES: Long-term survival after cardiac surgery is determined by a number of different risk factors. Central venous oxygen saturation (S_vO_2) measures the balance between oxygen delivery and demand. S_vO_2 levels in the intensive care situation are reported to be associated with patient outcome. The present report explores the connection between S_vO_2 during cardiopulmonary bypass (CPB) and survival after cardiac surgery.

METHODS: Retrospective analysis of one thousand consecutive cardiac surgical patients was undertaken. S_vO_2 during CPB was monitored online. Registry data combining specific risk factors with S_vO_2 were selected for Kaplan–Meier and Cox regression analysis to examine the influence on 30-day and 3-year survivals.

RESULTS: Nine-hundred and thirty-two patient records were eligible for analysis. S_vO_2 below 75% during CPB was associated with significantly shorter 30-day and 3-year survivals. Based on Kaplan–Meier statistics, the survival rate decreased by 3.1% (98.1–95.0), $P = 0.011$ and 6.1% (92.7–86.6), $P = 0.003$, respectively. The influence of S_vO_2 on 3-year survival remained statistically significant after controlling for a series of risk factors in the Cox regression analysis. Patients with S_vO_2 <75% carried a 2-fold (odds ratio 2.1) increased relative risk of shortened 3-year survival ($P = 0.003$). Other risk factors statistically significantly associated with 3-year survival were age, gender, duration of CPB, blood temperature, hypertension, haematocrit and type of surgical procedure.

CONCLUSIONS: We report decreased 30-day and 3-year survival expectancy for patients experiencing S_vO_2 lower than 75% during CPB.

Keywords: Survival • Cardiopulmonary bypass • Venous oxygen saturation • Systemic blood flow

INTRODUCTION

Central venous oxygen saturation (S_vO_2) reflects the balance between oxygen delivery and oxygen demand [1, 2]. Oxygen delivery is determined by cardiac output and the availability of oxygen carriers, while oxygen demand reflects the actual metabolic state [2]. S_vO_2 exceeding 75% is generally regarded as normal [2], where the demand of oxygen equals 25% of total availability. If more oxygen is needed, the demand for oxygen can be met either by increasing delivery or by increasing the extraction of oxygen from the haemoglobin molecule. Extraction rate exceeding 50% is described to increase the risk of regional tissue hypoxia [3]. The physiological adaption of oxygen delivery assumes normal cardiac function combined with sufficient amounts of oxygen carriers [4]. In a situation of compromised cardiac function or anaemia as in cardiac surgical patients, the informative value of S_vO_2 is paramount [5–8]. S_vO_2 deviating from the norm may indicate a state of low cardiac output or need for blood transfusion [4, 9, 10].

S_vO_2 can be monitored online or intermittently from the pulmonary artery or the right atrium by appropriately placed catheters [1, 5]. In cardiac surgery using cardiopulmonary bypass (CPB), the S_vO_2 value is readily available within the CPB circuit [11]. The S_vO_2 level in the intensive care situation and after cardiac surgery is reported to be associated with patient outcome [5–7, 12, 13]. Normal organ function relies on continuous oxygen supply [14]. Lack of oxygen as indicated by subnormal S_vO_2 values is an early warning sign of temporary or permanent upcoming organ dysfunction [2, 12] and should for this reason be treated accordingly.

The present study aimed to investigate the impact of S_vO_2 during CPB, with respect to patient outcome and survival in a consecutive cohort of cardiac surgical patients.

MATERIALS AND METHODS

Information based on one thousand consecutive cardiac surgical patients was extracted from the hospital's clinical database and

the database linked to the heart–lung machine. The study was approved by the Regional Ethical Review Board in Umeå, Sweden.

The following background variables were selected: age, gender, body surface area, diabetes, hypertension, smoker, chronic obstructive lung disease, left ventricular function, EuroSCORE, New York Heart Association classification, surgical intervention, neurological disorder, atrial fibrillation and serum creatinine. Variables specifically associated with CPB were: duration of CPB, systemic blood flow, mean arterial pressure, body temperature, S_vO_2 and haematocrit. Outcome variables comprised: postoperative confusion, length of stay in hospital and intensive care and 30-day and 3-year survival dates.

Computation and data collection from the heart–lung machine

The computer interfaced to the heart–lung machine (S5 Stöckert, Sorin Group, Italy) collected a predefined set of data produced from the heart–lung machine and surrounding patient monitors once every minute. The information was stored in a database, Stöckert Data Management system (DMS). S_vO_2, haematocrit and temperature were measured in the venous line of the extracorporeal circuit (Data Master, Sorin Group, Italy). Patient mean arterial pressure, central venous pressure and nasal pharyngeal temperature were transferred from the patient monitor (Marquette Solar System 9000).

DMS data were organised into six time-specific intervals each with 10 min duration covering the first and last 30 min of CPB. The mean value of every recorded variable within the six observation periods were calculated and used as input for the statistical analysis.

Application of cardiopulmonary bypass

Non-pulsatile perfusion using Stöckert S5 roller pump and membrane oxygenation with integrated venous and cardiotomy reservoir was performed with mean arterial blood pressure >50 mmHg and S_vO_2 >75% as targets. The great majority of cases were conducted under moderate hypothermia (34°C) using St Thomas II crystalloid cardioplegia for myocardial protection. Blood cardioplegia and profound hypothermia were used in selected cases. Acid–base control followed the alpha-stat regimen. The CPB circuit was primed with 1000-ml Ringer-Acetate and 400-ml Mannitol. Transfusion of erythrocytes per CPB was considered at haematocrit <20% combined with hypovolemia or S_vO_2 below target.

Surgical and anaesthesiological techniques

Surgical techniques followed generally accepted concepts adjusted for specific interventional requirements. Arterial perfusion was, in the majority of cases, established by cannulation of the ascending aorta or if required, the femoral artery. The right atrium was cannulated for venous access or, if indicated, separate cannulation of superior vena cava and inferior, respectively. Surgical bleeding was balanced by cardiotomy suction. In cases of major blood loss, post-CPB cell salvage was used.

Anaesthesia comprised propofol and pancuronium for induction combined with fentanyl and isoflurane for maintenance. Ventilation was adjusted to maintain normocapnia. Systemic vascular resistance was adjusted by administering phenylephrine or norepinephrine as indicated. Epinephrine and milrinon were the preferred intropic agents. Intra-aortic balloon pump was inserted on occasions of severe heart failure.

Anticoagulation was achieved by administering a sufficient dose of heparin (350 IE/kg) verified by the activated clotting in excess of 480 s.

Statistical analysis

Patients with complete S_vO_2 records per CPB were considered for statistical analysis. The resultant population was dichotomised at S_vO_2 = 75%. The two formed groups were analysed using univariate statistics including Student's *t*-test or chi-square tests as appropriate. The value of η was applied for ordinal by interval comparisons. In the case of sequential intraoperative data differentiated by the six predefined time periods (three consecutive 10-min intervals at commence and termination of CPB), repetitive measurements of variance (ANOVA) were implemented. Kaplan–Meier statistics was used to predict 30-day and 3-year survivals based on S_vO_2 below or above 75% using Mantel–Cox log-rank statistics. A final model for 3-year survival based on Cox regression analysis was applied to control for statistically and clinically significant covariates. A P-value < 0.05 was considered statistically significant. Mean values are given with its associated standard deviation, if not otherwise stated. Analyses were made using SPSS statistical package version 18.

RESULTS

Nine-hundred and thirty-two patients fulfilled statistical entry requirements by demonstrating complete S_vO_2 records. Characteristics of the population included for further statistical analyses are outlined in Table 1.

General physiological effects of S_vO_2 level during cardiopulmonary bypass

The mean arterial pressure varied between 58 ± 9.5 and 61.5 ± 10.5 mmHg during the initial and final 30 min of CPB, whereas the systemic blood flow varied between 4.3 ± 1.0 and 5.2 ± 0.7 l per minute.

Twenty-eight percent of the investigated patient population demonstrated S_vO_2 levels lower than 75% at weaning from CPB (E-10). Influences on systemic blood flow, body temperature, haematocrit and mean arterial pressure depending on S_vO_2 levels below or above 75% are shown in Figure 1. S_vO_2 below 75% during CPB was associated with significantly lower systemic blood flow (P = 0.000) and haematocrit levels (P = 0.000), whereas no statistical differences were detected either with respect to body temperature (P = 0.941) or mean arterial blood pressure (P = 0.831).

Table 1: Characteristics of patient population

Variable	
Age (years)	66.8 ± 10
Gender [male/female (%)]	73/27
BSA (m^2)	1.9 ± 0.2
Duration of cardiopulmonary bypass (min)	88.4 ± 5.2
EuroSCORE	5.2 ± 3.5
Surgical interventions (%)	
CABG	66.6
Valve surgery	15.2
CABG + valve surgery	11.9
Aortic surgery	5.1
Redo	0.2
Miscellaneous	1.1
Medical history (%)	
Diabetes	20.5
Hypertension	69.0
Smoker	13.2
Chronic pulmonary disease	6.7
Neurological disease	4.1
NYHA (%)	
I	4.6
II	19.8
III	51.6
IV	19.9
Missing	4.1
Left ventricular function (%)	
Normal (ejection fraction 41–50%)	67.3
Subnormal (ejection fraction 31–40%)	29.5
Poor (ejection fraction <30%)	3.2

Factors contributing to the development of decreasing S_vO_2 level

Factors possibly associated with development of low S_vO_2 level were tested in a univariate model. Main findings are presented in Table 2.

Survival analyses

The sensitivity of S_vO_2 as a predictor of survival using different time estimates of CPB is presented in Table 3. Initiation and termination of CPB identified the two periods most sensitive in relation to survival, both for 30-day and 3-year survivals.

Thirty-day survival was best predicted by the S_vO_2 determination made during the last 10 min (E-10) of CPB. Survival rate was 98.1% for patients with S_vO_2 exceeding 75% compared with 95.0 for S_vO_2 lower than 75% accounting for a 3.1% absolute difference ($P = 0.011$) or a relative difference in mortality of 62%.

Prediction of 3-year survival based on the same time period (E-10) resulted in 92.7% survival for S_vO_2 >75 and 86.6% survival rate for S_vO_2 <75%, with an absolute difference of 6.1% ($P = 0.003$), equivalent to a relative mortality difference of 46%.

The preoperative left ventricular function had significant effects on 3-year survival. Survival rate was ∼80% for patients with poor left ventricular function compared with ∼95% for patients with normal function (Kaplan–Meier, $P = 0.007$).

Cox regression analysis of 3-year survival for the S_vO_2 level during time phase E–10 is presented in Table 4. A 2-fold increased risk (odds ratio 2.1) of shortened 3-year life expectancy was observed for patients with S_vO_2 lower than 75% at weaning from CPB. Corresponding survival curves are presented in Figure 2.

Short-term outcome

The S_vO_2 level during CPB had no statistically significant effects on short-term outcome as outlined in Table 5.

DISCUSSION

We report the relative risk of premature death over a 3-year period after cardiac surgery to increase by 2-fold for patients with S_vO_2 <75% at weaning from CPB. Analysis of long-term survival after cardiac surgery based on S_vO_2 has, to the best of our knowledge, not been previously addressed. However, in the short-term perspective, we know that S_vO_2 is strongly linked to indices of both morbidity and mortality as demonstrated by Svedjeholm *et al.* [8] and Holm *et al.* [5] and later confirmed by Ranucci *et al.* [7] in a group of paediatric patients. The use of S_vO_2 as a prognostic marker and guidance for treatment is manifold [2]. Its applicability throughout the perioperative process from emergency until discharge from intensive care is notable [15]. Pölönen *et al.* [6] demonstrated improved patient outcome using goal-oriented therapy based on S_vO_2 levels >70%. Also, in the treatment of septic patients, S_vO_2 seems useful, as indicated by significantly lower mortality rates [12].

The mechanisms of S_vO_2 related to survival remain speculative. It may reflect imbalances between oxygen delivery and demand. Oxygen delivery is determined by pump rate and arterial oxygen content [16]. Current guidelines recommend the patient's body surface area as reference for systemic blood flow control [17], a rationale going back to the early era of cardiac surgery [18]. The apparent limitation of having a static reference [17] sets aside variations in pump rate to compensate for deficits in oxygen-carrying capacity [11]. Numerous publications address low haematocrit level as an independent risk factor for adverse outcome after cardiac surgery [14, 19, 20]. However, haematocrit signifies only one of two components responsible for the arterial oxygen transport [19]. Pump rate [14] or cardiac output [6] in the intensive care situation must also be considered under the same premises. Using S_vO_2 as a target for blood flow management during CPB will safeguard global oxygenation or the delivery of oxygen at a rate equal to the actual demand and access of oxygen carriers denoted by the haematocrit level [11].

Regional oxygenation is very much governed by local regulatory mechanisms, which functions from the clinical therapeutic perspective are difficult to influence upon [21]. One component of immense importance in this context is the availability of oxygen, whereby 90% is utilized for mitochondrial activity in the production of Adenosine triphosphate [21]. A state of oxygen deficiency will promptly lead to cellular hypoxia and development of lactatemia and if sustained untreated, will significantly affect patient outcome [7, 22]. Regional hypoxia related to inadequacy in global oxygenation under the conditions of CPB may therefore represent an important cause relation link for the

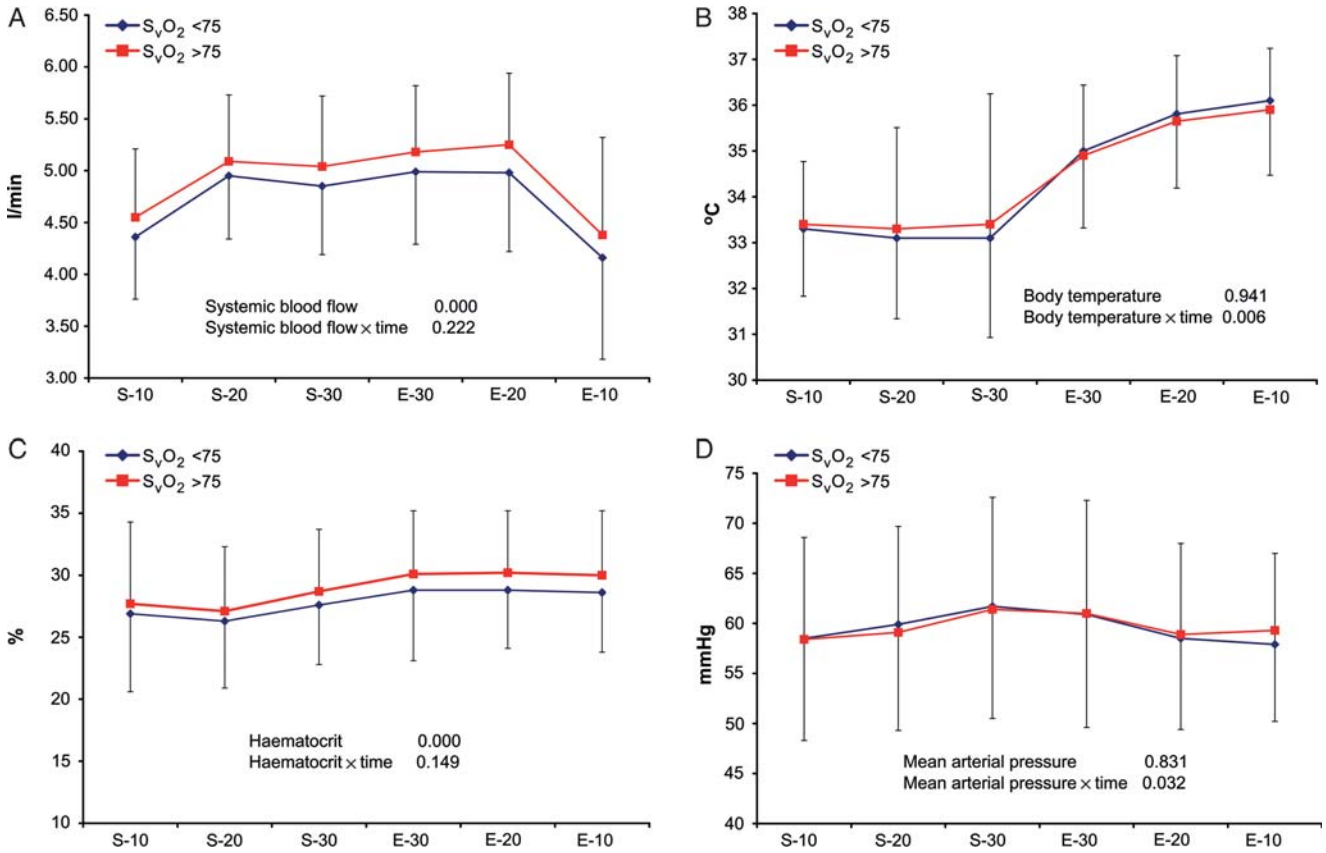

Figure 1: S_vO_2 level in relation to specific physiological parameters. Depiction of systemic blood flow (**A**), body temperature (**B**), haematocrit (**C**) and mean arterial blood pressure (**D**) at S_vO_2 below or above 75% during cardiopulmonary bypass (CPB). *P*-values (ANOVA) represent group differences based on the S_vO_2 level and interaction effects of included time periods. S10–S30 denote commence and E30–E10 termination of CPB each with a time frame of 10 min (means ± SD).

Table 2: Univariate analyses of factors with possible association with S_vO_2

Factors	S_vO_2 <75%	S_vO_2 >75%	*P*-value
Age (years)	66.4 ± 9.9	67.0 ± 10.0	0.379
Body surface area (m^2)	1.95 ± 0.2	1.93 ± 0.2	0.135
Gender (male/female) (%)	71.3/28.7	73.5/26.5	0.496
CPB duration (min)	95.5 ± 66	85.5 ± 45	0.026
Blood temperature (°C)	36.1 ± 1.1	35.9 ± 1.4	0.033
Haematocrit (%)	28.5 ± 4.7	29.9 ± 5.2	0.000
Mean arterial pressure (mmHg)	57.9 ± 9.2	59.3 ± 7.9	0.026
Creatinine preoperative (μmol/l)	92.2 ± 39	93.468 ± 47	0.614
Atrial fibrillation (%)	6.9	10.2	0.050

Blood temperature and haematocrit refer to time period E-10 denoting the last 10 min of cardiopulmonary bypass (CPB).

Table 3: S_vO_2 at different time phases of cardiopulmonary bypass related to survival

	30-day survival S_vO_2 level			3-year survival S_vO_2 level		
Time interval	<75%	>75%	*P*-value	<75%	>75%	*P*-value
S-10	95.0	97.9	0.021	87.7	92.0	0.043
S-20	95.2	97.6	0.081	89.8	91.2	0.524
S-30	95.2	97.7	0.077	90.9	91.0	0.935
E-30	96.0	97.7	0.156	89.2	91.7	0.203
E-20	96.0	98.0	0.073	89.2	92.2	0.104
E-10	95.0	98.1	0.011	86.6	92.7	0.003

Kaplan–Meier-derived survival statistics for 30-day and 3-year based on S_vO_2 from different time phases of cardiopulmonary bypass (CPB). Time intervals include S10–S30 and E30–E10 for commence and termination of CPB, respectively. Each time span covers 10 min of CPB. *P*-values represent log-rank statistics.

development of organ failure [7, 14] and as demonstrated, significantly influence survival after cardiac surgery [23].

S_vO_2 can assist clinicians in decisions regarding blood transfusion [4]. The haemoglobin concentration serves otherwise as a gold standard. The trigger level at which transfusions should be performed is, however, debated and consensus is lacking [9]. Since the amount of circulating haemoglobin determines the arterial oxygen transport [16], inclusion of the S_vO_2 level as a transfusion criterion may enhance the quality of decision making [9, 10]. For instance, a patient demonstrating relative anaemia, but preserved S_vO_2 levels should probably be re-assessed before being transfused [10]. To combine information from S_vO_2 with haemoglobin concentration may avoid unnecessary transfusions and thereby reduce transfusion rates [10].

The normal level of oxygen consumption in conjunction with CPB is not defined. The consumption may vary considerably in a

Table 4: Cox regression analysis of 3-year survival with respect to S_vO_2 level during cardiopulmonary bypass

Covariate	*B*	Odds ratio	*P*-value	95% CI, low limit	95% CI, high limit
Age	0.060	1.062	0.000	1.032	1.092
Female gender	−0.727	0.483	0.011	0.275	0.849
CPB duration	0.009	1.009	0.000	1.005	1.013
Blood temperature	−0.231	0.794	0.000	0.710	0.887
Hypertension	0.706	2.025	0.015	1.144	3.585
Haematocrit	−0.051	0.950	0.046	0.903	0.999
Atrial fibrillation	0.684	1.981	0.018	1.125	3.490
Creatinine	0.008	1.008	0.000	1.005	1.010
Left ventricular function	0.145	1.157	0.127	0.960	1.394
Mean arterial pressure	−0.009	0.991	0.445	0.969	1.014
Surgical procedure	0.309	1.363	0.011	1.075	1.728
S_vO_2 <75%	0.719	2.051	0.003	1.075	1.728

Results from Cox regression analyses with reference to included covariates. Overall score for omnibus tests of coefficients arrived at chi-square equal to 126.199 ($P = 0.000$). Odds ratio presented with its associated 95% CI. Haematocrit and mean arterial pressure refer to the period of cardiopulmonary bypass.

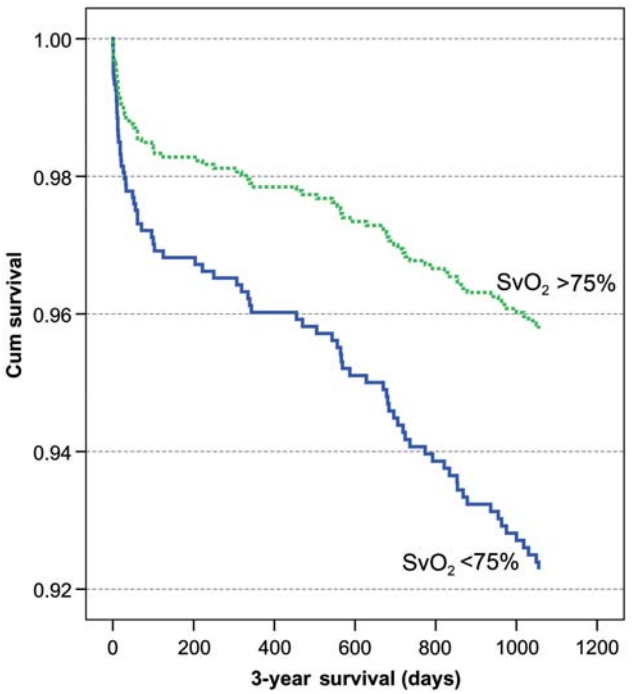

Figure 2: Three-year survival based on S_vO_2 during cardiopulmonary bypass (CPB). Three-year survival categorized on S_vO_2 below or above 75% during the last phase of CPB after controlling for possible confounders as defined in the Cox regression analysis.

particular patient due to influences of hypothermia and anaesthesia [24]. The magnitude of change is revealed by variations in S_vO_2. Maintaining S_vO_2 within the normal range assumes adaption of the oxygen delivery by altering the pump rate [11]. The strategy strives to mimic normal physiological circulatory

Table 5: Impact of S_vO_2 level during cardiopulmonary bypass on short-term outcome

Variable	S_vO_2 <75%	S_vO_2 >75%	*P*-value
Stay in hospital >10 days (%)	7.3	7.0	0.883
Postoperative confusion (%)	3.0	3.1	0.946
Stroke within hospital stay (%)	2.3	2.1	0.837
Dialysis in intensive care (%)	1.5	2.7	0.301
Intra aortic balloon pump (%)	0.8	1.2	0.573

concepts based on metabolic demand-driven changes of cardiac output [1, 4]. The relevance of applying a similar approach in the regulation of systemic blood flow per CPB has, to date, scarcely been investigated [11]. Our previous experience would indicate that dynamic systemic blood flow control may be safely implemented based on favourable outcomes in a group of low-risk coronary artery bypass surgical patients [11].

S_vO_2 during CPB was identified as an independent risk factor for survival in the Cox regression analysis. The measure reflects oxygen balance as reflected by the patient's respiratory and circulatory status. The complexity of S_vO_2 per se necessitates further analysis to validate the consequences of abnormal S_vO_2 readings. The respiratory component may, in theory, be ruled out in the case of CPB, provided the incorporated oxygenator is functioning normally. Hence, the consequences of hypoperfusion would seem more likely. Inadequacies of the pump rate, combined with low cardiac output will both lower S_vO_2 significantly [1]. The strongest statistical association between survival and S_vO_2 was identified at the commencement and termination of bypass, indicating low cardiac output involvement. The impact of S_vO_2 in relation to other risk factors on survival after cardiac surgery is intriguing. Low S_vO_2 seems to distinguish a certain group of patients, where the survival expectancy is hampered. Whether this solely reflects hypoperfusion remains uncertain. Other mechanisms disturbing the uptake of oxygen should be considered, but remain beyond the scope of this investigation.

Patient age, duration of CPB, creatinine level and hypertension were all significantly associated with survival, which concurs with previous findings [25]. Blood transfusions were not included in the analysis. Transfusions were performed only in very rare cases per CPB. The haematocrit level was, on the other hand, measured online, concomitantly with S_vO_2 and included in the statistical analysis to control for its influence on oxygen balance. Increasing haematocrit levels served as protection for survival, probably by increasing the oxygen-carrying capacity, which once again underlines the crucial impact of oxygen delivery. To our surprise, haematocrit carried only a border-line statistical significance. The reason for this may be attributed to the use of higher pump rates within this particular group of patients, thereby serving as a compensatory mechanism. Furthermore, left ventricular function showed no statistically significant influence on survival. Left ventricular function is described as a significant risk factor [25]. Univariate statistical analysis of our dataset confirmed this. However, in the multivariable setting, the statistical significance disappeared.

We can only speculate on why oxygen imbalances during CPB had such a strong influence on survival, but very limited effects on the rate of postoperative complications, such as stroke, postoperative renal insufficiency, need for intra-aortic balloon pump

and in-hospital mortality. One suggestion would be that the level of S_vO_2 delineates a group of risk patients where survival is compromised already from the start. Whether this is attributed to disturbances in oxygen uptake and as a consequence interferes with long-term organ function needs to be verified. Abnormalities in S_vO_2 can also serve as a surrogate for one or several other risk factors, however, contrary to the fact that S_vO_2 emerged as an independent risk factor in the multivariable analysis. We also observed that the initial (S-10) and terminal (E-10) recordings of S_vO_2 were the time-phases during CPB with the statistically strongest impact on survival. This might indicate that the involvement of the S_vO_2 level before and after CPB also should be considered, i.e. despite efforts to maintain S_vO_2 normal during CPB. These efforts were superimposed by pre-existing low S_vO_2 or failure to maintain S_vO_2 normal postoperatively.

Limitations

The present report is based on prospectively collected registry data analysed in a retrospective fashion. The cohort represents a true consecutive series of patients, where no exclusions were made based on patient criteria and describes therefore a 'real world' situation derived from clinical routines. Nonetheless, the finding needs to be verified in a randomised trial.

CONCLUSION

We report a statistically significant association between the S_vO_2 level during CPB and 3-year survival after cardiac surgery. The finding may be important in the way blood flow is controlled per CPB.

Conflict of interest: none declared.

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