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Association between postoperative delirium and postoperative cerebral oxygen desaturation in older patients after cardiac surgery

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Abstract

Background: Near-infrared spectroscopy non-invasively measures regional cerebral oxygen saturation. Intraoperative cerebral desaturations have been associated with worse neurological outcomes. We investigated whether perioperative cerebral desaturations are associated with postoperative delirium in older patients after cardiac surgery.

Methods: Patients aged 70 yr and older scheduled for on-pump cardiac surgery were included between 2015 and 2017 in a single-centre, prospective, observational study. Baseline cerebral oxygen saturation was measured 1 day before surgery. Throughout surgery and after ICU admission, cerebral oxygen saturation was monitored continuously up to 72 h after operation. The presence of delirium was assessed using the confusion assessment method for the ICU. Association with delirium was evaluated with unadjusted analyses and multivariable logistic regression.

Results: Ninety-six of 103 patients were included, and 29 (30%) became delirious. Intraoperative cerebral oxygen saturation was not significantly associated with postoperative delirium. The lowest postoperative cerebral oxygen saturation was lower in patients who became delirious (P=0.001). The absolute and relative postoperative cerebral oxygen saturation decreases were more marked in patients with delirium (13 [6]% and 19 [9]%, respectively) compared with patients without delirium (9 [4]% and 14 [5]%; P=0.002 and P=0.001, respectively). These differences in cerebral oxygen saturation were no longer present after excluding cerebral oxygen saturation values after patients became delirious. Older age, previous stroke, higher EuroSCORE II, lower preoperative Mini-Mental Status Examination, and more substantial absolute postoperative cerebral oxygen saturation decreases were independently associated with postoperative delirium incidence.

Conclusions: Postoperative delirium in older patients undergoing cardiac surgery is associated with absolute decreases in postoperative cerebral oxygen saturation. These differences appear most detectable after the onset of delirium.

Clinical trial registration: NCT02532530.

Keywords: cardiac surgery; cerebral oxygen saturation; delirium; intensive care unit; near-infrared spectroscopy; neurological outcome; postoperative delirium

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Editor's key points

- Delirium after cardiac surgery is common and consequential, but the underlying pathophysiology remains unknown.
- Some previous studies have found that pre- and intraoperative cerebral desaturation events were predictive of postoperative delirium, suggesting a potentially modifiable causal link.
- In contrast, this study found that only postoperative cerebral desaturations, probably occurring mostly during or after episodes of delirium, were significantly associated with postoperative delirium.
- This hypothesis-generating finding suggests that cerebral desaturation might be a manifestation or consequence of postoperative delirium rather than a causal mediator thereof.

Older patients undergoing cardiac surgery are at risk of developing postoperative delirium (POD).[1] Delirium has been associated with a prolonged intensive care and hospital stay, long-term neurocognitive deterioration, and increased mortality. Identifying predictors for the development of POD is therefore important in the prevention and early treatment of this condition.[2–5] Intraoperative cerebral hypoperfusion and hypoxia have frequently been suggested as important factors contributing to the development of POD after cardiac surgery.[6–9] Near-infrared spectroscopy (NIRS) non-invasively measures the regional cerebral oxygen saturation ($S_{ct}O_2$) at the microvascular level in the frontal lobe, thereby enabling the detection of a mismatch between oxygen delivery and consumption.[10] In recent years, studies have reported an association between a prolonged intraoperative cerebral oxygen desaturation as measured by NIRS and neurological complications.[11–15] However, the incidence of these postoperative neurological complications remained unchanged when a protocol-based interventional strategy was used to treat intraoperative cerebral desaturations.[16,17] Other studies have indicated that cerebral desaturations continue to occur in the ICU.[18,19] As such, we hypothesised that there is an association between postoperative cerebral desaturation and POD. The primary aim of this prospective observational study was to assess the association between postoperative cerebral desaturations on the ICU and the presence of delirium after cardiac surgery.

Methods

The study was conducted in a tertiary care hospital (Ziekenhuis Oost-Limburg, Genk, Belgium). Patients were enrolled between June 2015 and July 2017. The study protocol was approved by the Institutional Committee for Medical Ethics (15/037U) and was registered on https://clinicaltrials.gov/ (NCT02532530). Adult patients (age ≥70 yr) undergoing elective on-pump aortic valve replacement, coronary artery bypass surgery, or a combination of both procedures were included. The exclusion criteria were inability to speak Dutch, alcohol consumption of more than 2 units of alcohol per day, Mini-Mental State Examination (MMSE) score ≤20, and preoperative use of antipsychotic drugs. As the maximum duration of $S_{ct}O_2$ monitoring was 72 h, patients in whom the duration of postoperative mechanical ventilation exceeded 36 h were excluded from the data analysis. One day before surgery, written informed consent was requested, after which the preoperative cognitive status was assessed with the MMSE. The surgical risk assessment was based on the logistic EuroSCORE II.

General anaesthesia was induced using propofol (0.5 mg kg^{-1}) or diazepam (0.05–0.1 mg kg^{-1}) and sufentanil (0.5–1 μg kg^{-1}). Tracheal intubation was facilitated by a bolus of cisatracurium (0.2 mg kg^{-1}). At the discretion of the anaesthesiologist, general anaesthesia was maintained with either target-controlled infusion of propofol or sevoflurane in an O_2–air mixture. In either instance, there was a sufentanil infusion (0.025 μg kg^{-1} h^{-1}) and continuous administration of cisatracurium.

The cardiopulmonary bypass (CPB) circuit was primed with 1.0 L Plasma-Lyte® A (Baxter S.A., Lessines, Belgium) and 500 ml Volulyte® 6% (Fresenius Kabi, Schelle, Belgium). Before CPB initiation, an initial dose of heparin (300 U kg^{-1}) was administered, followed by a continuous infusion (100 U kg^{-1} h^{-1}) during CPB to attain an activated clotting time above 480 s. The ascending aorta and right atrium were cannulated. Myocardial protection was provided by either anterograde or retrograde blood cardioplegia, which was repeated every 15–30 min. Management of CPB comprised pH-stat management with strict normocapnia, mean arterial pressure targeted at 6.7–10.7 Kpa, and maintenance of CPB flow between 2.4 and 2.8 L min^{-1} m^{-2}. Haemodynamic monitoring was applied according to institutional guidelines.

After sternal closure, the patients were transferred to the ICU where they received a continuous propofol infusion (0.3–4.0 mg kg^{-1} h^{-1}) until the extubation criteria were fulfilled (i.e. adequate oxygenation with oxygen partial pressure >8.0 Kpa with inspired oxygen fraction ≤40%; adequate ventilation with spontaneous tidal volumes >5 ml kg^{-1}, spontaneous ventilatory frequency >8 min^{-1}, and end-tidal P_aCO_2<6.7 Kpa; haemodynamic stability; and following verbal commands). Postoperative analgesic management consisted of a loading dose of morphine (0.1 mg kg^{-1}) with additional boluses on demand (i.v. drug pump was operated by the patient) combined with paracetamol.

In the ICU, the presence of delirium was assessed by a trained investigator three times per day using the confusion assessment method for the ICU (CAM-ICU) during the first 72 h after ICU admission (i.e. at the end of each 8 h nursing shift), with the first one starting 4 h after extubation.[20] First, the sedation status was determined using the Richmond Agitation–Sedation Scale (RASS), where a RASS score of at least −3 is necessary before the CAM-ICU can be performed. The CAM-ICU consists out of four features: (i) acute change or fluctuating course of the mental condition, (ii) inattention, (iii) altered consciousness level, and (iv) disorganised reasoning. The CAM-ICU is considered positive when the first two features are present together with either Feature 3 or 4. The RASS score was used for the differentiation amongst motor subtypes of delirium (hyperactive, hypoactive, and mixed type).[21,22] Delirium was regarded as present based either on a positive CAM-ICU assessment or on the administration of antipsychotic medications to treat delirium. After ICU discharge, a second MMSE was performed.

On the day before cardiac surgery, bilateral $S_{ct}O_2$ sensors (FORE-SIGHT ELITE™; CAS Medical systems, Branford, CT, USA) were placed on the patients' foreheads, and preoperative $S_{ct}O_2$ was determined without supplemental oxygen during 5

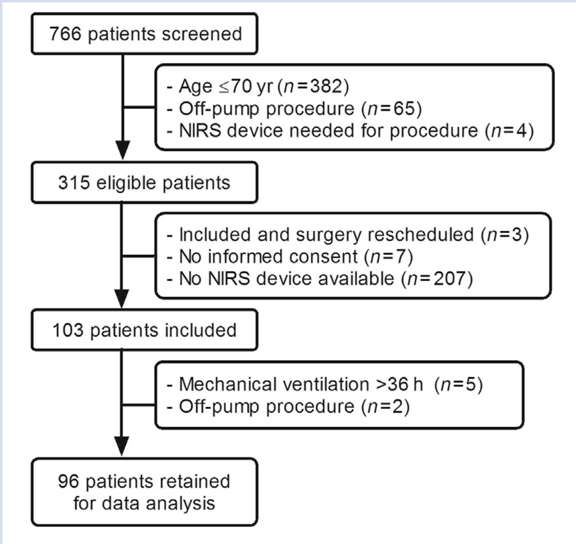

Fig 1. Flow diagram presenting patient enrolment. NIRS, Near-infrared spectroscopy.

min. In the operating room, $S_{ct}O_2$ sensors were placed bilaterally (before pre-oxygenation and induction) and remained in place up to 72 h after operation. NIRS monitoring was stopped before 72 h in case of earlier discharge from the ICU. Throughout surgery and during the entire ICU stay, physicians and nursing staff were blinded to $S_{ct}O_2$ values. As such, clinical decisions were never based on $S_{ct}O_2$ values. All $S_{ct}O_2$ values were captured every 2 s. The left and right $S_{ct}O_2$ values were averaged, and the mean $S_{ct}O_2$ values were used for data analysis. Subsequently, the lowest $S_{ct}O_2$, the absolute and relative decrease in $S_{ct}O_2$, and the incidence of desaturations below the absolute $S_{ct}O_2$ values of 60% and 55% and the incidence of desaturations below 80% of baseline were calculated for both the intra- and postoperative periods. Intraoperative baseline $S_{ct}O_2$ was defined during a 2 min period before the induction of anaesthesia whilst the patients were breathing room air. The preoperative $S_{ct}O_2$, in contrast, was considered as baseline $S_{ct}O_2$ for the postoperative period. In addition, the area under the curve (AUC) of the $S_{ct}O_2$ values below 60% and 55% was calculated.

Statistical analysis was with SPSS version 24 (IBM Corp., Armonk, NY, USA). Normal distribution of data was assessed using the Kolmogorov–Smirnov test. Categorical variables are shown as *n* (%). Continuous data are expressed as mean (standard deviation) when normally distributed, or as median with first and third quartiles when non-normally distributed. Depending on normality, categorical data were compared between patients with and without delirium with a χ^2 test or Fisher's exact test, and continuous data were compared using an unpaired Student's *t*-test or a Mann–Whitney *U*-test. Baseline patient characteristics and postoperative $S_{ct}O_2$ parameters that were significant in the univariable analysis at a threshold $P<0.1$ were entered into a forward multivariable logistic regression model. All included variables were checked for multicollinearity in advance, and variables with a variance inflation factor >3 were excluded. The Hosmer–Lemeshow test was used for the evaluation of the goodness of fit of the final multivariable logistic regression model. The predictive ability of this final model was assessed by a receiver operating characteristic curve, and the AUC was calculated to assess the performance in predicting POD. Finally, markers of general hypoperfusion might confound any association between postoperative $S_{ct}O_2$ and POD. Therefore, those markers that were significant in the univariable analysis were entered into a second forward multivariable logistic regression model, combined with postoperative $S_{ct}O_2$ parameters. Statistical significance was set at $P<0.05$.

Results

From June 2015 until July 2017, 103 patients scheduled for cardiac surgery with CPB were included in this prospective observational study (Fig 1). Seven patients were excluded for data analysis. In two patients, the procedure was performed without CPB after patient enrolment, and in five patients, the duration of postoperative mechanical ventilation exceeded 36 h. Ninety-six patients were included in the data analysis. Coronary artery bypass surgery, aortic valve replacement, and a combined procedure were performed in 27 (28%), 32 (33%), and 37 (39%) patients, respectively. Twenty-nine (30%) patients developed POD, of whom 13 (45%) experienced the hyperactive, 12 (41%) the hypoactive, and four (14%) the mixed form of delirium. In patients with and without POD, a median of 5[4–7] and 4[3–5] CAM-ICU were performed, respectively (P=0.005). The median duration of POD was 17[9–34] h. There were no missing CAM-ICU assessments. The patient characteristic data of both patient cohorts are presented in Table 1. The patients with POD were older, had a worse preoperative cognitive status based on MMSE, and had a higher EuroSCORE II compared with the patients without POD. Whilst the duration of the surgical procedure was similar in both groups (P=0.080), the duration of postoperative mechanical ventilation and the length of ICU stay were longer in patients who developed POD (both with $P<0.001$; Table 1). The patients with POD scored lower on the postoperative MMSE ($P<0.001$; Table 1).

Intra- and postoperative baseline $S_{ct}O_2$ were similar (both 68 [3]%; P=0.824). The univariable comparison of perioperative $S_{ct}O_2$ parameters between the patients with and without POD is shown in Table 2. The preoperative $S_{ct}O_2$ was not different between the patients with and without POD (P=0.785). Likewise, intraoperative baseline $S_{ct}O_2$ did not differ between both groups (P=0.679). In general, none of the investigated intraoperative $S_{ct}O_2$ variables was predictive of POD (Table 2). In contrast to $S_{ct}O_2$ measured intraoperatively, the lowest postoperative $S_{ct}O_2$ was lower in the group with POD (P=0.001). The absolute and relative decreases in postoperative $S_{ct}O_2$ were higher in the POD group (P=0.002 and P=0.001, respectively). Furthermore, the times below a postoperative absolute $S_{ct}O_2$ threshold of 55% and below 80% of postoperative baseline $S_{ct}O_2$ were significantly higher in the patients with POD (P=0.014 and P=0.023, respectively). The AUC values of postoperative $S_{ct}O_2$ values below 60% and 55% were higher in the patients with POD (P=0.021 and P=0.021, respectively). None of the patients had more than 5% missing postoperative $S_{ct}O_2$ values (median proportion of missing values was 0 [0–0.1]%). Finally, a higher postoperative decrease in absolute $S_{ct}O_2$ was associated with POD, independent of age, previous stroke, preoperative cognitive status based on MMSE, and EuroSCORE II (AUC=0.824; $P<0.001$; Table 3).

Table 1 Patient characteristics. CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; MMSE, Mini-Mental Status Examination; PCI, percutaneous coronary intervention.

Parameter	Delirium (*n*=29)	No delirium (*n*=67)	P-values
Baseline patient characteristics			
Male sex, *n* (%)	19 (66)	45 (67)	1.000
Age (yr)	79 (75–83)	75 (73–79)	0.001
BMI (kg m^{-2})	27 (5)	28 (3)	0.146
Cognitive status			
Preoperative MMSE	28 (24–29)	29 (28–29)	0.012
Postoperative MMSE	24 (23–29)	29 (27–30)	<0.001
Surgical procedure, *n* (%)			0.072
Aortic valve replacement	7 (24)	20 (30)	
CABG	6 (21)	26 (39)	
Combined procedure	16 (55)	21 (31)	
Preoperative morbidity, *n* (%)			
Previous stroke	3 (10)	1 (1)	0.081
Previous myocardial infarction	3 (10)	9 (13)	0.752
Previous PCI	5 (17)	16 (24)	0.595
Previous cardiac surgery	1 (3)	0 (0)	0.302
Arterial hypertension	21 (72)	52 (78)	0.609
COPD	6 (21)	5 (8)	0.083
Chronic kidney insufficiency	5 (17)	19 (28)	0.311
Atrial fibrillation	4 (14)	12 (18)	0.770
Diabetes mellitus	9 (31)	13 (19)	0.290
EuroSCORE II	2.61 (1.75–4.68)	1.86 (1.02–3.37)	0.019
Surgery variables			
Duration of surgical procedure (min)	372 (93)	342 (69)	0.080
Duration of CPB (min)	149 (114–186)	132 (103–159)	0.263
Duration of aortic cross clamp (min)	114 (44)	105 (37)	0.314
Duration of reperfusion (min)	23 (18–36)	20 (13–25)	0.037
ICU variables			
Duration of mechanical ventilation (min)	614 (508–1118)	449 (377–627)	<0.001
Duration of ICU stay (h)	74 (47–118)	46 (42–59)	<0.001

Some patients with POD did not experience postoperative desaturations. Five (17%), 12 (41%), and 13 (45%) of the 29 patients who developed POD did not experience postoperative desaturations below absolute $S_{ct}O_2$ values of 60% and 55%, and 80% of baseline, respectively.

A positive correlation was present between the absolute decrease in $S_{ct}O_2$ and the length of ICU stay (r=0.412; P<0.001). Therefore, a sensitivity analysis was performed based on the initial 24 h of $S_{ct}O_2$ monitoring after ICU admission. Calculated within this time frame, the lowest $S_{ct}O_2$ remained lower

Table 2 Perioperative cerebral tissue oxygenation in patients with and without postoperative delirium. AUC, area under the curve; $S_{ct}O_2$, regional cerebral tissue oxygen saturation.

$S_{ct}O_2$ variable	Delirium (*n*=29)	No delirium (*n*=67)	P-values
Preoperative $S_{ct}O_2$	68(3)	68(3)	0.785
Intraoperative $S_{ct}O_2$ variables			
Baseline $S_{ct}O_2$ (%)	68 (65–69)	68 (66–70)	0.372
Lowest $S_{ct}O_2$ (%)	60 (55–62)	59 (55–62)	0.533
Absolute $S_{ct}O_2$ decrease (%)	10(7–12)	9(5–13)	0.533
Relative $S_{ct}O_2$ decrease (%)	13(7–19)	14(10–18)	0.462
AUC 60% (% × min)	0 (0–4)	0.23 (0–23)	0.350
AUC 55% (% × min)	0 (0–0)	0 (0–0)	0.639
Desaturation <60%, *n* (%)	14 (48)	36 (54)	0.661
Desaturation <55%, *n* (%)	8(28)	22(33)	0.642
Desaturation <80% of baseline, *n* (%)	7(24)	16(24)	1.000
Postoperative $S_{ct}O_2$ variables			
Lowest $S_{ct}O_2$ (%)	56 (53–59)	58 (56–61)	0.003
Absolute $S_{ct}O_2$ decrease (%)	13(6)	9(4)	0.002
Relative $S_{ct}O_2$ decrease (%)	19(9)	14(5)	0.001
AUC 60 (% × min)	36 (1–170)	1 (0–80)	0.021
AUC 55 (% × min)	0 (0–2)	0 (0–0)	0.045
Desaturation <60%, *n* (%)	24 (83)	38 (57)	0.019
Desaturation <55%, *n* (%)	17 (59)	21(31)	0.014
Desaturation <80% of baseline, *n* (%)	16 (55)	20(30)	0.023

Table 3 Univariable and multivariable logistic regression analysis for prediction of postoperative delirium after cardiac surgery, including baseline patient characteristics and postoperative $S_{ct}O_2$ data. CI, confidence interval; COPD, chronic obstructive pulmonary disease; MMSE, Mini-Mental State Examination; OR, odds ratio; $S_{ct}O_2$, regional cerebral tissue oxygen saturation. Only significant ($P<0.1$) variables in the univariable logistic regression analysis are reported. The following parameters showed collinearity and were not included in the forward multivariable logistic regression analysis: lowest $S_{ct}O_2$ and relative $S_{ct}O_2$ decrease.

Variable	Univariable			Multivariable		
	OR	95% CI	P-values	OR	95% CI	P-values
Baseline characteristics						
Age	1.17	1.05–1.30	0.003	1.15	1.01–1.31	0.029
COPD	3.24	0.90–11.63	0.072	—	—	—
MMSE preoperative	0.73	0.61–0.89	0.001	0.80	0.64–0.99	0.047
EuroSCORE II	1.23	1.02–1.48	0.028	1.23	1.02–1.49	0.030
Previous stroke	7.62	0.76–76.6	0.085	15.97	1.22–209.2	0.035
Postoperative $S_{ct}O_2$						
Absolute $S_{ct}O_2$ decrease	1.17	1.04–1.31	0.006	1.19	1.03–1.38	0.019
Relative $S_{ct}O_2$ decrease	1.13	1.04–1.23	0.004	—	—	—
Lowest $S_{ct}O_2$	0.84	0.75–0.94	0.003	—	—	—
Desaturation <55%	3.10	1.26–7.64	0.014	—	—	—
Desaturation <60%	3.66	1.25–10.8	0.018	—	—	—
Desaturation <80% baseline	2.89	1.18–7.11	0.021	—	—	—

Table 4 Haemodynamic variables in the ICU.

Variable	Delirium (n=29)	No delirium (n=67)	P-values
SpO_2			
Lowest (%)	73 (67–78)	80 (76–84)	0.001
Mean (%)	98 (97–98)	98 (97–99)	0.821
HR			
Lowest (beats min^{-1})	57 (53–67)	59 (53–66)	0.817
Mean (beats min^{-1})	80(9)	78(8)	0.424
Mean arterial pressure			
Lowest (kPa)	5.7 (0.8)	6.0 (1.1)	0.186
Mean (kPa)	9.7 (9.3 –10.5)	9.9 (9.5–10.4)	0.767
Cardiac output			
Lowest (L min^{-1})	3.0 (2.5–3.5)	3.4 (3.0–3.9)	0.064
Mean (L min^{-1})	4.4 (3.7–4.9)	4.5 (4.1–5.2)	0.340
Cardiac index			
Lowest (L min^{-1} m^{-2})	1.6 (1.5–1.9)	1.8 (1.6–1.9)	0.077
Mean (L min^{-1} m^{-2})	2.4 (0.4)	2.4 (0.3)	0.890
Blood variables			
Lowest haemoglobin (g dl^{-1})	8.0 (7.1–9.2)	8.9 (7.9–10.1)	0.002
Lowest haematocrit (%)	25.1 (22.4–28.4)	27.4 (24.2–30.9)	0.003
Lowest SaO_2 (%)	93.1 (77.8–94.3)	94.7 (93.6–96.3)	<0.001
Lowest PaO_2 (kPa)	8.26 (6.96–9.04)	9.38 (8.51–10.1)	0.001
Lowest $PaCO_2$ (kPa)	4.27 (0.49)	4.56 (0.45)	0.004
Highest lactate (mmol L^{-1})	2.9 (2.2–3.5)	2.4 (2.0–3.2)	0.162
Postoperative fluid management			
Total blood transfusion (ml)	690 (400–1222)	551 (475–761)	0.409
Cell saver (ml)	460 (0–596)	500 (409–551)	0.254
Packed cells (ml)	0 (0–353)	0 (0–0)	0.001
Thrombocytes (ml)	0 (0–164)	0 (0–0)	0.023
Plasma (ml)	0 (0–360)	0 (0–0)	0.114
Albumin (ml)	0 (0–0)	0 (0–0)	0.800
Total fluid administration (ml)	9250 (7475–11 078)	7650 (6733–8939)	0.006
Blood loss (ml)	770 (685–1475)	720 (470–1180)	0.040
Total fluid balance (ml)	4407 (3358–5565)	3893 (2842–4853)	0.069
Postoperative vasopressor support			
Norepinephrine (μg kg^{-1})	98 (38–255)	29 (8–124)	0.016
Postoperative sedation			
Propofol (mg kg^{-1})	20.8 (12.6–34.8)	17.2 (12.5–22.6)	0.083

Table 5 Univariable and multivariable logistic regression analysis for prediction of postoperative delirium after cardiac surgery, including postoperative haemodynamics and $S_{ct}O_2$ data. CI, confidence interval; OR, odds ratio. Only significant (P<0.1) variables in the univariable logistic regression analysis are reported. The following variables showed collinearity and were not included in the forward multivariable logistic regression analysis: lowest haemoglobin, total fluid administration, blood loss, relative $S_{ct}O_2$ decrease, and lowest $S_{ct}O_2$.

Variables	Univariable			Multivariable		
	OR	95% CI	P-values	OR	95% CI	P-values
Postoperative haemodynamics						
Lowest SpO_2	0.89	0.82–0.95	0.001	0.89	0.81–0.97	0.007
Lowest haemoglobin	0.54	0.37–0.80	0.002	—	—	—
Lowest haematocrit	0.83	0.73–0.95	0.005	0.80	0.66–0.97	0.025
Lowest SaO_2	0.90	0.85–0.97	0.003	0.91	0.84–0.98	0.012
Lowest PaO_2	0.93	0.89–0.97	0.001	—	—	—
Lowest $PaCO_2$	0.83	0.73–0.95	0.007	—	—	—
Packed cells administered (ml)	1.00	1.00–1.00	0.012	—	—	—
Thrombocytes administered (ml)	1.00	1.00–1.00	0.017	—	—	—
Total fluid administration	1.00	1.00–1.00	0.012	—	—	—
Blood loss	1.00	1.00–1.00	0.032	—	—	—
Total fluid balance	1.00	1.00–1.00	0.099	—	—	—
Norepinephrine dose	1.00	0.99–1.01	0.099	—	—	—
Postoperative $S_{ct}O_2$						
Absolute $S_{ct}O_2$ decrease	1.17	1.04–1.31	0.006	1.18	1.02–1.35	0.023
Relative $S_{ct}O_2$ decrease	1.13	1.04–1.23	0.004	—	—	—
Lowest $S_{ct}O_2$	0.84	0.75–0.94	0.003	—	—	—
Desaturation <55%	3.10	1.26–7.64	0.014	—	—	—
Desaturation <60%	3.66	1.25–10.8	0.018	—	—	—
Desaturation <80% baseline	2.89	1.18–7.11	0.021	—	—	—

(P=0.025), and the absolute and relative $S_{ct}O_2$ decreases (P=0.031 and P=0.021, respectively) remained higher in the patients with POD. Other $S_{ct}O_2$ variables no longer differed significantly between the patients with and without POD (Supplementary Table 1). Another sensitivity analysis, in which all $S_{ct}O_2$ values after the 8 h shift when POD was first diagnosed were omitted, showed that $S_{ct}O_2$ was no longer different between the patients with and without POD (Supplementary Table 2).

The haemodynamic variables monitored in the ICU are displayed in Table 4. The patients with POD experienced lower SpO_2, haemoglobin, haematocrit, SaO_2, PaO_2, and $PaCO_2$ values throughout their ICU stay. Additionally, blood loss, transfusion of packed cells and platelets, and total fluid administration were all higher in the group with POD (P=0.040, P=0.001, P=0.023, and P=0.006, respectively). Positive correlations were shown between the lowest postoperative $S_{ct}O_2$ and the lowest PaO_2 (r=0.282; P=0.005), $PaCO_2$ (r=0.252; P=0.013), and SaO_2 (r=0.283; P=0.005). A negative correlation existed between the lowest $S_{ct}O_2$ and the total fluids administered (r=−0.259; P=0.011). Whilst postoperative mean arterial pressures were similar in both groups (P=0.186), the patients with POD received more norepinephrine after operation (P=0.016). Univariable logistic regression was performed on all haemodynamic variables, and significant associations are summarised in Table 5. Based on the final multivariable model, a higher absolute decrease in $S_{ct}O_2$ remained associated with POD, independent from the lowest SpO_2, SaO_2, and haematocrit values (AUC=0.880; P<0.001; Table 5).

Discussion

In older adults undergoing cardiac surgery, POD is associated with the absolute decrease in postoperative $S_{ct}O_2$. As the brain is known to consume around 20% of the total amount of oxygen supplied to the body, the cerebral function is extremely vulnerable to hypoxaemia. In the setting of high-risk cardiac surgery, the importance of avoiding cerebral oxygen deficiency has paved the way for cerebral oximetry as a non-invasive tool to assess the adequacy of cerebral oxygen delivery.[13,23–25] In recent years, observational studies have shown that a compromised cerebral oxygenation during cardiothoracic surgery was associated with worse neurological outcomes, thereby concluding that a persisting cerebral desaturation should be avoided.[12,14,26] However, the clinical benefit of NIRS technology during cardiac surgery has been questioned recently, as protocol-based interventions to restore acute cerebral desaturation events were not effective in reducing the incidence of postoperative neurological complications.[16,17,27] In line with these trials, none of the investigated intraoperative $S_{ct}O_2$ variables in our study differentiated the patients with POD from the patients without. Correspondingly, $S_{ct}O_2$ measured on the day before surgery was not predictive for POD, in contrast to previous reports.[15,28,29]

This current study showed that the patients with POD had lower $S_{ct}O_2$ values after ICU admission. The patients with POD more frequently experienced longer cerebral desaturations below the absolute values of 55% and 60%, and below 80% of preoperative baseline. Moreover, a higher absolute decrease in postoperative $S_{ct}O_2$ was associated with POD, independent of known risk factors, such as previous stroke, the patients' age, their surgical risk as assessed by the EuroSCORE II, and their preoperative cognitive status based on MMSE.[15,30,31]

As each CAM-ICU assessment was conducted at the end of an 8 h shift, it was impossible to determine the exact time point at which the patients became delirious. This made it hard to determine whether a decrease in $S_{ct}O_2$ preceded the onset of delirium, or became apparent during or after an episode of delirium. The sensitivity analysis, in which the $S_{ct}O_2$ values after the 8 h shift when POD was first diagnosed were omitted, was informative in this regard; none of the calculated $S_{ct}O_2$ parameters remained significantly different between the patients with and without POD. Therefore, it seems more likely that a decrease in $S_{ct}O_2$ is detectable only after the onset of POD. Importantly, this sensitivity analysis questions the prognostic value of cerebral oximetry for patients at risk for delirium. Our data might also clarify why some studies did and others did not find an association between $S_{ct}O_2$ and the development of POD. Furthermore, our study found that some patients with POD did not experience cerebral desaturations.

This study had several limitations. First, this was a single-centre study with a small number of patients. Larger multicentre studies are needed to confirm the association between postoperative cerebral desaturation and POD after cardiac surgery. Second, this was an observational study; no causal link between POD and cerebral desaturations can be inferred. Third, FORE-SIGHT technology, known for its absolute rather than relative accuracy, was used to measure $S_{ct}O_2$. Unfortunately, each manufacturer's device responds differently to haemodynamic fluctuations.[32,33] Hence, study results obtained with one NIRS device might not be applicable when another NIRS device is being used, which might partially explain why the results from published studies are conflicting. Fourth, not all eligible patients were included, as there were few available NIRS devices. This could have introduced an unintended selection bias (Fig 1). Fifth, the CAM-ICU reportedly has lower sensitivity than the CAM for the detection of delirium in non-intubated patients.[34,35] Sixth, the generalisability of the study might be reduced, given certain aspects of clinical care, including induction with diazepam and a median length of ICU stay of 46–74 h. Seventh, the NIRS only provides information on the frontal cortex and does not reflect the adequacy of cerebral perfusion in other parts of the brain. Compared with the NIRS alone, transcranial Doppler combined with brain imaging before, during, and after delirium episodes might yield more insights into the underlying pathophysiology of delirium.[6,8,9,36]

Conclusion

This study found that postoperative delirium in older patients after cardiac surgery is associated with decreased cerebral saturation, most likely occurring during and after the episodes of postoperative delirium.

Authors' contributions

Study conception: PV, CDD, FJ.
Study design: MB, TF, HG, MVL, WB, RH, DM, PV, CDD, FJ.
Study execution: WE, PV, CDD, FJ.
Data management: WE, CG, BM, SB.
Data analysis: WE.
Data interpretation: WE, PV, CDD, FJ.
Result interpretation: WE, DM, PV, CDD, FJ.
Writing manuscript: WE.
Editing manuscript: WE, MB, TF, HG, MVL, WB, RH, DM, PV, CDD, FJ.
Critically revising manuscript: WE, CG, BM, SB, MB, TF, HG, MVL, WB, RH, DM, PV, CDD, FJ.
All the authors read and approved the final manuscript.

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Declaration of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2019.09.042.

References

1. Djaiani G, Silverton N, Fedorko L, et al. Dexmedetomidine versus propofol sedation reduces delirium after cardiac surgery: a randomized controlled trial. *Anesthesiology* 2016; **124**: 362–8
2. Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med* 2001; **27**: 1892–900
3. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013; **369**: 1306–16
4. Inouye SK, Marcantonio ER, Kosar CM, et al. The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients. *Alzheimers Dement* 2016; **12**: 766–75
5. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004; **291**: 1753–62
6. Yokota H, Ogawa S, Kurokawa A, Yamamoto Y. Regional cerebral blood flow in delirium patients. *Psychiatry Clin Neurosci* 2003; **57**: 337–9
7. Siepe M, Pfeiffer T, Gieringer A, et al. Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium. *Eur J Cardiothorac Surg* 2011; **40**: 200–7
8. Fong TG, Bogardus Jr ST, Daftary A, et al. Cerebral perfusion changes in older delirious patients using 99mTc HMPAO SPECT. *J Gerontol A Biol Sci Med Sci* 2006; **61**: 1294–9
9. Caplan GA, Lan Z, Newton L, Kvelde T, McVeigh C, Hill MA. Transcranial Doppler to measure cerebral blood flow in delirium superimposed on dementia. A cohort study. *J Am Med Dir Assoc* 2014; **15**: 355–60
10. Ikeda K, MacLeod DB, Grocott HP, Moretti EW, Ames W, Vacchiano C. The accuracy of a near-infrared spectroscopy cerebral oximetry device and its potential value for estimating jugular venous oxygen saturation. *Anesth Analg* 2014; **119**: 1381–92
11. Goldman S, Sutter F, Ferdinand F, Trace C. Optimizing intraoperative cerebral oxygen delivery using noninvasive

cerebral oximetry decreases the incidence of stroke for cardiac surgical patients. *Heart Surg Forum* 2004; **7**: E376–81
12. de Tournay-Jette E, Dupuis G, Bherer L, Deschamps A, Cartier R, Denault A. The relationship between cerebral oxygen saturation changes and postoperative cognitive dysfunction in elderly patients after coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth* 2011; **25**: 95–104
13. Slater JP, Guarino T, Stack J, et al. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. *Ann Thorac Surg* 2009; **87**: 36–44
14. Yao FS, Tseng CC, Ho CY, Levin SK, Illner P. Cerebral oxygen desaturation is associated with early postoperative neuropsychological dysfunction in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 2004; **18**: 552–8
15. Schoen J, Meyerrose J, Paarmann H, et al. Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial. *Crit Care* 2011; **15**: R218
16. Lei L, Katznelson R, Fedorko L, et al. Cerebral oximetry and postoperative delirium after cardiac surgery: a randomised, controlled trial. *Anaesthesia* 2017; **72**: 1456–66
17. Rogers CA, Stoica S, Ellis L, et al. Randomized trial of near-infrared spectroscopy for personalized optimization of cerebral tissue oxygenation during cardiac surgery. *Br J Anaesth* 2017; **119**: 384–93
18. Greenberg SB, Murphy G, Alexander J, Fasanella R, Garcia A, Vender J. Cerebral desaturation events in the intensive care unit following cardiac surgery. *J Crit Care* 2013; **28**: 270–6
19. Cerebral Oxygenation and Neurological Outcomes Following Critical Illness (CONFOCAL) Research Group, Canadian Critical Care Trials Group, Wood MD, *et al*. Low brain tissue oxygenation contributes to the development of delirium in critically ill patients: a prospective observational study. *J Crit Care* 2017; **41**: 289–95
20. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001; **286**: 2703–10
21. Peterson JF, Pun BT, Dittus RS, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc* 2006; **54**: 479–84
22. Pandharipande P, Cotton BA, Shintani A, et al. Motoric subtypes of delirium in mechanically ventilated surgical and trauma intensive care unit patients. *Intensive Care Med* 2007; **33**: 1726–31
23. Murkin JM, Adams SJ, Novick RJ, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. *Anesth Analg* 2007; **104**: 51–8
24. Palmbergen WA, van Sonderen A, Keyhan-Falsafi AM, Keunen RW, Wolterbeek R. Improved perioperative neurological monitoring of coronary artery bypass graft patients reduces the incidence of postoperative delirium: the Haga Brain Care Strategy. *Interact Cardiovasc Thorac Surg* 2012; **15**: 671–7
25. Fischer GW, Lin HM, Krol M, et al. Noninvasive cerebral oxygenation may predict outcome in patients undergoing aortic arch surgery. *J Thorac Cardiovasc Surg* 2011; **141**: 815–21
26. Tang L, Kazan R, Taddei R, Zaouter C, Cyr S, Hemmerling TM. Reduced cerebral oxygen saturation during thoracic surgery predicts early postoperative cognitive dysfunction. *Br J Anaesth* 2012; **108**: 623–9
27. Kok WF, van Harten AE, Koene BM, et al. A pilot study of cerebral tissue oxygenation and postoperative cognitive dysfunction among patients undergoing coronary artery bypass grafting randomised to surgery with or without cardiopulmonary bypass. *Anaesthesia* 2014; **69**: 613–22
28. Morimoto Y, Yoshimura M, Utada K, Setoyama K, Matsumoto M, Sakabe T. Prediction of postoperative delirium after abdominal surgery in the elderly. *J Anesth* 2009; **23**: 51–6
29. Heringlake M, Garbers C, Kabler JH, et al. Preoperative cerebral oxygen saturation and clinical outcomes in cardiac surgery. *Anesthesiology* 2011; **114**: 58–69
30. Gosselt AN, Slooter AJ, Boere PR, Zaal IJ. Risk factors for delirium after on-pump cardiac surgery: a systematic review. *Crit Care* 2015; **19**: 346
31. Rudolph JL, Jones RN, Levkoff SE, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation* 2009; **119**: 229–36
32. Tomlin KL, Neitenbach AM, Borg U. Detection of critical cerebral desaturation thresholds by three regional oximeters during hypoxia: a pilot study in healthy volunteers. *BMC Anesthesiol* 2017; **17**: 6
33. Moerman A, Vandenplas G, Bove T, Wouters PF, De Hert SG. Relation between mixed venous oxygen saturation and cerebral oxygen saturation measured by absolute and relative near-infrared spectroscopy during off-pump coronary artery bypass grafting. *Br J Anaesth* 2013; **110**: 258–65
34. McNicoll L, Pisani MA, Ely EW, Gifford D, Inouye SK. Detection of delirium in the intensive care unit: comparison of confusion assessment method for the intensive care unit with confusion assessment method ratings. *J Am Geriatr Soc* 2005; **53**: 495–500
35. Shi Q, Warren L, Saposnik G, Macdermid JC. Confusion assessment method: a systematic review and meta-analysis of diagnostic accuracy. *Neuropsychiatr Dis Treat* 2013; **9**: 1359–70
36. Omiya H, Yoshitani K, Yamada N, et al. Preoperative brain magnetic resonance imaging and postoperative delirium after off-pump coronary artery bypass grafting: a prospective cohort study. *Can J Anaesth* 2015; **62**: 595–602

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