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SCIENTIFIC ARTICLE

Effects of cerebral oxygen changes during coronary bypass surgery on postoperative cognitive dysfunction in elderly patients: a pilot study[☆]



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Postoperative cognitive dysfunction;
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Abstract

Background and objectives: Postoperative cognitive dysfunction is common after cardiac surgery. Adequate cerebral perfusion is essential and near infrared spectroscopy (NIRS) can measure cerebral oxygenation. Aim of this study is to compare incidence of early and late postoperative cognitive dysfunction in elderly patients treated with conventional or near infrared spectroscopy monitoring.

Methods: Patients undergoing coronary surgery above 60 years, were included and randomized to 2 groups; control and NIRS groups. Perioperative management was NIRS guided in GN; and with conventional approach in control group. Test battery was performed before surgery, at first week and 3rd month postoperatively. The battery comprised clock drawing, memory, word list generation, digit span and visuospatial skills subtests. Postoperative cognitive dysfunction was defined as drop of 1 SD (standard deviation) from baseline on two or more tests. Mann-Whitney *U* test was used for comparison of quantitative measurements; Chi-square exact test to compare quantitative data.

Results: Twenty-one patients in control group and 19 in NIRS group completed study. Demographic and operative data were similar. At first week postoperative cognitive dysfunction were present in 9 (45%) and 7 (41%) of patients in control group and NIRS group respectively. At third month 10 patients (50%) were assessed as postoperative cognitive dysfunction; incidence was 4 (24%) in NIRS group ($p:0.055$). Early and late postoperative cognitive dysfunction group had significantly longer ICU stay ($1.74+0.56$ vs. $2.94+0.95$; $p<0.001$; $1.91+0.7$ vs. $2.79+1.05$; $p<0.01$) and longer hospital stay ($9.19+2.8$ vs. $11.88+1.7$; $p<0.01$; $9.48+2.6$ vs. $11.36+2.4$; $p<0.05$).

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Conclusion: In this pilot study conventional monitoring and near infrared spectroscopy resulted in similar rates of early postoperative cognitive dysfunction. Late cognitive dysfunction tended to ameliorate with near infrared spectroscopy. Early and late cognitive declines were associated with prolonged ICU and hospital stays.

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PALAVRAS-CHAVE

Disfunção cognitiva no pós-operatório;
Oximetria cerebral;
Cirurgia cardíaca;
Paciente idoso

Efeitos das alterações no oxigênio cerebral durante cirurgia de revascularização do miocárdio sobre a disfunção cognitiva no pós-operatório em pacientes idosos: estudo piloto

Resumo

Justificativa e objetivos: A disfunção cognitiva no pós-operatório é comum após cirurgia cardíaca. A perfusão cerebral adequada é essencial, e a espectroscopia no infravermelho próximo (NIRS) pode medir a oxigenação cerebral. O objetivo deste estudo foi comparar a incidência de disfunção cognitiva no pós-operatório, precoce e tardio, em pacientes idosos tratados com monitorização convencional ou espectroscopia no infravermelho próximo.

Métodos: Os pacientes submetidos à cirurgia coronariana, acima de 60 anos de idade, foram incluídos e randomicamente alocados em dois grupos: Grupo controle e Grupo NIRS. O manejo dos pacientes no período peroperatório foi realizado com NIRS no grupo NH e com abordagem convencional no grupo controle. A bateria de testes foi feita antes da cirurgia, na primeira semana e no terceiro mês de pós-operatório. A bateria incluiu o desenho do relógio, a memória, a geração de uma lista de palavras, a sequência de dígitos e subtestes que exigem habilidades visuoespaciais. Disfunção cognitiva no pós-operatório foi definida como queda de um DP (desvio-padrão) da fase basal em dois ou mais testes. O teste *U* de Mann Whitney foi usado para comparação de medidas quantitativa e o teste exato do qui-quadrado para comparar dados quantitativos.

Resultados: Vinte e um pacientes do grupo controle e 19 do grupo NIRS concluíram o estudo. Os dados demográficos e operacionais foram semelhantes. Na primeira semana, nove pacientes (45%) do GC e sete pacientes (41%) do grupo NIRS apresentaram disfunção cognitiva no pós-operatório. No terceiro mês, 10 pacientes (50%) foram avaliados como disfunção cognitiva no pós-operatório; a incidência foi de quatro (24%) no grupo NIRS ($p = 0,055$). O grupo que apresentou disfunção cognitiva no pós-operatório precoce e tardio teve uma permanência significativamente maior na UTI (1,74 + 0,56 vs. 2,94 + 0,95; $p < 0,001$; 1,91 + 0,7 vs. 2,79 + 1,05; $p < 0,01$) e permanência hospitalar mais longa (9,19 + 2,8 vs. 11,88 + 1,7; $p < 0,01$; 9,48 + 2,6 vs. 11,36 + 2,4; $p < 0,05$).

Conclusão: Neste estudo piloto, a monitorização convencional e espectroscopia no infravermelho próximo resultaram em taxas semelhantes de disfunção cognitiva no pós-operatório precoce. A disfunção cognitiva tardia tende a melhorar com espectroscopia no infravermelho próximo. Os declínios cognitivos precoces e tardios foram associados a internações prolongadas tanto em UTI quanto hospitalares.

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Introduction

Postoperative cognitive dysfunction (POCD) is a well-known phenomenon defined as decline in multiple intellectual domains such as language comprehension, memory, mathematical function or vigilance. Diagnosis is based on neuropsychometric tests. Incidence appears in a wide range from 30% to 80% in early postoperative period.¹⁻⁴ Recognized risk factors related to patients are advanced age, preoperative cognitive impairment or previous stroke, lower

educational level, alcohol abuse, genetic predisposition (with some alleles) and severe atherosclerosis.^{5,6} Older people suffer frequently from cardiovascular diseases, diabetes or organ dysfunctions, and are more disposed to complications. Then again older brain is more susceptible as size, distribution and type of neurotransmitters, metabolic function, and capacity for plasticity are all impaired. It is associated with impaired regulatory mechanisms and also, reduced ability to cope with operative stresses. Persistent cognitive decline is associated with loss of independence,

reduced life quality and even mortality.⁵ Thus, measures to decrease incidence of POCD should be encouraged.

Besides age, surgical risk factors have been discussed in previous reports; cardiac and some orthopedic procedures are mainly found to be related with POCD. Microembolism, perfusion problems and inflammatory response probably contribute in the pathogenesis of cognitive decline among cardiac surgical patients.^{7,8} All conditions lead to cerebral tissue hypoxia. Maintenance of "adequate" blood pressures, various degree of hyperoxia or off-pump cardiac surgery were all used to optimize cerebral oxygenation and to improve cognitive outcome with conflicting results.⁹⁻¹³

Regional cerebral oxygen saturation may be measured noninvasively by near infrared spectroscopy (NIRS) in perioperative period. In the management of CPB, NIRS is frequently used with a clinical algorithm.¹⁴ Studies have shown an association of low cerebral local oxygen saturation with neurological complications and cognitive impairment with the use of NIRS.^{10,11} Similarly shortened duration of hospitalization and decreased damage in vital organs were also demonstrated with intraoperative use of NIRS.¹⁵

The aim of this pilot study is to compare the incidence of early and late POCD in elderly undergoing elective coronary surgery, managed according to conventional or NIRS monitoring during intraoperative period.

Methods

After approval of institutional Ethical Committee (n° 2013/15), patients undergoing elective coronary surgery, above 60 years with preserved left ventricle function who gave their consent were included in the study. Other inclusion criteria were fluency in Turkish and graduation at least from primary school. Exclusion criteria were hearing or language disabilities, symptomatic carotid stenosis, alcohol abuse, psychiatric disorders, central nervous degenerative disease, severe hepatic or renal dysfunction, combined intracardiac procedures. Prior to the enrolment subjects were assessed with Mini-Mental State Examination (MMSE) and patients with a score below 23 were excluded.

Anesthesia induction was achieved with 10–15 $\mu\text{g}\cdot\text{kg}^{-1}$ fentanyl, 0.1–0.2 $\text{mg}\cdot\text{kg}^{-1}$ midazolam, and 0.6 $\text{mg}\cdot\text{kg}^{-1}$ rocuronium. Sevoflurane based inhalational anesthesia and remifentanyl infusion with supplemental rocuronium doses were used for maintenance including the cardiopulmonary bypass period. Pressure-controlled mechanical ventilation with $\text{FiO}_2:0.5$, inspiratory pressure level to obtain a tidal volume of $8\text{ mL}\cdot\text{kg}^{-1}$, respiration frequency to obtain an ETCO_2 of 35–40 mmHg, and 5 cm H_2O PEEP were adjusted. During the cardiopulmonary bypass, the lungs were passively deflated.

All patients were operated on by the same surgical team at 32 °C and a mild level of hemodilution (Hct: 26–28%). Pump flow rates were adjusted to $2.5\text{ L}\cdot\text{min}^{-1}$ per m^2 for the normothermic phase and $2.25\text{--}2.5\text{ L}\cdot\text{min}^{-1}$ per m^2 for the hypothermic phase during which the target systemic arterial pressure was 70 mmHg. Intermittent antegrade blood cardioplegia was applied in a $20\text{ mL}\cdot\text{kg}^{-1}$ induction dose and $10\text{ mL}\cdot\text{kg}^{-1}$ in every 30 min as maintenance. At the end of the intervention, patients were transferred to the intensive care unit under propofol and midazolam sedation and

controlled ventilation. The weaning process from sedation, mechanical ventilation, and inotropic support was managed by the intensive care team according to their routine clinical procedure. Finally the need for postoperative inotropic support and mechanical ventilation time were recorded for every patient.

Randomization and NIRS follow-up

Prior to anesthesia induction patients were randomized with sealed envelope system to conventional (GC) or near-infrared spectroscopy group (GN). In the conventional monitoring group, the global perfusion goals including pump flow rates during extracorporeal circulation were determined and achieved by mean arterial pressure, hemoglobin level and oxygen values (arterial and venous). In GN regional cerebral oxygen saturation was added to standard monitoring and prior to induction to anesthesia oximeter sensors (Invos 5100C, Cerebral/Somatic oximeter; Medtronic®) were placed bilaterally on the forehead to obtain baseline cerebral oxygen saturation (rSO_2) values. During surgery a drop of more than 20% from baseline value or rSO_2 lesser than 50% are determined as an indication of intervention. The algorithm to correct intraoperative cerebral desaturation proposed by Denault was used to define interventions.¹⁴ According to this algorithm, the first step was to rule out any mechanical obstruction which can impede pump flow, than to increase mean arterial pressure and to verify systemic oxygenation. The latter steps were to normalize PaCO_2 , to optimize hemoglobin level, to evaluate cardiac function and finally to decrease cerebral metabolic rate of oxygen.

Neuropsychological assessment

Cognitive function was assessed by an investigator blinded to study allocation. An initial MMSE was performed, and patient eligibility was determined according to the score obtained on this first assessment. The MMSE is a quantitative and practical testing used to detect a patient's cognitive status such as orientation, memory, attention, language, and visuo-spatial functioning as well as orientation with 30 points at best. If patients scored more than 23 on the MMSE, they were considered eligible for the study and were assessed with a comprehensive neuropsychological test battery. Wechsler Memory Scale (WMS) – Logical Memory subtest detects short and long-term memory from a story (two different stories pre- and postoperatively); patients were asked to repeat or to answer about it, with a maximum score of 10. Clock Drawing Test investigates planning, and visual comprehension; its best score is 10. Word List Generation Test assesses sustained attention also called perseverance with a maximum score of 20; patients had to say animal or fruit names with the same initial. Digit Span subtest detects global attention with concentration, and consists of repeating numbers forward or backward after investigator; with 10 points at best. Visuo-Spatial Skills Test evaluates perceptual functions; patients were asked to make a ring, scissors, etc. with their hands.

Except for the MMSE, all patients were examined 2–3 days before surgery (baseline), postoperatively at the first week (early), and at 3rd month (late). All evaluation was conducted by the same anesthesiologist (CS) who was blinded

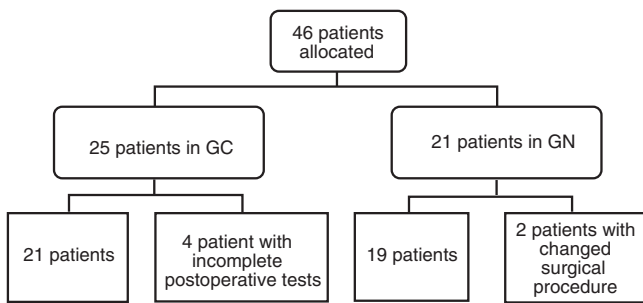


Figure 1 Flowchart.

to perioperative monitoring, and who was trained and supervised by the faculty's Neurology Clinic's consultants during the entire study period. The neuropsychological test battery lasted approximately 45 min. All tests were administered in same time of day and same location, a private room at surgical service. Each subject was evaluated three times during study: preoperatively, at first week and at 3rd month postoperatively.

Postoperative cognitive dysfunction (early or late) was defined as a drop of 1 standard deviation from baseline on two or more neuropsychological tests as described by Höcker et al. in their recent study.¹⁶ Because of the lack of a non-surgical control group, the cognitive function evaluation was performed only as a between-group comparison. The standard deviation (SD) of each preoperative test was calculated, and the number of patients who deteriorated or improved postoperatively was determined.¹⁶

Statistical analysis

The results of the study, SPSS 19.0 for WINDOWS software were used for statistical analysis. In assessing the study data, statistical methods (median, range, mean, standard deviation) and Mann-Whitney *U* test was used for intergroup comparison of quantitative measurements. Chi-square test and Fischer's exact test, where necessary, was used in a four-fold design to compare quantitative data. Friedmann test was used for intragroup changes in time. Results were evaluated by applying 95% Confidence Interval and $p < 0.05$ significance level.

Results

Forty-six patients meeting the criteria were included in this study. In GC 4 patients whose postoperative tests could not be completed, were excluded from data analysis. Moreover one patient who experienced a late cerebrovascular event (at 2 months postoperatively), was not excluded in terms of "intention-to-treat" principle. Two patients were excluded from GN due to change in surgical plan (additional intracardiac procedure). Another 2 patients in GN required reoperation due postoperative bleeding; they were enrolled in the study, similarly in terms of "intention-to-treat" principle. Thus, the study was completed with 21 patients in GI and 19 patients in the GII (Fig. 1).

Demographic and operative data were comparable between groups (Table 1).

Table 1 Patient characteristics and operative data.

	GC (n = 21)	GN (n = 19)	<i>p</i>
Age (years)	66.8 ± 6.3	64.8 ± 5.7	0.37
Sex (M/F)	19/2	15/4	0.40
Level of education (>8 years/<8 years)	7/14	6/13	1.00
Euroscore (>3/<3)	14/7	14/5	0.73
Preoperative creatinine (mg.dL ⁻¹)	1.08 ± 1.08	1.01 ± 0.65	0.81
COPD	3 (14%)	4 (21%)	0.68
Diabetes	12 (57%)	9 (47%)	1.00
Operation time (min)	303 ± 52.5	284.5 ± 57	0.29
CPB time (min)	112 ± 16.6	106 ± 9.7	0.18
CC time (min)	58.7 ± 10.5	55.8 ± 6.9	0.31
Number of side clamps	2.8 ± 0.8	3.01 ± 0.65	0.37
Minimum temperature (°C)	28.9 ± 0.91	29.1 ± 0.79	0.47

Data expressed in mean with SD or number of patients with ratio. M, male; F, female; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CC, cross clamp.

In the NIRS group 6 patients experienced desaturation requiring intervention. In 3 of them significant cerebral saturation desaturation (a drop more than 50% compared to baseline and lasting for 15–10 min), the resting had a moderate desaturation (less than 40% and lasting for 5–8 min). Restoration of blood pressure improved cerebral oximetry in the moderate group. In the severe desaturation group, normal values were obtained in a few minutes subsequent erythrocyte transfusion according to algorithm.

Neuropsychological test results were presented in Table 2.

Early POCD was detected in 10 of 21 subjects (45%) of control group while the incidence was 7 of 19 (37%) in GN ($p > 0.05$) (Table 3). In GN 4 of 7 patients among early POCD cases recovered at 3rd postoperative month; whereas all patients in control group showed persistent cognitive decline. In both groups, a new patient who was not detected as cognitively impaired in the early period was added to those with late cognitive dysfunction. Late POCD was detected among patients with severe desaturation.

ICU and hospital stays were both similar between GC and GN (ICU stay 2.4 ± 0.9 and 2.1 ± 1.2 days; hospital stay 11.1 ± 4.7 and 9.25 ± 4 respectively). However both early and late POCD were found to be associated with prolonged ICU and hospital stays (Table 4).

Discussion

In this pilot study, conventional monitoring compared to NIRS guided management resulted in similar rates of early POCD in coronary surgery. Late cognitive dysfunction tended to ameliorate in NIRS group but without statistical difference.

Table 2 Summary of neuropsychological tests.

Test	PREOP		At 1st week		At 3rd month	
	GC	GN	GC	GN	GC	GN
MMSE	28 ± 2.2	29 ± 1.5	28 ± 2.1	28 ± 1.8	28 ± 1.9	28.5 ± 1.6
Wechsler memory	6.7 ± 2.4	6.6 ± 2.8	6.1 ± 3	6.2 ± 2.9	6.9 ± 3.1	7 ± 4
Digit span	8 ± 2.8	9 ± 2.6	7 ± 2.9	8 ± 2.6	7 ± 2.8	8 ± 2.5
Word list generation	15 ± 2.6	16 ± 3	15 ± 3.2	15 ± 1.6	16 ± 3.3	17 ± 3.8
Clock drawing	3.2 ± 1.3	4.2 ± 1.2	3 ± 1.4	3.6 ± 1.3	4.1 ± 1.4	4.3 ± 1.3
Visuo-spatial skills	8.8 ± 1.8	8.9 ± 1.8	8.2 ± 1.6	8.4 ± 1.4	9 ± 1.9	10.1 ± 1.4 ^a

MMSE, mini-mental state exam.

^a $p < 0.05$ compared to preoperative values.

Both early and late cognitive declines were found to be associated with prolonged ICU and hospital stays.

Major neurological complications decreased over decades; cognitive decline remains a concern for caregivers as it can persist during months to years. Preventive measures to improve neurological outcome implies maintenance of pressures, assessment of adequate perfusion or management of metabolic state.^{9–12,17,18} Evaluation of cerebral perfusion with cerebral oximetry is easy with fast signal response time and allows early recognition of brain perfusion abnormalities.¹⁹ Relationship between neurological complications and cerebral oximetry has been investigated after cardiac surgery with inconsistent results.^{10,11,15,20} Denault et al. proposed an algorithm for intraoperative use of near-infrared spectroscopy regarding blood pressures, systemic saturation and arterial CO₂ pressure.¹⁴ In a large study referring Denault's algorithm, patients with POCD had significantly higher desaturation scores (considering both deep and duration of desaturation below the 50% threshold).¹⁰ However in the multivariate analysis, reduction of cognitive decline was not significantly different in the interventional group. Authors commented that lack of impact might be due to poor compliance to treatment protocol. Another investigation focused on early follow-up affirmed that cerebral desaturation below 50% was a predictor of POCD in 6 days.²⁰ Patients with desaturation had lower initial values as well as worse baseline test performance. They unsurprisingly showed increased incidence of early cognitive decline. More recently both early (at first week) and late (at first month) POCD in coronary surgery were found to be associated with cerebral desaturation.¹¹ Patients with rSO₂ values below 50% were approximately 8 times at increased risk. Investigators affirmed that a

Table 3 Comparison of POCD incidence in groups.

	GC (n=21)	GN (n=19)
At 1st week	10 (45%)	7 (37%)
At 3rd month	11 (50%)	4 (21%)

fall of more than 30% cerebral oximetry was a predictor of late POCD, but not of early POCD. In our study control and cerebral oximetry groups showed similar incidence of early POCD. We found a trend of recovery of POCD in late assessment (at 3rd month) for cerebral oximetry group; whereas cognitive decline persisted in control group. It is well known that cognitive deterioration is multifactorial. Surgically triggered inflammation, microembolism, inadequate pain control, metabolic problems (glycemic control, presence of metabolic syndrome) and hypoperfusion are mainly responsible in the beginning of phenomenon. In our study optimized cerebral saturation appeared to intervene in recovery period among patients with early cognitive impairment; but not in early period of cardiac surgery.

Definition of cerebral desaturation was not uniform in all trials as threshold values indicating cerebral ischemia have been derived from carotid surgery.²¹ Slater et al. described a rSO₂ score by the product of levels below rSO₂ with time. However Schoen accepted absolute values below 50%. Another approach that we adopted, defines a decrease more than 30% compared to baseline and an absolute value below 50% as well.¹¹

The incidence of POCD varies between 30–80% at discharge and falls 20–40% after 6 month.²² In oximetry-guided studies POCD was 60–75% at initial assessment and

Table 4 Comparison of ICU and hospital stays in patients with or without POCD.

	Early POCD		Late POCD	
	(–)	(+)	(–)	(+)
ICU stay	1.74 ± 0.56 ^c	2.94 ± 0.95	1.91 ± 0.7 ^b	2.79 ± 1.05
Hospital stay	9.19 ± 2.8 ^b	11.88 ± 1.7	9.48 ± 2.6 ^a	11.36 ± 2.4

(–), absent; (+), present.

^a $p < 0.05$.

^b $p < 0.01$.

^c $p = 0.001$.

decreased to 35% at 3rd month.^{10,11,13} Consistent with these reports incidence of early POCD was about 50%. At 3rd month there was no recovery in control group what is different from aforementioned studies. Moreover, we observed one new diagnosis of POCD in each group. Newman noticed new cognitive decline after coronary surgery which occurred in years compared to our study.²³ Selnes et al. pointed out the relation between severity of atherosclerosis and late cognitive impairment.²⁴

Most remarkable result of this study is the association of prolonged ICU and hospital discharge and cognitive decline at any time. Patients with early or late POCD had approximately 2 days longer hospital stay and the difference in ICU stay was about 1 day. In one hand cerebral desaturation was found to be associated longer hospital stay in both cardiac^{10,15,25} and noncardiac surgery.^{26,27} Fischer et al. suggested to accept brain as a sentinel organ and cerebral oximetry as an overall monitoring organ perfusion.²⁵ On the other hand patient with cognitive decline – with or without desaturation – require more care and have longer hospital stay.¹⁵ Thus cognitive decline – as a sign of global hypoperfusion or itself – is found to be associated with increased need for medical support. Moreover long term cognitive decline results in reduced activity in daily living, severe neurological prognosis even mortality.^{6,28} The problem seems to have medical, social and economic aspects.

Although POCD is a well-known phenomenon assessment is still problematic; there is no clear agreement for threshold or cut-off points.²⁹ Commonly each subject has to respond to questionnaires 2 or 3 times. Preoperative assessment constitutes basic performance and subsequent answers (at early and late postoperative course) are compared to the initial evaluation. Diagnosis is based on a decrease more than 1SD on neuropsychological tests. Learning effect (due to repeated tests), floor-ceiling (too easy or too difficult), reliability of preoperative assessment (due to anxiety or pain) and timing are known problematic issues of neuropsychological tests.²⁹ We used a test battery of Behavioral Sciences Unit of the Neurology Department. In our study, tests are predisposed to evaluate all intellectual domains such as memory, vigilance, mathematical thinking, and psychomotor abilities. Assessing investigator began performing the assessments after receiving training from psychologists with relevant qualifications. Patients were initially assessed 2 or 3 days prior to surgery with a preliminary Mini-Mental test to exclude subjects less than 22 points. Second evaluation was performed when patients were at ward in pain free status to avoid any sedative/opioid interaction. Not surprisingly some participants had higher scores in memory or language tests; but in a similar rate within study groups. Despite these inconvenient issues, neuropsychological tests remain the only valid tool to diagnose POCD.

Primary limitation of our pilot study is the relative small sample size. Second, the cerebral saturation monitoring was not applied “blindly” in the control group to permit more suitable intergroup comparison, due to financial issues. Thus, the control group patients were totally treated with conventional approach using perfusion pressures, hemoglobin values, etc. Third, we excluded patients with impaired left ventricle function and carotid stenosis who could benefit more from NIRS. Finally, we did

not follow cerebral oxygenation postoperatively which could be interesting as written in a recent multi-centric study.³⁰

In conclusion cognitive dysfunction is common after coronary surgery. Conventional and cerebral oximetry monitoring resulted similar rates of cognitive decline; however cerebral desaturation tended to be associated with persistent POCD.

Conflicts of interest

The authors declare no conflicts of interest.

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