Reduced cerebral oxygen saturation during thoracic surgery predicts early postoperative cognitive dysfunction

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Editor’s key points
- It is vital to understand the etiology of postoperative cognitive dysfunction (POCD).
- Authors correlated cerebral oxygenation during thoracic surgery with POCD in 76 patients.
- Twenty-nine per cent of the patients had decreased Mini-Mental State Exam score 3 h after surgery.
- Importantly, even 5 min of cerebral oxygenation reduced to <65% led to cognitive dysfunction with odds ratio of 2.03.

Background. The objective of this prospective study is to determine cognitive dysfunction after thoracic surgery.

Methods. Seventy-six patients undergoing thoracic surgery with single-lung ventilation (SLV) of an expected duration of >45 min were enrolled. Monitoring consisted of standard clinical parameters and absolute oximetry (SctO2). The Mini-Mental State Exam (MMSE) test was used to assess cognitive function before operation and at 3 and 24 h after operation. Data were analysed using Spearman correlation test; risks for cognitive dysfunction were expressed as odds ratios. P<0.05 and data are presented as median (interquartile range).

Results. One patient was excluded from the study. SctO2 during SLV decreased to critical values of <65%, 60%, and 55% in 40 (53%), 15 (20%), and 5 patients (7%), respectively. Twenty-two patients (29%) had a decrease of MMSE>2 points 3 h after surgery, eight patients (10%) had a decrease of MMSE>2 points 24 h after surgery. Postoperative cognitive dysfunction correlated at r²=0.272, 0.285, 0.297 with patient exposure times to SctO2<65% (P=0.018), <60% (P=0.013), <55% (P=0.010), respectively. The odds ratios of developing early cognitive dysfunction ranged from 2.03 (95% CI: 0.74–5.59) for a short (<5 min) exposure to SctO2<65% to a maximum of 9.56 (95% CI: 1.75–52.13) when SctO2 was <60% for more than 30 min.

Conclusions. Early cognitive dysfunction after thoracic surgery with SLV is positively related to intraoperative decline of SctO2.

Keywords: cerebral saturation; postoperative cognitive dysfunction; single-lung ventilation; thoracic surgery

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Monitoring cerebral oxygen saturation has become increasingly important in cardiac1–6 and non-cardiac surgery.7,8 Studies in cardiac surgery have shown that treating cerebral oxygen desaturations can improve postoperative cognitive function and reduce complications.5

There is a growing number of studies showing a significant incidence of cerebral oxygen desaturations in non-cardiac surgery, such as neurosurgery,9–11 carotid surgery,12–14 general surgery,8,15–16 and thoracic surgery.17–19 We have recently shown that the incidence of cerebral oxygen desaturations in patients undergoing thoracic surgery with single-lung ventilation (SLV) is similar to the incidence observed in cardiac surgery,17 and that these desaturations increase the risk of poor postoperative outcome.18,19

To the best of our knowledge, there is no study published which investigates cognitive function after thoracic surgery. The determination of cognitive function after thoracic surgery is impaired by possible difficulty to determine long-term cognitive dysfunction in a patient population with limited survival rates. In addition, the routine use of continuous high thoracic epidural analgesia for up to 5 days after surgery (our institution) limits more extensive and repetitive tests of cognitive function after thoracic surgery. Some studies15,20,21 have shown that evaluation of cognitive dysfunction only at 1 week after surgery—not immediately after surgery—might miss early cognitive dysfunction; therefore, tests seem necessary which can easily and reliably be performed at several time points within the first 24 h after surgery.

The Mini-Mental State Exam (MMSE)22 is an easy test to do, and can be performed under the specific perioperative conditions of thoracic surgery. The test has been shown to be a valid and reliable method of cognitive screening widely used in both clinical and research settings.22,23
It was the objective of this prospective study to determine the possible correlation between cerebral oxygen desaturations during SLV and postoperative cognitive dysfunction (POCD) in patients undergoing thoracic surgery.

**Methods**

We conducted a prospective, observational, single-blinded study. After approval from the Local Ethics Committee and written informed consent, 76 patients, aged 18 yr or greater, undergoing elective thoracic surgery with SLV of an expected duration of more than 45 min were enrolled. Patients who had previous cerebral disease, dementia, severe problems in hearing and understanding, or who were unable to provide informed consent were excluded.

Before general anaesthesia, an epidural catheter was inserted at T4,5 or T5,6 level for perioperative administration of bupivacaine 0.1% and fentanyl 3 μg ml⁻¹. After radial arterial line placement, anaesthesia was induced with propofol 0.5–1.5 mg kg⁻¹, fentanyl 4–7 μg kg⁻¹, and rocuronium 0.6 mg kg⁻¹. A left-sided double-lumen tube was inserted under bronchoscopic assistance. Anaesthesia was provided using sevoflurane to maintain a bispectral index of 45 (BIS, Aspect A-2000 monitoring system, Aspect Medical System, MA, USA).

Rocuronium boluses were given at the discretion of the anaesthesiologist. Analgesia was maintained using 6–10 ml h⁻¹ of bupivacaine 0.1%+fentanyl 3 μg ml⁻¹ commenced immediately after insertion of the epidural catheter. For surgery, the patient was placed in the left or the right lateral decubitus position. Intermittent positive pressure ventilation provided 100% oxygen to maintain an oxygen peripheral saturation of >90%; continuous positive airway pressure (CPAP) was applied for a limited time to the non-dependent lung when the peripheral saturation decreased below 90%.

Brain oxygen saturation was monitored continuously using the FORESIGHT cerebral oximeter (CAS Medical Systems, CT, USA) started before anaesthesia induction until extubation. After wiping the patient’s forehead with an alcohol pad, the sensors were positioned bilaterally on the patient’s forehead and covered in order to prevent ambient light to affect the measurements. Surgeons and anaesthesiologists were blinded to the measurement of cerebral oximetry (values were hidden), no anaesthetic decision was taken based on the absolute SctO₂ values. The average, left and right absolute SctO₂ values were collected every 5 min. Baseline absolute SctO₂ values were taken in the patient who is awake after 2 min of breathing 100% oxygen through a face mask. Standard monitoring variables such as peripheral oxygen saturation, BIS, mean arterial pressure (MAP), and heart rate were recorded every 5 min. In addition, arterial blood-gas analysis (pH, PCO₂, PO₂, Na⁺, K⁺, Ca²⁺, glucose, lactate, haematocrit, haemoglobin, SO₂) was performed every 15 min.

The average, left and right absolute SctO₂, the highest and lowest values were used for analysis. Baseline SctO₂ value was defined as the average saturation value during a period of 1 min, obtained 5 min after administration of the sensors. The absolute SctO₂ decrease was calculated by subtracting the minimum absolute SctO₂ value during SLV from the baseline absolute SctO₂ value regardless of right, left, or average for each patient; the relative SctO₂ decrease was defined as the absolute SctO₂ decrease divided by the baseline SctO₂ value.²⁻¹⁸ SctO₂ minutes and the area under the threshold (AUT) spent beneath the absolute threshold limits of 65%, 60%, and 55% were calculated for right, left, and average SctO₂ values. AUT was calculated based on this formula: AUT (present)=AUT (past)+(SctO₂ threshold−SctO₂ value)×sample rate. AUT is 0 if the SctO₂ value is above the defined SctO₂ threshold.²⁶

The MMSE tests neurocognitive functions, such as orientation, registration, attention, calculation, recall, and language.²² This test combines high validity and reliability with brevity and ease of application, and suggests decline in cognitive function with repeated tests. The maximal score of MMSE is 30 points, and MMSE score ≤23 is considered as abnormal. The MMSE was performed by a research assistant, not aware of intraoperative oximetry values, before surgery and then repeated twice, 3 and 24 h after surgery, respectively, to assess postoperative cognitive function. A decrease in MMSE score >2 points from baseline was defined as POCD.⁸⁻¹⁵⁻¹⁶

To calculate the sample size for this study, we hypothesized that the POCD is correlated with cerebral oxygen desaturations during surgery as defined by the exposure time spent beneath the absolute threshold limit of 65%. Thus, considering a coefficient correlation of 0.3 to be a fair correlation and consequently to be clinically relevant, we used an effect size of 0.3 for a one-sided type I error of 0.05, a statistical power of 80%, resulting in a sample size of 64 patients (Correlation Point Biserial Model, *G*Power, v. 3.1.2, University Kiel, Germany). We planned to recruit 76 patients under the assumption that some would be excluded for protocol violation.

Data were analysed using SPSS (v. 15.0, SPSS Inc., Chicago, IL, USA) and presented as median [interquartile range (IQR); range] for continuous data and number (proportion) for nominal data. Spearman correlation test was used to test the correlation between POCD (defined as decrease in MMSE score >2 points from baseline) and age, SLV duration, relative maximum SctO₂ decrease, exposure time under threshold limits of SctO₂ of 65%, 60%, and 55% and other selected clinical parameters. Effects of exposure time under threshold limits of 65%, 60%, and 55% on cognitive dysfunction were calculated using risk-analysis and were expressed in terms of odds ratios. A P-value <0.05 was considered as statistically significant.

**Results**

A total of 76 patients were enrolled between August 2008 and February 2010 in Montreal General Hospital, Montreal, Canada. One patient was excluded from the analysis.
because the patient was not willing to repeat the MMSE test after surgery. Data of 75 patients were taken into analysis. Characteristics of the patients, including age, sex, ASA grade, duration of surgery, duration of SLV, and type of surgery are listed in Table 1. No patient needed additional CPAP or oxygen insufflations. No surgical site infection, post-operative haemorrhage, or stump leakage were observed.

The patients had a baseline $S_{ctO_2}$ value [median (IQR; range)] of 79% (77, 84; 67, 96) in the awake state, which decreased to a minimum $S_{ctO_2}$ of 63% (59, 68; 33, 76) during SLV. This is equivalent to a decrease of $S_{ctO_2}$ by 21% (17, 27; 5, 54). Fifty-seven per cent of the patients had a relative maximum decrease of more than 20% in comparison with the baseline $S_{ctO_2}$ values (Fig. 1). The patients recovered to $S_{ctO_2}$ values of 69 (65, 73; 53, 86) within 5 min after the end of SLV. There was no significant difference between the $S_{ctO_2}$ of the site of surgery and the opposite site.

The minimal absolute $S_{ctO_2}$ values attained by patients during SLV are presented in Figure 2. The median exposure times to $S_{ctO_2}$ values of <65%, 60%, and 55% were 45, 45, and 15 min, respectively, which accounts for 30%, 25%, and 6% of the time of surgery, respectively. The integrals of $S_{ctO_2}$ under the specific threshold (AUT) of 65%, 60%, and 55% are presented in Table 2.

The patients had a baseline MMSE value of 28 points (27, 29; 20, 30), which decreased to 26 points (25, 29; 13, 30) 3 h after surgery, then returned to 28 points (27, 30; 20, 30) 24 h after surgery. When tested at 3 h after surgery, a total of 22 patients (29%) had a decrease of MMSE $\geq$ 2 points. Out of these 22 patients, 10 patients (13%) showed a decrease of MMSE $\geq$ 3 points, and 6 patients (8%) a decrease of MMSE $\geq$ 4 points, respectively. When tested at 24 h after surgery, only eight patients (10%) still had a decrease of MMSE $\geq$ 2 points. Out of all the selected clinical parameters (age, duration of SLV less than surgery, relative decrease of haemoglobin, haematocrit, peripheral oxygen saturation, partial oxygen, carbon dioxide pressure in arterial blood, or MAP), only the exposure time spent below the $S_{ctO_2}$ thresholds of <65%, 60%, and 55% were found to be significantly correlated with POCD at $r^2 = 0.272$ ($P = 0.018$), $r^2 = 0.285$ ($P = 0.013$), and $r^2 = 0.297$ ($P = 0.01$), respectively.

Table 4 demonstrates the odds ratios with 95% confidence intervals for POCD (decrease of MMSE $\geq$ 2 points) related to

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**Table 1** Patient data. Data are given as median (IQR; range) or values. SLV, single-lung ventilation; MMSE, Mini-Mental State Exam

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64 (58, 76; 32, 86)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>35/40</td>
</tr>
<tr>
<td>ASA grade (I/II/III)</td>
<td>1/38/36</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>175 (145, 210; 40, 435)</td>
</tr>
<tr>
<td>Duration of SLV (min)</td>
<td>135 (100, 170; 15, 405)</td>
</tr>
<tr>
<td>Baseline $S_{ctO_2}$ values (%)</td>
<td>79 (77, 84; 67, 96)</td>
</tr>
<tr>
<td>Baseline MMSE scores</td>
<td>28 (27, 29; 20, 30)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>Lobectomy: 45 Wedge resection: 18 Pneumonectomy: 10 Segmentectomy: 2</td>
</tr>
</tbody>
</table>

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**Fig 1** Number of patients with relative $S_{ctO_2}$ decreases of <15%, 15–20%, 21–25%, and >25% from baseline values.

**Fig 2** Minimal absolute $S_{ctO_2}$ values reached by patients (n=75) during SLV, with cutoff values of 55, 60, and 65.
the incremental exposure time of $S_{ctO2}$ values under thresholds of $<65\%$, $60\%$, and $55\%$.

MAP values throughout surgery for patients with or without significant cerebral oxygen desaturations were similar and are shown in Figure 3.

Discussion

This study confirms previous findings of our group that a significant number of patients experience cerebral oxygen desaturations during SLV in thoracic surgery; one-third of the patients showed relative decreases of more than 25\% from the baseline values. Half of the study patients had decreases of absolute $S_{ctO2}$ values $<65\%$, a threshold identified as indicative for an increased risk of postoperative complications.24 Almost one-third of our patients showed a significant impairment of early (<3 h after surgery) postoperative cognitive function with 90\% of them returning to normal cognitive function at 24 h after surgery. Even short periods of absolute $S_{ctO2}$ values of $<65\%$ during SLV double the risk of POCD.

This study investigated patients undergoing thoracic surgery with SLV; in an initial small size study of 20 patients, we found that 35\% of the patients showed a significant relative decrease of more than 25\% of cerebral oxygen saturation from the respective baseline values. In another study,18 in 50 patients undergoing thoracic surgery with SLV, the significant incidence of cerebral oxygen desaturations was confirmed with more than half of the patients showing minimum $S_{ctO2}$ values of $<65\%$. In a cohort study by Tobias and colleagues,19 in 40 patients undergoing thoracic surgery with SLV, 21\% of the patients showed absolute changes of cerebral oxygen saturation of at least 20\% less than the baseline values. Changes in cerebral oxygen saturation were presented in these former three studies in different ways, either as relative, or absolute changes from baseline. There is some inconsistency when it comes to the threshold of clinically relevant changes; this might be owing to different monitoring methods (relative or absolute oximetry), different types of surgery, and different ways to calculate these changes from baseline values. A consensus
might be derived from two studies, one study used relative oximetry\textsuperscript{25} and the other used absolute oximetry.\textsuperscript{24} Samra and colleagues\textsuperscript{25} determined the threshold of cerebral oxygen desaturations for the occurrence of neurological symptoms in patients undergoing carotid surgery in the awake state. This study found that a threshold of more than 20% of relative decrease from baseline was related to an increased incidence of neurological symptoms during carotid surgery. A more recent study by Fischer and colleagues\textsuperscript{24} using absolute oximetry has shown that absolute S\textsubscript{cto2} values of 65% are related to an increased risk of postoperative complications in patients undergoing aortic arch replacement surgery.

As we used absolute oximetry to monitor cerebral oxygen saturation, we used Fischer’s\textsuperscript{24} thresholds to calculate the risk of developing POCD. We found that the risk was related to both the degree of desaturation and the duration during which these desaturations occurred. The risk of developing POCD ranged from two-fold even with a short (<5 min) exposure to S\textsubscript{cto2} concentrations of <65% to a 10-fold risk when desaturations of <60% occurred for more than 30 min. There is no other study which investigated the incidence of cognitive dysfunction after thoracic surgery, so our findings cannot be compared with other studies. However, there are studies determining the incidence and risk for cognitive dysfunction after non-cardiac surgery.

Few studies have looked at POCD after general anaesthesia in non-cardiac surgery. In one study, Casati and colleagues\textsuperscript{15} studied cognitive dysfunction after abdominal surgery in elderly patients. Using the MMSE, he determined that 35% of 56 patients showed a significant decrease in cognitive function when tested 1 week after surgery. This dysfunction was significantly correlated with cerebral oxygen desaturation during surgery at $r^2=0.26$. The cerebral oxygen desaturations in that study were correlated significantly to an increased stay in the hospital highlighting the economic impact of intraoperative cerebral oxygen desaturations. It is interesting to note that the present study showed a similar positive correlation between intraoperative cerebral oxygen decline and POCD: the correlation coefficient ranged from $r^2=0.27$ to $r^2=0.3$ depending on the exposure time to increased degrees of desaturation. In another study involving 60 patients undergoing abdominal surgery, Casati and colleagues\textsuperscript{16} confirmed the appearance of cognitive dysfunction—as determined using the MMSE—1 week after surgery only in patients with intraoperative cerebral oxygen decrease. Patients, who did not experience any desaturation during surgery, had a normal cognitive function 1 week after surgery. The desaturations were not correlated with the rate of complications, probably because of the small number of patients (a total of only 9 out of 60 patients showed complications after surgery). In one of our earlier studies in thoracic surgery,\textsuperscript{18} we could show an increased risk of having postoperative complications—as determined using a modified SOFA and Clavien score—when cerebral oxygen decline occurred during SLV.

This highlights the importance of timing of cognitive dysfunction tests after non-cardiac surgery. In contrast to cardiac surgery, where patients usually stay intubated for a significant time and cognitive function tests can hardly be performed before 24 h after surgery, the rapid recovery of cognitive function after non-cardiac surgery allows the
detection of early cognitive dysfunction. Chen and colleagues confirmed the importance of early cognitive function testing; they determined cognitive dysfunction after hip or knee arthroplasty in 70 patients without monitoring cerebral oximetry. When tested using MMSE 1 h after surgery, 51% of the patients showed a significant cognitive dysfunction, which disappeared in 85% of the patients at 3 h after surgery. When tested at 24 h after surgery, only one of 70 patients showed a cognitive dysfunction. These results agree with our findings with almost 90% of our patients showing normal cognitive function 24 h after surgery. In the present study, we also decided to determine early cognitive dysfunction and repeat MMSE tests at 24 h after surgery. Because of the specific nature of thoracic surgery—installation of patients in the PACU usually takes longer than in patients undergoing abdominal surgery, pain control might need some adjustments in the early periods of stay at the PACU—we designed the study for early testing of MMSE at 3 h after surgery. At that time, pain control was sufficient in all patients during MMSE testing, thus avoiding any pain-related bias. In order to exclude any bias from administration of systemic opioids, no patient received any opioids other than in the epidural infusion. However, there is a need for more studies indicating the impact of early cognitive dysfunction on general recovery from surgery, such as length of stay in the PACU or in the hospital.

One of the limitations of our study is that only one cognitive function test—MMSE—was used; this was based on the specifics of thoracic surgery, for example, an efficient epidural analgesia limits mobility of patients. Certain tests for cognitive function, such as the 6-min walk test or finger tapping test, can thus not be used in the immediate postoperative period. In order to maintain patients’ cooperation for the cognitive function test in the early postoperative period after such a major surgery, it was decided to have them undergo only one test. Although we are aware that this test does not completely test mental function, studies in non-surgical subjects have shown that it reliably indicates the occurrence of cognitive dysfunction.

At present, there is no study that has investigated the relationship between very early (<24 h after surgery) cognitive dysfunction with long-term cognitive function (more than 3 months), which will be the focus of future work and also to determine the clinical relevance of a two-point decline in MMSE after surgery.

Another limitation of this study is the fact that we did not assess the impact of the cognitive dysfunction on the duration of stay in either the hospital or in the PACU. Studies of such nature are very difficult to perform in our hospital setting—as in most hospital settings—because discharge from either PACU or hospital is influenced by various non-medical issues, such as bed shortage on the normal ward, nursing staff preferences, and other organizational issues. However, it needs to be pointed out that Casati and colleagues have shown that intraoperative cerebral oxygen desaturations are significantly correlated with the length of hospital stay. As PACU nurses regularly assess the cognitive status in our hospital setting, it can be assumed that reduced cognitive function in the immediate postoperative period might lead to delayed discharge from the PACU.

We speculate that the significant cerebral oxygen desaturations during thoracic surgery with SLV could either be related to pathophysiological changes owing to changes in lung perfusion or ventilation or possible microemboli related to surgery. Future, more invasive studies will focus on revealing these mechanisms.

We conclude that 50% of patients undergoing thoracic surgery show cerebral oxygen desaturation during SLV of SrO2 of <65%. These desaturations are positively correlated with early POCD. The risk of POCD after intraoperative cerebral oxygen desaturations ranges from two-fold to 10-fold, depending on the time and degree of the decline.

Declaration of interest
See Funding statement below.

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