Continuous Monitoring of Cerebral Oxygen Saturation in Elderly Patients Undergoing Major Abdominal Surgery Minimizes Brain Exposure to Potential Hypoxia

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Elderly patients are more prone than younger patients to develop cerebral desaturation because of the reduced physiologic reserve that accompanies aging. To evaluate whether monitoring cerebral oxygen saturation (rSO_2) minimizes intraoperative cerebral desaturation, we prospectively monitored rSO_2 in 122 elderly patients undergoing major abdominal surgery with general anesthesia. Patients were randomly allocated to an intervention group (the monitor was visible and rSO_2 was maintained at ≥75% of preinduction values; n = 56) or a control group (the monitor was blinded and anesthesia was managed routinely; n = 66). Cerebral desaturation (rSO_2 reduction <75% of baseline) was observed in 11 patients of the treatment group (20%) and 15 patients of the control group (23%) ($P = 0.82$). Mean (95% confidence intervals) values of mean rSO_2 were higher (66% [64%–68%]) and the area under the curve below 75% of baseline ($AUCrSO2_2$< 75% of baseline) was lower (0.4 min% [0.1–0.8 min%]) in patients of the treatment group than in patients of the control group (61% [59%–63%] and 80 min% [2–144 min%], respectively; $P = 0.002$ and $P = 0.017$). When considering only patients developing intraoperative cerebral desaturation, a lower Mini Mental State Elimination (MMSE) score was observed at the seventh postoperative day in the control group (26 [25–30]) than in the treatment group (28 [26–30]) ($P = 0.02$), with a significant correlation between the $AUCrSO_2 < 75\%$ of baseline and postoperative decrease in MMSE score from preoperative values ($r^2 = 0.25$, $P = 0.01$). Patients of the control group with intraoperative cerebral desaturation also experienced a longer time to postanesthesia care unit (PACU) discharge (47 min [13–56 min]) and longer hospital stay (24 days [7–53] days) compared with patients of the treatment group (25 min [15–35 min] and 10 days [7–23 days], respectively; $P = 0.01$ and $P = 0.007$). Using rSO_2 monitoring to manage anesthesia in elderly patients undergoing major abdominal surgery reduces the potential exposure of the brain to hypoxia; this might be associated with decreased effects on cognitive function and shorter PACU and hospital stay.

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The number of aged patients requiring general anesthesia has increased to nearly 30% of the entire surgical population (1). This patient population is at increased risk for postoperative complications because of numerous comorbidities and reduction in physiologic reserve that accompanies aging (2,3), including cerebral ischemia and neurodegenerative disorders (4–6). Anesthesia has been recognized as a potential risk factor for postoperative neurodegenerative disorders (7). Nonetheless, the central nervous system, which is the primary end-point of most general anesthetics, is seldom directly monitored and anesthesia is usually managed using indirect variables of adequate brain oxygenation, such as heart rate, arterial blood pressure, and peripheral oxygenation.

In the last decade, technological research has expanded the application of near-infrared spectroscopy to allow continuous, noninvasive, and bedside monitoring of regional cerebral oxygen saturation (rSO_2)

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through the scalp and skull (8), providing information on the occurrence of cerebral desaturation that is as accurate as information obtained by means of invasive techniques (9). This new noninvasive monitoring of rSO_2 is clinically useful during open-heart surgery, in patients with head injury, and during carotid endarterectomy (10–12). A recent study on rSO_2 monitoring during orthotopic liver transplantation also demonstrated a close correlation between a decline in rSO_2 during the anhepatic phase and an increase in neuron-specific enolase used as index of cerebral damage resulting from hypoxia/ischemia (13). Furthermore, actively maintaining rSO_2 above a "safety threshold" in patients undergoing coronary artery bypass surgery is associated with fewer complications and shorter hospital stays (14).

Cerebral desaturations have been reported in more than 20% of cases when monitoring rSO_2 in elderly patients undergoing noncardiac abdominal surgery (15,16). We therefore conducted this prospective, multicenter, randomized, blinded investigation to evaluate whether using rSO_2 monitoring in elderly patients undergoing major abdominal surgery reduces the potential exposure of the brain to inadequate oxygen supply.

Methods

The study was conducted at five University Hospitals after obtaining approval from each Institutional Ethic Committee and written informed consent from all patients. Patients older than 65 years, scheduled for major abdominal, nonvascular surgery under general anesthesia (with an expected duration $\geq$2 h) were considered for the study. Surgical procedures were represented by major abdominal surgery with a xiphopubic skin incision and included laparotomic gastric resection, colonic resection, hepatic resection, and duodenocephalo-pancreasectomy. Patients with preexisting cerebral pathology (such as previous episodes of cerebral ischemia or stroke) and ASA physical status $\geq$IV or a baseline Mini Mental State Examination (MMSE) test $\leq$23 and patients whose follow-up was not probable (not expected to be discharged alive from the hospital or with an expected hospital stay $<$4 days) were excluded.

Standard monitoring was used throughout the procedure. Patients were actively warmed throughout the procedure using a forced-air warming system (Bair-Hugger, Augustine-Medical, Eden Prairie, MN) to maintain intraoperative normothermia. rSO_2 was continuously monitored using near-infrared spectroscopy (INVOS 4100; Somanetics Inc., Troy, MI). Sensors for cerebral oximetry were placed bilaterally on the right and left sides of the forehead according to the manufacturer's instructions before induction of general anesthesia; rSO_2 data were continuously recorded on a 3.5″ floppy disk at 10-s intervals during the entire procedure.

According to a computer-generated sequence of numbers and using a sealed-envelope technique, patients were randomly allocated to two groups: in the control group the screen of the INVOS monitor was blinded and general anesthesia was managed routinely maintaining arterial blood pressure and heart rate values within 20% of baseline values. In the treatment group the INVOS monitor was visible and anesthesia management was aimed at maintaining rSO_2 more than 75% of baseline values. Cerebral desaturation was defined as a reduction of rSO_2 less than 75% of baseline (80% if the baseline value was $<$50%) for $\geq$15 s. In case of cerebral desaturation in the treatment group, the attending anesthesiologist activated a two-step treatment: the first step included checking the ventilator, head position, and tubing system, increasing F_{IO_2}, increasing end-tidal CO_2 partial pressure if the ET_{CO_2} was $<$35 mm Hg, and increasing arterial blood pressure with intravascular fluid administration (250 mL hetastarch) and vasoconstrictors (ethylephrine 2–5 mg IV) if systolic arterial blood pressure was $\leq$90 mm Hg. If the first step did not restore acceptable rSO_2 values within 60 s, the second step included the reduction of brain oxygen consumption with an IV bolus of propofol (0.5 mg/kg).

Baseline rSO_2 was defined as the average saturation value over a 1-min period before induction of general anesthesia beginning approximately 3 min after the sensors were applied.

Standard general anesthesia was then induced with 2 μg/kg IV fentanyl and 5 mg/kg sodium thiopental IV. After administration of 0.2 mg/kg cisatracurium, tracheal intubation was performed and mechanical ventilation was started using a 40% oxygen-air mixture (tidal volume, 7 mL/kg; respiratory rate, 12 bpm; inspiratory-to-expiratory time, 1/2, with a 10% inspiratory pause). Mechanical ventilation was adjusted to maintain an ET_{CO_2} partial pressure ranging between 32 and 36 mm Hg. General anesthesia was maintained with sevoflurane by adjusting the end-tidal concentrations between 1% and 4% to maintain heart rate and mean arterial blood pressure within 15% of baseline values. Supplemental IV boluses of fentanyl (1 μg/kg) were administered if required to maintain cardiovascular stability, and muscle relaxation was maintained with 2-mg boluses of cisatracurium bromide at the discretion of the attending anesthesiologists and according to the surgeon's needs. In case of blood loss exceeding 20% of whole circulating volume, the actual hemoglobin concentration was measured and homologous blood transfused if hemoglobin concentration was $<$9 g/dL.

After discontinuation of sevoflurane at the end of the procedure the time required to recover spontaneous ventilation, open eyes on verbal command, squeeze the observer's hand, and time to tracheal extubation were recorded. Patients were then transferred to the postanesthesia care unit (PACU) and the Aldrete score was recorded every 15 min until achievement of readiness for PACU discharge (Aldrete score ≥9) (17). In each patient the anesthetic exposure was also calculated normalizing the end-tidal concentration of sevoflurane using the age-adjusted MAC values of sevoflurane (18).

Postoperative analgesia consisted of IV ketoprofen (100 mg every 8 h) and a patient-controlled analgesia infusion of morphine (1 mg bolus; lockout time, 6 min; maximum dose, 6 mg/h) for the first 72 h after surgery. Occurrence of any adverse event, including nausea, vomiting or other undesirable side effect, was also recorded.

Cognitive function of the patients was assessed using the MMSE test the day before surgery and then repeated 1 wk after surgery (19). In each hospital the same research fellow blinded to intraoperative treatment performed the MMSE test in a standardized manner. A decrease in MMSE score ≥2 points from baseline was also considered as an index of decline in cognitive function (20,21).

Patients were then followed daily after surgery until hospital discharge by the surgeons, ward nurses, and research fellows, who were blinded as to intraoperative management and patient grouping. Any occurrence of major respiratory, cardiovascular, surgical, or neurological complications requiring unplanned treatment was recorded. Duration of hospital stay was also recorded.

To calculate the required study size, we considered the results of previous studies performed in a similar population (15,16). To detect a difference of 4 points in mean rSO_2 values recorded during surgery accepting a two-tailed α error of 5% and a β error of 10%, 54 patients per group were required (22).

Data from the cerebral oximeter were analyzed using Microsoft Excel 5.0 (Microsoft, Redmond, WA). Cerebral desaturation was considered to occur when rSO_2 values decreased to <75% of baseline values for 15 s. If baseline rSO_2 was less than 50%, the threshold for defining cerebral desaturation was a reduction to less than 80% of baseline values. Mean and minimum values of rSO2 were then calculated in each patient, as were the area under the curve of rSO_2 readings less than 50% ($AUC_{rSO2 < 50\%}$) and the area under the curve of rSO_2 readings less than 75% of baseline ($AUC_{rSO2 < 75\% \text{ of baseline}}$).

Statistical analysis was performed using Systat 7.0 (SPSS Inc, Chicago, IL). The distribution of data was first evaluated using the Kolmogorov-Smirnov test. The Student's *t*-test and Mann-Whitney *U*-test were used to compare continuous variables as indicated. Categorical variables were analyzed using contingency table analysis and Fisher's exact test. Correlation and linear regression analysis were also used if indicated. Continuous variables are presented as mean ± SD or 95% confidence intervals (95% CIs) for normally distributed data or median (range) for not normally distributed data. Categorical variables are presented as numbers (percentage). A value of $P \leq 0.05$ was considered as significant.

Results

A total of 146 patients were screened for the study. Ten patients did not give their informed consent; 5 patients had a MMSE ≤ 23 and were excluded. A total of 122 patients completed the study in the 5 participating hospitals, 56 in the treatment group and 66 in the control group (Figure 1).

A center effect was excluded before performing complete statistical analysis of the whole population. No differences in anthropometric characteristics, duration of surgery, and anesthetic exposure were observed between the two groups (Table 1).

Surgery was performed uneventfully in all studied patients, and no severe intraoperative complication occurred in any patient. One patient of the control group died 20 days after surgery (colonic resection) (1.5%) as a result of the development of a surgical complication (rupture of the colonic anastomosis) leading to severe septic shock and multiple organ failure ($P = 0.45$).

No differences in arterial blood pressure values (systolic and diastolic), heart rate, or peripheral oxygen saturation were reported between the two groups. The maximum percentage decrease of systolic arterial blood pressure from baseline values was –24% ± 13% in the treatment group and -28% ± 13% in the control group ($P = 0.12$), and no differences in the median (range) number of observation times in which systolic arterial blood pressure was less than 80% of baseline values were reported between the two groups (2 [0–9] in the treatment group and 2 [0–12] in the control group; $P = 0.16$).

Table 2 shows the rSO_2-derived variables recorded in the two groups and MMSE score recorded before surgery and 7 days after surgery. Although there was a large patient-to-patient variability in rSO_2 values, baseline rSO_2 values were similar in the two groups. Cerebral desaturation (defined as an rSO_2 reduction <75% of baseline) was observed in 11 patients of the treatment group (20%) and 15 patients of the control group (23%) ($P = 0.82$). All episodes of cerebral desaturation occurred during the maintenance period of general anesthesia and the episodes were never associated with a concomitant reduction in arterial oxygen saturation. In 8 of the 11 patients of the treatment

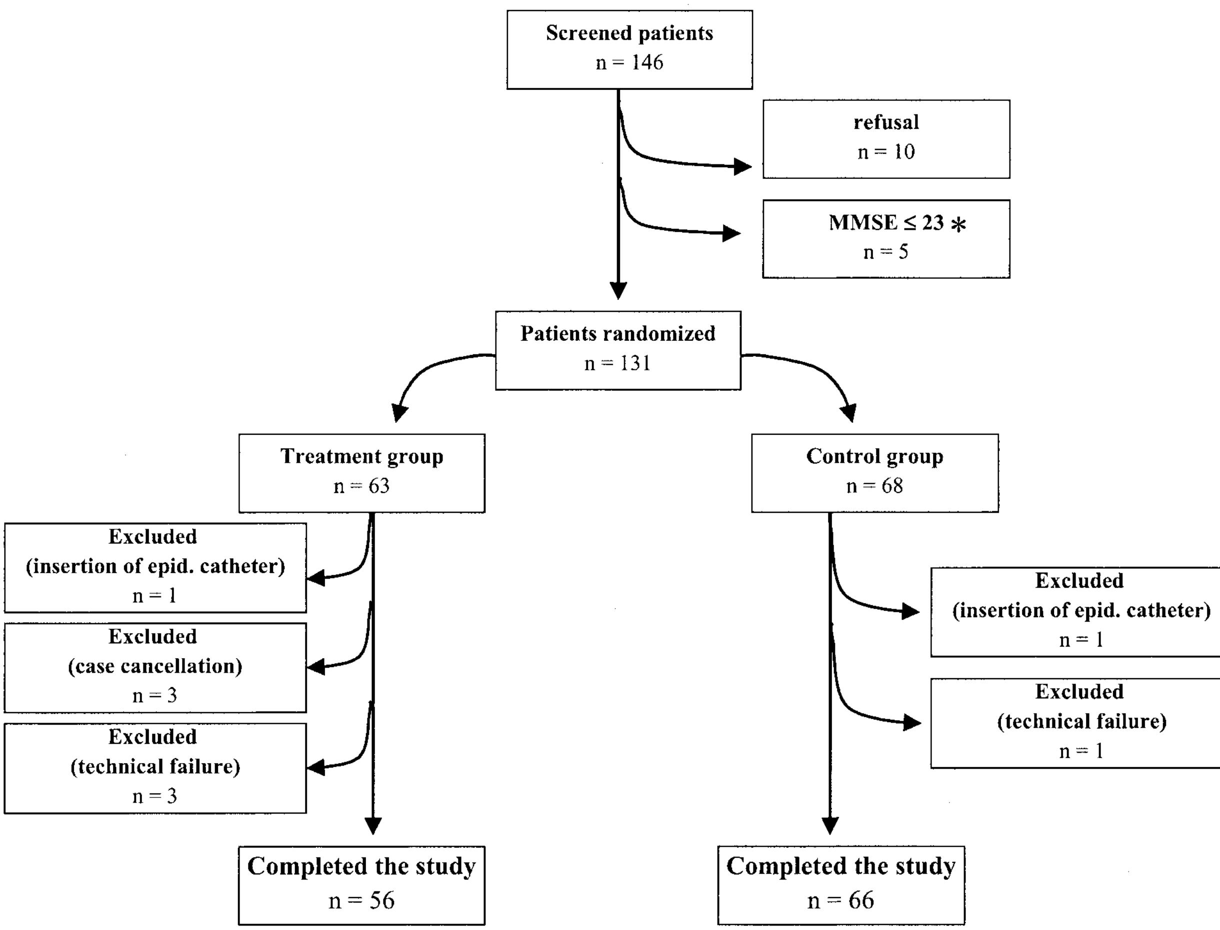

Figure 1. CONSORT flow of patients enrolled in the study. * MMSE = Mini Mental State Examination test.

Table 1. Anthropometric Variables, Duration of Surgery, and Anesthetic eExposure in Studied Patients

	Control (n = 66)	Treatment (n = 56)	P value
Age (yr)	72 ± 5	73 ± 5	0.48
Weight (kg)	69 ± 10	70 ± 10	0.49
Height (cm)	166 ± 7	167 ± 8	0.55
Gender (Male/ Female)	39/27	30/26	0.41
ASA physical status (II/ III)	40/26	36/20	0.64
Duration of surgery (min)	292 ± 100	259 ± 94	0.13
MAC-hour	2.4 (0.81–6.7)	2.5 (0.81–3.6)	0.92
Concomitant diseases			
Respiratory disease	9 (13%)	3 (5%)	–
Renal disease	4 (6%)	4 (7%)	–
Hypertension	46 (69%)	37 (67%)	–
Coronary artery disease	10 (16%)	6 (10%)	–
Chronic atrial fibrillation	5 (8%)	4 (7%)	–

Data are presented as mean (±SD), median (range) or numbers.

group with intraoperative desaturation, rSO_2 recovered to acceptable values with only the first treatment step (increasing F_{IO_2}, ET_{CO_2} partial pressure, and arterial blood pressure), whereas in 3 of them a propofol bolus followed by a further increase in the sevoflurane end-tidal concentration was necessary to restore acceptable rSO_2 values.

Postoperative complications requiring unplanned patient examination and diagnostic tests were observed in 12 patients of the control group (19%) and 6 patients of the treatment group (10%) (P = 0.20). Table 3 shows the distribution of different complications observed in the two groups. No statistically significant differences were observed between the two groups.

Table 2. Cerebral Oxygen Saturation Derived Variables and Mini Mental State Examination Score Recorded in Studied Patients

	Control (n = 66)	Treatment (n = 56)	P value
Baseline rSO_2 (%)	62 (60–64)	63 (61–66)	0.13
Minimum rSO_2 (%)	49 (47–52)	55 (52–57)	0.002
Mean rSO_2 (%)	61 (59–63)	66 (64–68)	0.002
$AUC_{rSO2<50\%}$ (min%)	287 (0.5–575)	39 (0.5–79)	0.006
$AUC_{rSO2<75\% \text{ of Baseline}}$ (min%)	80 (2–144)	0.4 (0.1–0.8)	0.017
MMSE baseline*	29 (24–30)	28 (24–30)	0.17
MMSE 7th day*	28 (22–30)	28 (22–30)	0.31

Data are presented as mean (95% confidence intervals), or *median (range). rSO_2= cerebral oxygen saturation; MMSE = Mini Mental State Examination score.

Table 3. Complications Requiring Unplanned Treatment Observed in Studied Patients

	Control (n = 66)	Treatment (n = 56)	P value
Respiratory	4 (6.4%)	1 (1.8%)	0.22
Cardiac	1 (1.6%)	1 (1.8%)	0.92
Surgical	7 (11%)	6 (11%)	0.99
Neurological	4 (6%)	0 (0%)	0.12
Patients with at least 1 complication	12 (19%)	6 (10%)	0.20
Patients with more than 1 complication	4 (6.4%)	1 (1.8%)	0.22

Data are presented as n (percentage).

We then extrapolated from the whole population the 26 patients (11 in the treatment group and 15 in the control group) who actually had an episode of intraoperative desaturation. These two subgroups were similar with respect to anthropometric variables, intraoperative hemodynamics, duration of surgery, and mean baseline rSO_2 values (61% [95% CI, 56%–72%] in the treatment group and 58% [95% CI, 53%–70%] in the control group (P = 0.169); however, rSO_2 was higher in the treatment group (65% [95% CI, 59%–71%) than in the control group (52% [95% CI, 47%–57%]; P = 0.005), and mean $AUCrSO_2$ <75% of baseline was much smaller in the treatment group (1.7 min% [95% CI, 0.8 min%–4.3 min%]) as compared with patients of the control group (292 min% [95% CI: 75 min%–660 min%]; P = 0.006).

No differences in MMSE score were observed between groups throughout the study (Table 2). However, when considering only those patients who had at least one episode of intraoperative desaturation, no differences were observed in median (range) baseline MMSE (29 [27–30]) in the treatment group and 29 [27–30] in the control group; P = 0.82), at the seventh postoperative day those patients of the control group who had intraoperative desaturation showed a significantly lower value of MMSE (26 [25–30]) as compared with patients of the treatment group (28 [26–30]) (P = 0.02). A significant correlation was also observed between the $AUCrSO_2$ <75% of baseline and postoperative decrease in MMSE score from preoperative values in the subgroup of patients who had intraoperative cerebral desaturation (Figure 2) (2 outliers were excluded before performing the regression analysis).

A decline in cognitive function (defined as a reduction in MMSE ≥2 points from baseline) during the first week after surgery was observed in 20 patients of the treatment group (35%) and 30 patients of the control group (54%) (P = 0.137); however, when considering only those patients who actually had at least one episode of intraoperative desaturation in both groups, a decline in cognitive function was observed in 10 patients of the control group only (66%) (P = 0.001).

No differences in times for recovery from anesthesia after discontinuation of sevoflurane were reported between groups in the whole population (Fig. 3); however, patients of the control group who had intraoperative desaturation also showed a longer time for PACU discharge and hospital stay (47 min [13–56 min] and 24 days [7–53 days]) as compared with those patients of the treatment group (25 min [15–35 min] and 10 days [7–23 days]; P = 0.01 and P = 0.007, respectively). Interestingly, in the 26 patients who actually had intraoperative cerebral desaturation the $AUCrSO_2$ <75% of baseline also showed a positive correlation with the duration of hospital stay after surgery (Figure 4).

Discussion

All general anesthetics produce cardiovascular depression that can be augmented in the aged patient, potentially exposing him or her to inadequate brain perfusion (2,3), and this might be related to the occurrence of postoperative cognitive decline often reported in these patients (23,24). Nonetheless, the brain is rarely monitored in routine practice. Near-infrared spectroscopy monitoring has been reported to provide information on the balance between oxygen demand

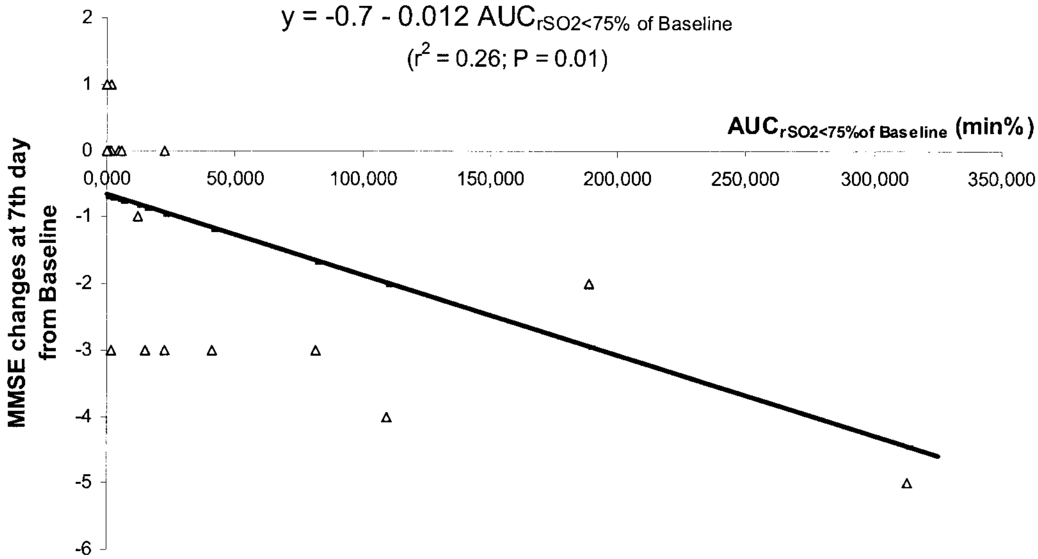

Figure 2. Correlation between AUCrSO$_2$ <75% of baseline and postoperative decrease in Mini Mental State Examination (MMSE) score from preoperative values measured in the 26 patients who actually had at least one episode of intraoperative cerebral desaturation.

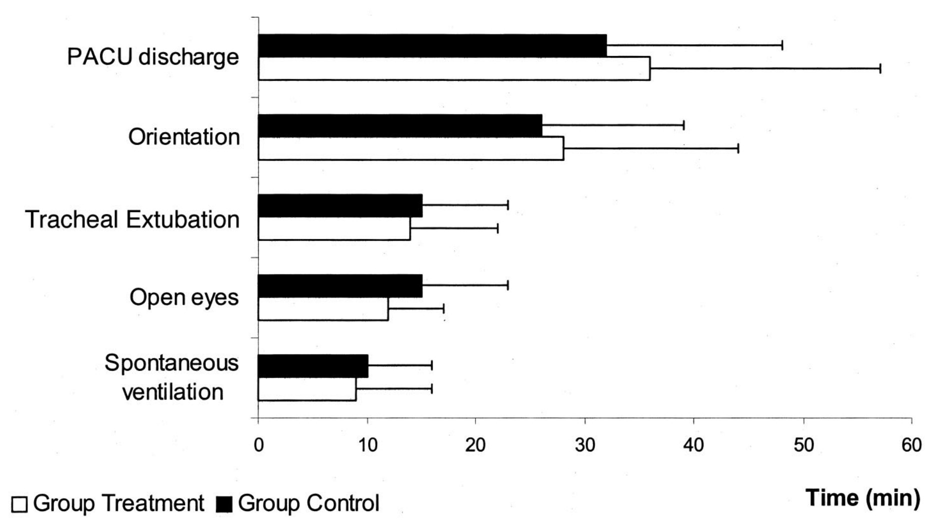

Figure 3. Times of recovery from general anesthesia and discharge from the postanesthesia care unit (PACU) (achievement of an Aldrete score ≥9) in the two groups. Data are presented as mean (± SD).

and supply to the brain (8,9), and the usefulness of intraoperative rSO$_2$ monitoring has been shown during cardiac and vascular surgery (10–12,14). This multicenter, prospective, randomized, blinded investigation showed that in a population of relatively healthy, elderly patients cerebral desaturation can occur in one of every five patients. Adjusting the anesthesia plan according to rSO$_2$ monitoring allowed us to minimize the exposure of the brain to a potentially inadequate oxygen supply.

Although no differences in MMSE were reported between groups in the entire population, when we considered only the 26 patients who actually had intraoperative cerebral desaturation (11 in the treatment group and 15 in the control group), the MMSE recorded at the seventh postoperative day was lower in the control group than in the treatment group, whereas the extent of MMSE reduction correlated with the exposure to potential brain hypoxia (AUCrSO$_2$ <75% of baseline).

Evaluating cognitive function with the MMSE test is a major pitfall, as this test does not completely evaluate mental function (7,23,24); nonetheless, a reduction in the MMSE in repeated testing suggests that a decline in cognitive function is occurring (19–21). In agreement with our findings, Monk et al. (16) evaluated postoperative cognitive dysfunction with more sensitive psychometric tests in patients of different ages, reporting that in aged patients cognitive dysfunction was associated with a more frequent incidence of intraoperative desaturation and longer hospital stay.

In agreement with our findings, Austin et al. (25) reported that active interventions based on a multimodal neurophysiologic monitoring, including transcranial cerebral oximetry, decreased the incidence of

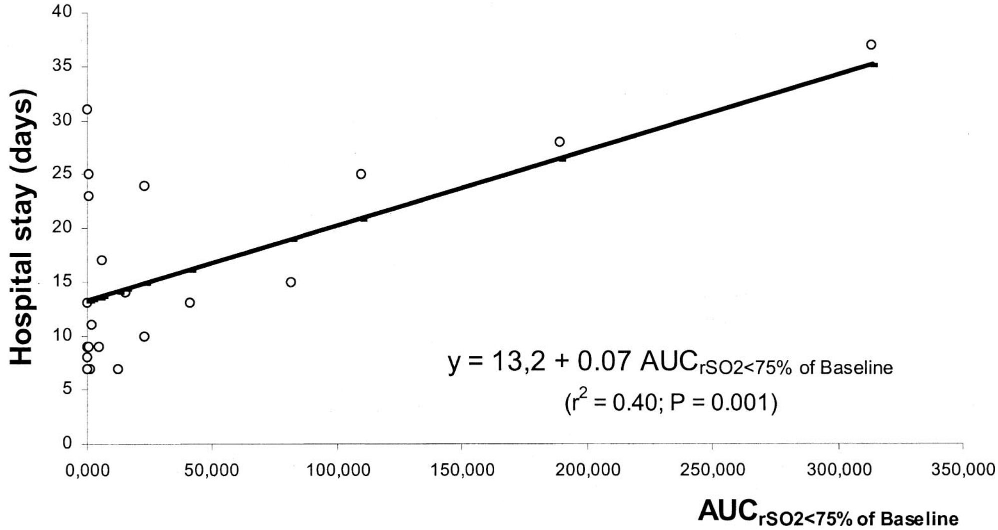

Figure 4. Correlation between AUCrSO_2 <75% of baseline and length of hospital stay measured in the 26 patients who actually had at least one episode of intraoperative cerebral desaturation.

postoperative neurological sequelae in a population of pediatric patients undergoing cardiac surgery, with marked reduction of hospital stay and costs. In a prospective, randomized, blinded study Iglesias et al. (14) evaluated the impact of interventions to improve rSO_2 on postoperative outcome after coronary artery bypass surgery and reported that monitoring and maintaining rSO_2 more than 75% of baseline was associated with a decreased length of stay after cardiac surgery.

Evaluating the intraoperative changes in rSO_2 during orthotopic liver transplantation with postoperative increases in neuron-specific enolase as an index of hypoxia/ischemia-related cerebral damage, Plachky et al. (13) observed that a decrease in cardiac output alone does not predict neurological damage, but they reported a close correlation between decreased rSO_2 readings and increased markers of neurological damage during the anhepatic phase. Accordingly, actively maintaining rSO_2 greater than a critical threshold should potentially reduce the severity of ischemia-induced brain damage.

We observed no differences in the incidence of postoperative complications between groups. However, it must be considered that this study was powered to detect a difference in mean rSO_2 between groups; whereas a *post hoc* power analysis based on the observed incidence of perioperative complications showed that more than 400 patients per group would be required to have a 5% α-error and 20% β-error in detecting a significant difference in the incidence of perioperative complication (22).

Importantly, the occurrence of cerebral desaturation was not associated with any difference in pulse oximetry. Although the study was not powered to evaluate the effects of pulse oximetry monitoring on patient outcome, this finding is in agreement with findings reported by Pedersen et al. (26), who failed to demonstrate any significant differences in the incidence of perioperative complications or duration of hospital stay by monitoring pulse oximetry perioperatively. Similar results have been reported by Plachky et al. (13) during liver transplantation.

In conclusion, this multicenter, prospective, randomized, blinded study shows that cerebral desaturation occurs in nearly 20% of elderly patients undergoing major abdominal nonvascular surgery; using rSO_2 monitoring to adjust the anesthesia plan during surgery reduces the exposure of the brain to potential hypoxia. Interestingly, in those patients developing intraoperative cerebral desaturation this approach to anesthesia management seems to result in less cognitive decline and shorter hospital stay, suggesting that cerebral hypoxia might be involved in the physiopathology of cognitive decline observed after surgery in the aged patient

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Appendix

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