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Pre- and intraoperative cerebral near-infrared spectroscopy and postoperative delirium

Results of a prospective cross-sectional trial

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Abstract

Postoperative delirium (PODE) is a serious complication that can occur during the first few days after surgery. A number of causes can make delirium more likely; one factor to consider is hypoxia during anesthesia. In this study, the pre- and intraoperative cerebral regional oxygen saturation (rSO_2) as measured by near-infrared spectroscopy (NIRS) was to be examined with regard to an association with the occurrence of PODE in patients undergoing major abdominal procedures. Data from 80 patients (33 women, 47 men) was examined. The mean age was 66.31 ± 10.55 years (between 42 and 84 years). Thirteen patients developed PODE. The preoperative rSO_2 values (P = .10) and the rSO_2 values during the steady state of anesthesia (P = .06) tended to be lower in the delirium group than in the non-delirium group. There was a significant correlation between the preoperative rSO_2 and the preoperative hemoglobin values (P < .001). The variance of rSO_2 during the steady state of anesthesia was significantly greater in the delirium group compared to the non-delirium group (P = .03). In two patients from the delirium group, rSO_2 dropped below 50%; they also had a minimum mean arterial pressure below 50 mm Hg, which could have disturbed cerebral autoregulation. The duration of rSO_2 decreases (>10%, >15%, >20%) and increases (>10%) compared to the preoperative values was not significantly different between patients with and without PODE. The results suggest that NIRS could be a useful monitoring method for patients undergoing abdominal surgical procedures, on the one hand to recognize patients with low pre- or intraoperative rSO_2 values, and on the other hand to detect changes in rSO_2 values during anesthesia.

Abbreviations: 3D-CAM = 3-Minute Diagnostic Interview for Confusion Assessment Method-defined Delirium, EEG = electroencephalogram, Hb = hemoglobin, MAP = mean arterial pressure, NI = Narcotrend Index, NIRS = near-infrared spectroscopy, PODE = postoperative delirium, rSO_2 = regional oxygen saturation, SAS = Statistical Analysis System.

Keywords: anesthesia, autoregulation, mean arterial pressure, near-infrared spectroscopy, postoperative delirium, regional oxygen saturation

1. Introduction

Delirium can develop postoperatively as a serious complication. Postoperative delirium (PODE) can affect patients of all ages, but is particularly common in elderly patients.[1–3] The symptoms of delirium are disturbances in attention, awareness, and cognition; they develop over a short period of time and fluctuate in severity.[4] Patients with PODE have worse perioperative and long-term outcomes than patients who do not develop delirium.[2,3]

When it comes to factors that contribute to the development of delirium, a distinction can be made between predisposing and precipitating factors.[1] Predisposing factors, such as comorbid disease, are related to the patient.[1] Precipitating factors, such as disturbances in intraoperative homeostasis, inadequately controlled pain, and excessive anesthesia depth, are elements that occur throughout the perioperative period and may trigger delirium onset.[1,3,5] One factor that has to be considered in PODE is hypoxia during anesthesia.[6,7]

Near-infrared spectroscopy (NIRS) is a technology for noninvasive monitoring of cerebral blood flow. Based on the transmission and absorption of near-infrared light in tissues, NIRS measures the relative proportions of oxy- and deoxy-hemoglobin.[8] NIRS provides an index of regional oxygen saturation (rSO_2),[8] and can be used for noninvasive, continuous assessment of cerebral oxygenation.[9] Areas of application for cerebral NIRS monitoring are, for example, heart surgery and carotid endarterectomies.[10]

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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In literature, there are only few studies investigating cerebral oxygenation as measured by NIRS in patients undergoing abdominal surgical procedures.[10]

The aim of this study was therefore to evaluate whether there are abnormalities in rSO_2 in the NIRS in the course of major abdominal surgery, and whether these are associated with an increased incidence of PODE. In particular, it was to be investigated whether a low preoperative baseline value of rSO_2 and an intraoperative decrease or increase in rSO_2 in the NIRS are associated with the occurrence of PODE.

2. Methods

Ethical approval for the study was obtained from the Ethics Committee of Hannover Medical School, Hannover, Germany (Approval No. 3070-2016, 12 February 2016). The inclusion criteria for the single-center, prospective, observational, cross-sectional study were: patients older than 18 years who had to undergo planned major abdominal surgery. The exclusion criteria were: incapability to consent, insufficient command of the German language, severe hypoacusis or anacusis, and revision surgery during the investigation period.

A total of 99 patients aged 42 to 84 years participated in the study between April 2016 and September 2017; 40 of the participants were female, and 59 were male.

Our analysis includes patients who received balanced anesthesia with sevoflurane and remifentanil. The analysis does not include patients receiving continuous intravenous propofol (n = 5) or a combination of sevoflurane and intravenous propofol (n = 2) for maintenance of anesthesia,[11,12] nor does it include patients with prolonged postoperative sedation at the intensive care unit (n = 9) since proper screening for delirium was not feasible. Two patients withdrew their consent to participate in the study, and one patient had to be excluded due to missing data.

The data analysis regarding NIRS monitoring includes 80 patients. Results of a previous analysis of data of the 80 patients with regard to blood pressure, electroencephalogram (EEG), and sevoflurane concentrations were published recently.[13]

The day before surgery, the Montreal Cognitive Assessment was used to assess the patient's preoperative cognitive function.[13,14] The patients were also screened for major depression using the Patient Health Questionnaire-2.[13,15,16] A preoperative delirium test was not carried out.

One hour before induction of anesthesia, patients who asked for oral premedication were given 3.75 mg or 7.5 mg midazolam; one patient received 150 µg clonidine. Anesthesia was performed according to clinical routine. For induction of anesthesia, propofol or thiopental, sufentanil, and atracurium or rocuronium were administered. After tracheal intubation, the patients received sevoflurane and intravenous boli of sufentanil for maintenance of anesthesia. Depth of anesthesia was maintained according to clinical assessment, with normoventilation as the goal. Anesthesiologists and nurses were blinded to the NIRS measurements. After surgery, the patients were transferred to the intensive care unit, where they were kept sedated until they were hemodynamically stable and extubation was possible.

During anesthesia, the following parameters were recorded: ventilation parameters including end-tidal sevoflurane concentration, electrocardiography, pulse oximetry, capnography, noninvasive blood pressure, arterial blood pressure, temperature, and EEG (blinded measurements; EEG monitor: Narcotrend-Compact M, Bad Bramstedt, Germany; EEG index: Narcotrend Index [NI]). Additionally, NIRS (INVOS™ 5100C Cerebral/Somatic Oximeter, Medtronic, Watford, UK) was used to document the cerebral oxygenation. For this analysis, rSO_2 values collected at 1-min intervals were used.

The 3-Minute Diagnostic Interview for Confusion Assessment Method (CAM)-defined delirium (3D-CAM) was selected as screening tool for PODE. The 3D-CAM is a 3-minute structured diagnostic assessment using the CAM (Confusion Assessment Method) algorithm.[17] Use of the 3D-CAM determines the absence or presence of four features: a) acute onset of changes and fluctuations in the course of mental status, b) inattention, c) disorganized thinking, and d) altered level of consciousness. A patient is classified as delirious if features a) and b) plus either feature c) or d) are present.[14] The patients were examined twice daily with regard to signs of delirium on postoperative days 1-7. Members of the study group performed the examinations.

2.1. Parameters included in the statistical analysis

The unit of rSO_2 is percent (%). In clinical studies and treatment algorithms, it is common practice to determine a baseline value, e.g. directly before induction of anesthesia. During anesthesia, the rSO_2 measurements are then assessed either as absolute values or as a reduction or increase in percent relative to the individual baseline. Denault et al[18] defined an abnormal rSO_2 as a 20% reduction from baseline values or an absolute decrease below 50%.

The following parameters related to rSO_2 were analyzed:

- Preoperative value before start of induction of anesthesia
- Maximum value during induction of anesthesia
- During the course of anesthesia:
- Length of time with rSO_2 values which were more than 10%, 15%, or 20% smaller than the individual preoperative value
- Length of time with rSO_2 values which were more than 10% higher than the individual preoperative value
- Number of patients with rSO_2 values below and above the value of 50%
- Variance of rSO_2

Furthermore, preoperative hemoglobin (Hb) values were evaluated.

Duration of anesthesia was defined as the time between the start of induction and the end of the last suture. The term steady state was used for the time period between the end of induction and the last suture.

For each patient, the lowest value during steady state for each of the variables mean arterial pressure (MAP), NI, and rSO_2 was determined.

2.2. Statistics

Statistical analysis was performed by logistic regression, analysis of regression, and correlation as well as *t* test. A *P* value <.05 was deemed to be statistically significant.

Logistic regression was performed using the occurrence of PODE as dependent variable. The relevant covariates were analyzed using univariate logistic regression. Receiver operating characteristic analysis was performed to determine the cutoff value of preoperative rSO_2 predictive of delirium.

The statistical analysis was carried out using the statistical software SAS (SAS Institute, Cary, NC), version 9.3.

Cases where some data was missing were only excluded for analyses involving the missing data.

3. Results

Eighty patients, 33 women and 47 men, who received balanced anesthesia with sevoflurane and sufentanil, were included in the data analysis. One patient received a hemihepatectomy due to echinococcosis. The other patients had surgery because of diagnosed or suspected malignancies (gynecological surgery [n = 3], liver surgery [n = 39], pancreatic surgery [n = 16], gastric surgery [n = 3], esophageal surgery [n = 8], intestinal surgery [n = 4], and other surgery [n = 7]). The mean age was 66.31 ± 10.55 years (between 42 and 84 years). Of these patients, 13 developed

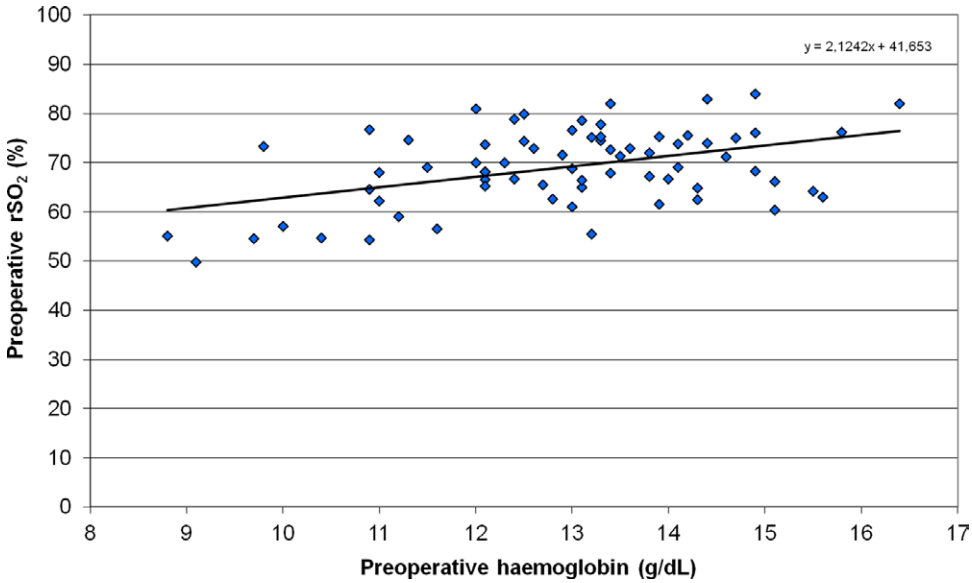

Figure 1. Preoperative hemoglobin and preoperative rSO_2. rSO_2 = regional oxygen saturation.

PODE (9 men and 4 women). There was a tendency towards higher age in the delirium group compared to the non-delirium group (70.68 ± 9.41 vs 65.46 ± 10.61 years, P = .11). Delirium-positive and delirium-negative patients did not show significant differences regarding the Montreal Cognitive Assessment (P = .89) or the Patient Health Questionnaire-2 (P = 1.0) test.[13] Preoperative rSO_2 values were available for 68 patients, and rSO_2 values recorded during anesthesia were available for 73 patients.

3.1. Preoperative rSO_2 and Hb

The preoperative rSO_2 values were between 49.75% and 84.00%. The mean preoperative value was 68.42 ± 8.16% in women and 70.76 ± 7.02% in men (P = .22). The preoperative rSO_2 tended to decrease with increasing age (P = .20).

There was a significant correlation between preoperative rSO_2 and preoperative Hb (Fig. 1). The correlation (correlation coefficient according to Pearson) was 0.44204 (P < .001). According to the regression equation, an increase in the Hb value of 1 g/dL was linked to an increase in the rSO_2 value of 2.12%.

The preoperative Hb was 12.28 ± 1.77 g/dL in the delirium group and 13.03 ± 1.62 g/dL in the non-delirium group (P = .14).

The preoperative rSO_2 tended to be lower in the delirium group than in the non-delirium group (P = .10) (Table 1). The optimal cutoff value of the preoperative rSO_2 to predict delirium was less than 66.38% (area under the curve 68.62% [95% CI 45.81–91.43], P = .11, sensitivity 71.43%, specificity 72.13%).

3.2. rSO_2 during induction and maintenance of anesthesia

With administration of 100% O_2 during induction of anesthesia, rSO_2 increased up to a value of 95%. This is the highest displayable value for the INVOS device used. A maximum value of 95% was reached by 7 patients. On average, the highest rSO_2 value per patient during induction was 77.67 ± 8.78% in the delirium group and 82.87 ± 8.38% in the non-delirium group (P = .09).

During the steady state of anesthesia, the mean rSO_2 in the delirium group was lower than in the non-delirium group, but this was not statistically significant (P = .06) (Table 1).

The variance of rSO_2 tended to be higher in the period from induction to the last suture (P = .10), and was significantly higher during the steady state (P = .03) in the delirium group compared to the non-delirium group (Table 1).

Table 1

Comparison of rSO_2 between the groups of patients with and without delirium (mean ± standard deviation).

	Delirium	No delirium	P
Preoperative rSO_2	64.75 ± 8.33	69.92 ± 7.56	.10
Steady-state rSO_2	68.91 ± 5.84	74.52 ± 8.19	.06
Variance of rSO_2, induction until last suture	33.10 ± 22.77	22.90 ± 15.77	.10
Variance of rSO_2, steady state	32.88 ± 36.06	16.00 ± 13.64	.03

rSO_2 = regional oxygen saturation.

Table 2

Duration (min) with a decrease in rSO_2 relative to the preoperative value in patients with and without delirium (mean ± standard deviation).

Decrease in rSO_2	Delirium	No delirium	P
>10%	13.57 ± 21.17	10.70 ± 27.16	.79
>15%	6.29 ± 11.74	4.07 ± 13.87	.68
>20%	0.43 ± 0.79	1.82 ± 8.32	.69

rSO_2 = regional oxygen saturation.

With regard to the duration of a decrease in rSO_2 of more than 10%, more than 15%, or more than 20% below the individual preoperative value, there was no significant difference between the delirium group and the non-delirium group (P = .79, P = .68, P = .69) (Table 2).

Two of the patients, both undergoing surgery including partial liver resection, had rSO_2 values below 50% during the intraoperative course (patients A and B, Figs. 2 and 3). These two patients belonged to the delirium group. Before induction of anesthesia and without oxygen, one of these patients (patient B, Fig. 3) displayed rSO_2 values in the range of 51% to 55%. These two patients had noticeably high fluctuations in MAP during the intraoperative phases in which low rSO_2 values occurred. In the non-delirium group, no patient displayed rSO_2 values below 50% during the intraoperative course. Among the 80 patients included in the evaluation, there was one other patient (patient C) undergoing liver surgery and experiencing PODE who had an intraoperative episode with low rSO_2 close to 50%

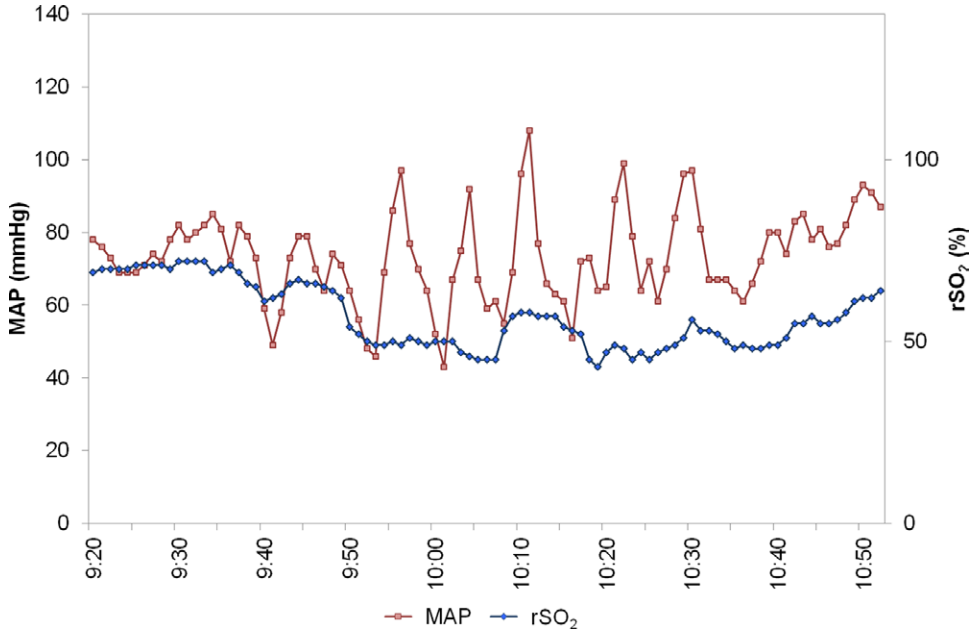

Figure 3. Section of the intraoperative course of rSO_2 und MAP (patient B). MAP = mean arterial pressure, rSO_2 = regional oxygen saturation.

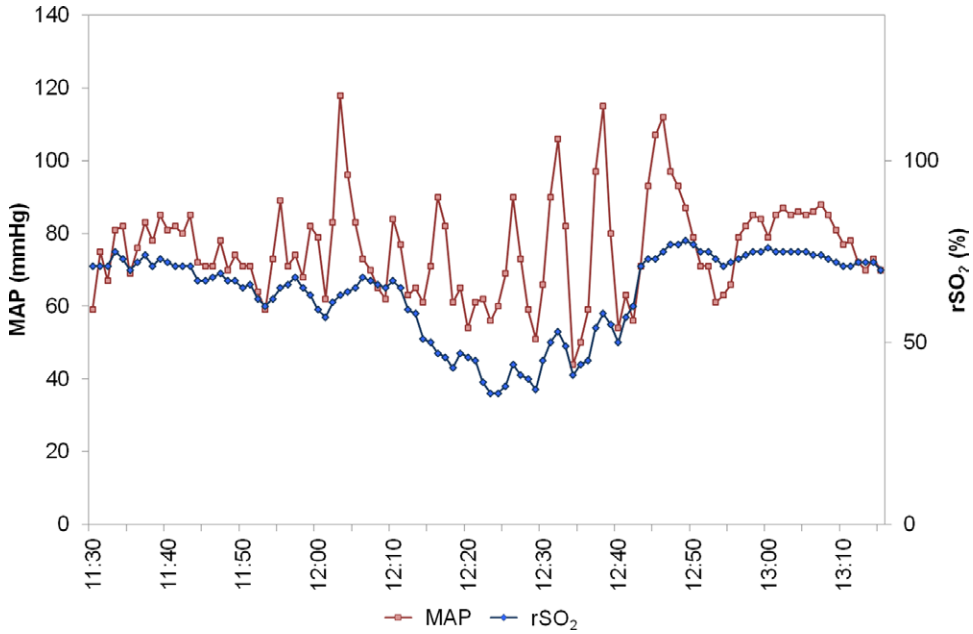

Figure 2. Section of the intraoperative course of rSO_2 und MAP (patient A). MAP = mean arterial pressure, rSO_2 = regional oxygen saturation.

(minimum 53%) and fluctuating MAP (minimum 55 mm Hg) similar to the episodes of patients A and B. In patients A, B, and C, during the phases with drop in rSO_2, the Hb was reduced compared to preoperative values. But in patients A and B even lower Hb values occurred with rSO_2 values of 60 or higher. A correlation between intraoperative MAP and Hb values was not evident. In all three patients, the NI decreased during the phases with MAP fluctuations and reduced rSO_2. The end-expiratory sevoflurane concentration first increased and then decreased in patients A and B during this time. The NI values before, during, and after rSO_2 reduction were as follows: patient A 10/1/11, patient B: 48/35/51, patient C 46/34/42.

The mean time during anesthesia with rSO_2 values that were more than 10% higher than the preoperative value was longer in patients with delirium compared to patients without delirium, but the difference was not significant (102.43 ± 75.96 vs 88.23 ± 88.73 min, $P = .68$).

To investigate correlations between variance of MAP, MAP, NI, and rSO_2, for each patient, the lowest value during steady state for each of the variables MAP, NI, and rSO_2 was determined. Only between the minimum MAP and the minimum rSO_2 was there a significant correlation ($P = .003$).

4. Discussion

In this study, the preoperative rSO_2 values and the rSO_2 values during the steady state of anesthesia tended to be lower in the delirium group than in the non-delirium group. There was a significant correlation between the preoperative rSO_2 and the preoperative Hb values.

The variance of the rSO_2 during the steady state was significantly greater in the delirium group compared to the non-delirium group; in two patients of the delirium group, the rSO_2 dropped below 50%.

The data published to date on the perioperative NIRS measurement of rSO_2 in relation to the occurrence of PODE mainly relate to cardiac and vascular surgery operations. In contrast, only a few studies have been published that deal with the measurement of perioperative rSO_2 in abdominal surgery.[10]

In this study, preoperative and intraoperative rSO_2 were on average lower in patients with PODE compared to patients without PODE (Table 1).

In 20 patients over 65 years of age undergoing elective abdominal surgery, Morimoto et al[19] observed that the group of patients who developed PODE had a significantly lower mean rSO_2 baseline than the non-delirious group ($60 \pm 5\%$ vs $66 \pm 7\%$). With regard to the rSO_2 values after start of surgery, there were no significant differences between the groups.[19]

In patients undergoing heart surgery, significantly lower preoperative rSO_2 values were observed in the patients who developed delirium postoperatively compared to patients without PODE.[20–22]

In patients who already have low initial rSO_2 values, it is more easily possible that a range of rSO_2 is reached intraoperatively where there is insufficient cerebral oxygen supply and an increased risk of cerebral damage.[20]

Preoperative anemia has been shown to be a risk factor for adverse outcomes and mortality in different surgical specialties, and it is associated with an increased risk of perioperative allogeneic blood transfusion.[23,24] International guidelines provide recommendations regarding preoperative anemia assessment and treatment.[25–27]

In this study, preoperative rSO_2 and preoperative Hb values were significantly correlated. The results of our study regarding the tendency towards a lower preoperative Hb in the delirium group are consistent with observations reported by Hirsch et al[28], who found significantly lower preoperative Hb ($P = .034$) in patients who developed PODE after non-cardiac surgery. Other authors also identified preoperative anemia as a risk factor for delirium after non-cardiac as well as after cardiac surgery.[29–32]

Recently, consensus recommendations from an international conference on the role of perioperative cerebral NIRS were published.[33] With regard to preoperative values, the authors state that they recommend the use of preoperative cerebral oximetry to identify patients at increased risk of adverse outcomes after cardiac surgery.[33] This recommendation does not include non-cardiac surgery. Given the evidence from the smaller study cited above regarding non-cardiac surgery[19] and the observations from this study, it seems appropriate to investigate preoperative rSO_2 in non-cardiac surgery further.

The need for studies in non-cardiac interventions is also evident from the fact that the consensus recommendations state that there is insufficient evidence to recommend using intraoperative cerebral oximetry to improve outcomes after non-cardiac surgery. The authors state that the majority of studies have been conducted in patients undergoing cardiac surgery.[33]

A general statement from the consensus recommendations is that perioperative cerebral oximetry measurements should be interpreted in the context of a pre-induction baseline value.[33] In this study, regarding the duration of a decrease in rSO_2 of >10%, >15% or >20% below the individual preoperative value, there was no significant difference between the delirium group and the non-delirium group. Several studies in patients undergoing cardiac surgery indicate that hyperoxia could be a risk factor for the development of postoperative delirium.[34,35] In the delirium group from our analysis, the mean time with rSO_2 values >10% greater than the preoperative value was longer than in the non-delirium group, but the difference was not significant.

On average, during steady state, rSO_2 values in the delirium group of the current study showed a significantly higher variance than those in the non-delirium group. There was a drop in rSO_2 below 50% in hemodynamically unstable phases in two patients from the delirium group (Figs. 2 and 3). During these phases, there were large fluctuations in the MAP in both cases. Wachtendorf et al[36] observed in a retrospective study comprising 316,717 patients undergoing non-cardiac surgery that a MAP < 55 mm Hg was associated with PODE, contrary to no MAP < 55 mm Hg ($P < .001$). The concept of autoregulation states that the cerebral blood flow can be kept constant by adjusting the cerebral vascular resistance when the systemic blood pressure changes, thus preventing cerebral hypo- and hyperperfusion.[37] The limits of the MAP within which autoregulation is possible are often reported to be 50 or 60 to 150 mm Hg.[37–39] The lower blood pressure limit up to which the autoregulation is effective, however, varies greatly from person to person,[38] and has been observed in the range between 43 and 90 mm Hg.[40–42] Both patients from the delirium group reached a minimum MAP below 50 mm Hg. There could have been a disruption of cerebral autoregulation and, as a result, a reduced supply of oxygen to the brain and a drop in rSO_2. Both patients received norepinephrine during these phases in order to stabilize their blood pressure. The fact that norepinephrine was given could have contributed to the observed decreases in rSO_2. A mechanism that is discussed in literature and that may have played a role here is that sympathetic nerve activity from the superior cervical ganglion increases with a vasopressor-induced increase in MAP; this could have caused cerebral vasoconstriction.[42,43] Furthermore, it cannot be ruled out that norepinephrine affected the NIRS measurements by constriction of extracranial vessels.[44,45]

An adequate supply of oxygen is essential for maintaining undisturbed brain function, which makes a method for noninvasive continuous monitoring of cerebral oxygenation such as NIRS desirable. However, to date there is no consensus on normal values[46] nor on safety margins[47–49] of rSO_2 during anesthesia. In our study, the preoperative rSO_2 values tended to be age-dependent. This implies that normal values and safety margins would have to be defined for different age groups. Clearly defined standard values would be very helpful for a simplified interpretation of the measurement data, and could contribute to improved acceptance of NIRS as monitoring method.[50,51] On the other hand, rSO_2 values are a result of, and need to be interpreted in the complex context of, physiological parameters that contribute to cerebral oxygen delivery and demand.[50,52,53] At present, NIRS devices from different manufacturers can deliver measured values that differ from one another.[46,53,54] It would be desirable if there was a standardization here.

Numerous different factors can lead to the development of delirium.[1] In this study, regional cerebral oxygen saturation was examined. From a previous, already completed, investigation it is known that, in the evaluated data set, the variance of MAP was greater ($P = .04$), the duration of EEG burst suppression or suppression was longer ($P = .03$) and the minimum alveolar concentration of sevoflurane was higher ($P = .03$) in patients with PODE compared to patients without PODE.[13]

5. Limitations

The evaluated data set comprises only 80 patients. Another limitation relates to the NIRS method, which only allows the assessment of oxygen saturation in a small area of the frontal cortex.

6. Conclusions

The results suggest that NIRS could be a useful monitoring method for patients undergoing abdominal surgical procedures, on the one hand to recognize patients with low pre- or intraoperative rSO_2 values, and on the other hand to detect changes in rSO_2 values during anesthesia.

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