

**SEMMELWEIS UNIVERSITY
DOKTORAL COLLEGE**

PhD Thesis

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Cardiovascular Medicine and Research Division

**Cardiovascular Disorders: Physiology and Medicine of Ischemic Circulatory
Diseases**

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1. Introduction

The role of carotid surgery in the prevention of stroke has been well established for a long time. However, the impact of this intervention on cognitive function remains unclear. This issue is of considerable importance, as in our aging society, the preservation—and ideally the improvement—of mental health is crucial for maintaining an independent, balanced, and healthy life.

Decline in cognitive function not only deteriorates an individual's quality of life but also represents a substantial burden on both the patient's social environment and the economy. During carotid surgery, cerebral perfusion changes occurring during arterial clamping may constitute the greatest risk factor for postoperative cognitive decline. Near-infrared spectroscopy (NIRS), by providing information on tissue oxygenation status and its dynamic changes, represents a suitable tool for perfusion monitoring.

Conflicting data are available in the literature regarding the impact of changes in tissue oxygen saturation on cognitive function, and the potentially harmful threshold of oxygenation from a cognitive perspective also remains uncertain. Knowledge of these relationships and critical limits may substantially contribute to establishing optimal intraoperative conditions for patients.

Another major component of my dissertation focuses on risk analysis in patients suffering from one of the most common comorbidities, diabetes mellitus. Diabetes mellitus poses daily challenges to healthcare systems worldwide. Beyond morbidity and mortality data, changes in cognitive function represent a subtle but clinically meaningful endpoint of surgical success. Obtaining an accurate understanding of outcome characteristics in this patient population—regarding morbidity, mortality, and cognitive performance—may contribute to improving the quality of care.

Furthermore, identifying the trends of intraoperative vital parameters associated with this disease may also support the prevention of potential complications and facilitate the delivery of high-quality treatment.

2. Objectives

The results of this research were summarized in two original articles, which are presented and discussed in detail in this dissertation.

In Study A, the impact of intraoperative cerebral tissue oxygenation changes and absolute oxygenation levels monitored by near-infrared spectroscopy (NIRS) during carotid cross-clamping on postoperative cognitive function was analyzed. This investigation also included the assessment of clinical and perioperative factors potentially associated with postoperative cognitive decline or improvement. In addition, the influence of patient age on cerebral oxygenation parameters and cognitive outcome was examined in detail.

In Study B, the effect of one of the most prevalent comorbidities, diabetes mellitus, on perioperative risk and postoperative cognitive changes was evaluated. Furthermore, intraoperative trends and characteristic patterns of vital parameters associated with diabetes were analyzed.

3. Methods

Following approval by the institutional ethics committee (SE RKEB, 17/2019) and registration at ClinicalTrials.gov (NCT03907943), asymptomatic patients undergoing elective carotid surgery between 2019 and 2021 at the Városmajor Heart and Vascular Center of Semmelweis University were prospectively enrolled.

Exclusion criteria included atrial fibrillation, pre-existing dementia (defined as MMSE score < 24), symptomatic carotid stenosis, and lack of informed consent.

Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE). Both tests were administered on the day prior to surgery and repeated three months postoperatively, under the supervision of the same physician (SA- HU710556625-01).

Cognitive change was defined as a difference equal to or exceeding one standard deviation of the preoperative score (MMSE: 1.79, MoCA: 2.28). In addition to cognitive testing, a comprehensive medical history was obtained for all participants.

All patients underwent general anesthesia. For neuromonitoring, near-infrared spectroscopy (NIRS; INVO™ 5100C, Somanetics Corp., Troy, MI, USA) and entropy monitoring (GE

Entropy) were used. Adequate depth of anesthesia was maintained by targeting entropy values between 40 and 60.

Baseline cerebral tissue oxygen saturation (rSO₂) was defined as the median value recorded during the two-minute-long period preceding carotid cross-clamping. The minimum intraoperative rSO₂ value was calculated as the median of the lowest saturation values sustained for at least 30 seconds during cross-clamping. The degree of desaturation was calculated using the following formula:

$$(\text{rSO}_2_{\text{preclamp}} - \text{rSO}_2_{\text{clamp_minimum}}) / \text{rSO}_2_{\text{preclamp}} \times 100$$

4. Results

A total of 129 patients were initially enrolled. Three patients were excluded due to preoperatively diagnosed dementia. Eleven patients were excluded because of insufficient quality of intraoperative monitoring recordings, and another eleven patients failed to attend follow-up examinations. One patient died before the three-month follow-up visit.

Consequently, complete cognitive assessment data were available for 103 patients, of whom 36 had diabetes mellitus.

Baseline cognitive test results were as follows: median preoperative MMSE score was 29 (IQR: 27–29) and MoCA score was 27 (IQR: 26–29). Postoperative MMSE score was 29 (IQR: 28–30) and MoCA score was 27 (IQR: 25–28). Based on our results, cognitive outcome classification was performed using MoCA score changes.

Improvement in cognitive function was observed in 18 patients, cognitive decline in 37 patients, and no relevant cognitive change in 48 patients.

The median of the desaturation during the cross-clamp period (rSO_{2desat}) 14.45% (IQR: 9.85%–23.37%), while the median of the lowest cerebral tissue saturation (rSO_{2low}) value was 59% (IQR: 51%–66%).

Significant correlations were found between the change in MoCA scores and both the degree of desaturation ($R = -0.707$, $p = 0.001$) and the lowest recorded cerebral tissue oxygen saturation ($R = 0.529$, $p = 0.001$).

Receiver operating characteristic analysis identified a desaturation threshold of 15.5% ($p = 0.001$, AUC = 0.876, sensitivity of 86.5%, specificity of 78.8%) and an absolute rSO₂

threshold of 57.5% ($p = 0.001$, AUC = 0.794, sensitivity of 75.7%, specificity of 69.7%) as predictors of postoperative cognitive decline.

In the case of cognitive improvement, we determined 12.65% (AUC = 0.728 $p = 0.002$, sensitivity of 72.2%, specificity of 67.1%, positive predictive value of 31.7%, negative predictive value of 91.9%) and 60.75% (AUC = 0.653, $p = 0.042$, sensitivity of 66.7%, specificity of 61.2%, positive predictive value of 26.7%, negative predictive value of 89.7%) as a threshold with regards to the degree of desaturation and absolute saturation values, respectively.

No significant associations were observed between MMSE score changes and either desaturation ($R = -0.193$, $p = 0.051$) or minimum rSO_2 ($R = -0.070$, $p = 0.483$).

Logistic regression analysis demonstrated that female sex ($p = 0.034$), non–insulin-dependent diabetes mellitus ($p = 0.027$), and intraoperative desaturation during cross-clamping ($p = 0.001$) were independently associated with postoperative cognitive decline. Cognitive improvement was predicted by lower baseline MoCA scores ($p = 0.001$) and smaller degrees of desaturation ($p = 0.046$).

Based on our results, there was a significant connection between the lowest rSO_2 values and the occurrence of long-term complications ($p = 0.009$).

The analysis of the impact of age on rSO_2 values and on the postoperative cognitive performance did not reveal any significant difference between the age groups. The explanation of this finding could be the higher BMI values ($p = 0.030$), higher cholesterol levels ($p = 0.042$), and elevated smoking rates ($p = 0.008$) found among our “younger” patients. These factors might have had a negative influence on the vascular status of these patients.

Based on the presence of diabetes mellitus, we created two groups. We found significantly higher fasting glucose levels ($p = 0.001$) and lower preoperative cholesterol levels ($p = 0.009$) among diabetic patients, while the frequency of intervention due to peripheral arterial disease ($p = 0.017$) and the occurrence of renal insufficiency based on the preoperative creatinine level ($p = 0.012$) were higher in this group.

The median follow-up duration was 37 months (IQR: 30–40.75 months).

Patients with diabetes exhibited greater MoCA score decline at both three-month and one-year follow-ups, and we observed a lower rate of cognitive improvement one year after the surgery. Similar trends were observed in the Memory Index Score (MIS), which is designed to assess the function of memory.

While perioperative complication rates did not differ significantly between groups ($p = 0.087$), long-term cardio- and cerebrovascular complications ($p = 0.04$) and mortality ($p = 0.04$) were significantly higher among diabetic patients.

Diabetic patients demonstrated higher systolic blood pressure values during all surgical phases (preclamping $p = 0.036$, cross-clamping $p < 0.001$, and postclamping $p = 0.034$ periods) and higher mean arterial pressure during the cross-clamp period ($p = 0.001$), which phenomenon can be explained by the significantly higher vasopressor necessity (preclamping $p = 0.005$, cross-clamping $p = 0.003$, and postclamping $p = 0.033$ periods).

Despite these hemodynamic trends, cerebral tissue oxygen saturation values were lower in the diabetes group before cross-clamping (67.4% vs. 74.6%, $p = 0.011$) and during cross-clamping (minimum rSO_2 : 54.4% vs. 60.0%, $p = 0.052$).

5. Conclusion

In this study, we aimed to analyze the connection between cerebral tissue saturation values during the cross-clamp period and postoperative status of cognitive performance in patients undergoing elective carotid endarterectomy.

Our results demonstrated that intraoperative cerebral tissue oxygenation during carotid cross-clamping has a significant impact on postoperative cognitive outcome.

The relative change from baseline proved to have a more determining effect on this outcome than absolute saturation values.

As critical thresholds, we identified desaturation equal or more than 15.5% and absolute value equal or lower than 57.5% with regard to postoperative cognitive decline and 12.65% and 60.75% (desaturation and absolute value, respectively) in the case of postoperative cognitive improvement.

Continuous monitoring of this parameter and timely correction of cerebral desaturation may substantially reduce the risk of postoperative cognitive decline.

Female patients and individuals with non-insulin dependent diabetes mellitus represent particularly vulnerable populations with regard to postoperative cognitive function and therefore require close neuromonitoring strategies during surgery.

No direct association was observed between patient age and cerebral oxygenation or cognitive outcome trends, likely due to the unfavorable cardiovascular risk profiles of our younger patients, raising the possibility of early vascular aging.

The lowest rSO₂ values indicated a significant connection to the occurrence of long-term complications.

Patients with diabetes demonstrated less favorable long-term outcomes, characterized by increased morbidity and mortality rates and a reduced likelihood of postoperative cognitive improvement. Despite higher intraoperative blood pressure values, lower cerebral tissue oxygen saturation levels were observed in this group, emphasizing the need for intensified intraoperative monitoring and individualized hemodynamic management.