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SÁNDOR ÁGNES DÓRA

Szív- és érrendszeri betegségek élettana és klinikuma

című program

Programvezető: Dr. Merkely Béla, egyetemi tanár

Témavezető: Dr. Székely Andrea, egyetemi tanár

ANALYSIS OF THE IMPACT OF CEREBRAL TISSUE SATURATION ON POSTOPERATIVE COGNITIVE FUNCTION AFTER CAROTID ENDARTERECTOMY AND RELATED OUTCOMES ASSOCIATED WITH DIABETES MELLITUS

PhD Thesis

Ágnes Dóra SÁNDOR MD

Doctoral School of Theoretical and Translational Medicine

Semmelweis University

Supervisor:	Andrea Székely MD DSc
Official reviewers:	Nguyen Tin Dat MD PhD Ádám László Balogh MD PhD
Head of the Complex Examination Committee:	István Karádi MD DSc
Members of the Complex Examination Committee:	Henriette Farkas MD DSc Mihály Kovács MD PhD

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List of abbreviations:

AD: Alzheimer's disease

ASA: score: American Society of Anesthesiologists physical status classification

BBB: blood-brain barrier

BMI: body mass index

CCA: common carotid artery

CEA: carotid endarterectomy

C.I.: confidence interval

COPD: chronic obstructive pulmonary disease

CoW: Circle of Willis

DAP: diastolic arterial blood pressure

EEA: eversion endarterectomy

$EtCO_2$: end-tidal carbon dioxide

HDL cholesterol: high-density lipoprotein cholesterol

HR: heart rate

ICA: internal carotid artery

IQR: interquartile range

LDL cholesterol: low-density lipoprotein cholesterol

MAP: mean arterial pressure

MCI: mild cognitive impairment

MIS: Memory Index Score

MMSE: Mini Mental State Examination

MoCA: Montreal Cognitive Assessment

NASCET: The North American Symptomatic Carotid Endarterectomy Trial

NCCF group: patients with no change in postoperative cognitive status proven by the MoCA

NIDDM: non-insulin dependent diabetes mellitus

NIRS: near-infrared spectroscopy

OR: odds ratio

PAD: peripheral arterial disease

PNCD: perioperative neurocognitive disorder

PNCD group: patients with postoperative cognitive decline confirmed by the MoCA

POCI: postoperative cognitive improvement

POCI group: patients with postoperative cognitive improvement confirmed by the MoCA

PWV: pulse wave velocity

ROC curve: receiver operating characteristic curve

rSO_2: regional cerebral oxygen saturation

rSO_{2desat}: median of the degree of regional cerebral oxygen saturation desaturation

rSO_{2low}: lowest rSO_2 values during clamping period

SAP: systolic arterial blood pressure

SD: standard deviation

TEA: thromboendarterectomy

Vascular-POSSUM: Vascular-Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity

1. Introduction

In this doctoral thesis, the connection between cerebral tissue saturation monitored by NIRS during carotid endarterectomy and postoperative changes of cognitive function is analyzed. As intact cognition is essential to the state of well-being and an independent life, this topic has utmost importance. Besides this, we investigated trends in postoperative cognitive changes, postoperative outcomes, intraoperative hemodynamic and cerebral alterations characteristic of the most frequent comorbidity, diabetes mellitus.

1.1. Carotid endarterectomy (CEA)

Atherosclerotic carotid artery disease significantly increases the risk of cerebrovascular disease and stroke, primarily through the embolization of atheromatous material or thrombotic occlusion. It accounts for approximately 20–25% of all ischemic stroke events. (1) (2)

Carotid endarterectomy (CEA) is a preventive surgical intervention designed to reduce the risk of stroke and improve patients' overall health and quality of life. Surgical treatment in individuals with moderate to severe carotid artery disease has been demonstrated to reduce stroke incidence and improve long-term survival markedly. The procedure involves removing atherosclerotic plaque from the common and/or internal carotid artery, thereby enhancing cerebral blood flow and eliminating potential sources of emboli. (2) (3)

The first CEA procedure was reported at St. Mary's Hospital in London in 1954. Since the 1970s, CEA has been widely accepted as the preferred treatment option for patients with high-grade carotid artery stenosis. (2) (3)

Current clinical guidelines base the indication for carotid revascularization therapy on the degree of carotid artery stenosis. (3) ICA/CCA stenosis can be defined using two widely accepted methods derived from large multicenter clinical trials. In both methods, the numerator is the minimal residual lumen diameter at the site of stenosis. According to the European Carotid Surgery Trial (ECST) definition, this is compared to the original vessel diameter at the same level. In contrast, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) definition compares the narrowest lumen to the

diameter of the distal, healthy ICA segment. (3) Hungarian national guidelines currently recommend endarterectomy if asymptomatic ICA stenosis exceeds 70%.

The only absolute contraindication for CEA is asymptomatic complete carotid occlusion. (2) Asymptomatic carotid atherosclerotic disease refers to the presence of carotid atherosclerosis in individuals with no history of ipsilateral ischemic stroke or transient ischemic attack (TIA) within the preceding six months. (2) In contrast, symptomatic carotid stenosis typically indicates stenosis greater than 50% accompanied by neurological symptoms within the last six months in the vascular territory supplied by the affected carotid artery (middle cerebral artery). Symptoms may include contralateral monoparesis or hemiparesis, hemisensory abnormalities (paresthesia), dysarthria, dysphagia, aphasia, ipsilateral amaurosis fugax, or blindness. (2)

Screening can be performed using carotid duplex ultrasonography (CDU), which allows for assessment of the degree of stenosis. (2) According to Poiseuille's Law, the severity of stenosis correlates with flow velocity—the narrower the lumen, the higher the flow velocity through the stenotic segment. Additional screening modalities include computed tomography angiography (CTA) and contrast-enhanced magnetic resonance angiography (CE-MRA). (1) (2) These imaging techniques provide complementary information on plaque morphology, intracranial collateralization, and cerebral perfusion. Combining CTA or CE-MRA with CDU facilitates comprehensive risk assessment when considering surgical intervention. (2)

Two main open surgical techniques are employed: conventional endarterectomy and eversion endarterectomy. (3) Following careful surgical exposure, the external, internal, and common carotid arteries are cross-clamped to isolate the carotid bifurcation from circulation. The artery is opened, and the plaque is meticulously removed. Typically, a longitudinal incision is used, and the artery is patched upon closure to reduce the likelihood of restenosis. In eversion endarterectomy, the internal carotid artery is transected and turned inside out to extract the plaque. Regardless of the technique, it is essential to ensure complete removal of intimal debris to prevent postoperative embolization. (3)

The two most significant perioperative complications associated with CEA are cerebrovascular accident and myocardial infarction. Other potential complications include cranial nerve injury, bleeding, airway swelling, and edema. (2) (3)

CEA is a well-established, evidence-based prophylactic surgical procedure that can substantially reduce the incidence of stroke in high-risk patients. The procedure is beneficial only when the surgical risks are lower than those of conservative medical therapy. Anesthetists play a crucial role in minimizing perioperative risks and optimizing patient outcomes during CEA.

1.2. Cognitive function

"Cognition modifies the knower so as to adapt him harmoniously to his acquired knowledge." This quote from Ludwik Fleck describes the essence as well as the relevance of cognition. The intactness of cognitive function is the basis of a healthy, happy, independent, and productive life.

Human cognition can be compared to a lens through which we understand everything in the world around us. This simile implies that mental health is essential to cope with everyday difficulties, to make proper decisions, to build relationships, and to make relevant contributions to the community around us. In summary, it is crucial to overall well-being, as unimpaired cognition is an indispensable foundation for a fulfilling life.

It is evident that preserving intact cognition has highlighted importance.

The deleterious consequences of impaired cognition affect many different areas of daily life, not to mention that it has a determining impact on morbidity and mortality. (4) (5) (6) (7) In a study evaluating the 5-year mortality risk among elderly women, cognitive deficit was associated with increased mortality, even after adjusting for mobility and conventional risk factors (8) In a similar population, poor cognition proved to be an independent predictor of higher inpatient health care utilization. (9)

It may influence even functional status, as a study found a significant connection between cognitive deficit and disability in hospitalized patients. (10) This impact was strengthened by other studies, which came to similar conclusions, examining the effect of cognitive performance and comorbidities on instrumental activity of daily living: the previous had a stronger negative impact on daily activities. (11) (12) Falls are a major problem in the elderly population, leading to higher health care utilization and/ or disability, mortality, and morbidity. The risk of falls is decidedly increased in the case of cognitive impairment. (13) Cognitive impairment has a determining role in the formation of self-neglect

syndrome. (14) Poor performance on MMSE proved to be a risk factor for harm in cognitively impaired seniors. (15)

Beyond everyday difficulties, the financial consequences of the disease have substantial relevance regarding both the lives of the affected families and the economy. (16) (17) A few years ago, not less than 500.000 people in the UK were affected by dementia, which meant a considerable socioeconomic burden, exceeding even the expenditures of heart diseases, cancer, and stroke combined. (18) Even mild cognitive impairment is associated with higher medical costs and resource use, which means more frequent physician visits, hospitalizations, longer hospital stays, and the need for home health services. (16) (19) (20) (21) (22) (23)

In addition to higher medical expenditures, this population is characterized by lower income. (16) As these cognitive disabilities are accompanied by a huge financial burden, preventing or at least delaying their onset would mean a significant cost saving. (24) (25)

From these facts, it is evident that preventing cognitive decline is not only the interest of an individual, but also the whole society.

1.2.1. Cognitive changes after surgical interventions

The phenomenon of postoperative neurocognitive disorder was first published in the British Medical Journal in 1887. (26) Since then, many trials paid attention to this incident, searching for the provoking factors. By definition, pNCD indicates a mild neurological disorder, a decline in neurocognitive function following surgical procedures, denoting a complication of the intervention. Social skills, memory, orientation, attention, and language fluency may be affected. (27) (28)

The new definition differentiates between delayed neurocognitive recovery (dNCR) if it occurs within 30 days after the intervention, and postoperative neurocognitive disorder (pNCD) if it is present within 1 year after the surgery. (26) (29)

Based on a recently published review, the incidence of postoperative cognitive dysfunction ranges from 2.2% to 31.5% following non-cardiac surgery and 11.8%-35.7% after cardiac surgeries. (30) Analyzing these rates with regard to the postoperative time, cognitive dysfunction 7 days after the surgery was present in 25.8% of the patients undergoing non-cardiac surgery under general anesthesia, while it decreased to 9.9 % at three months after the intervention. (31) Though these data of occurrence were registered

before the turn of the millenium, they are in accordance with the results of a recent publications. (28) (32)

The etiology of PNCD is multifactorial; nowadays the role of immune mechanisms is emphasized. Based on the results of the most recent trials, the key pathological element in this morbidity is neuroinflammation induced by surgical trauma. Due to the impact of the intervention, the immune system is activated in a nuclear factor-κβ (NF-κβ)- dependent manner. (33) This leads to the release of several pro-inflammatory mediators, like TNFα, IL-1β, IL-6, IL-17A, causing not only neuroinflammation, but also neuronal apoptosis. As a result of their action, the blood-brain barrier (BBB) gets compromised, and monocyte-derived macrophage migration is amplified. The levels of tight junction proteins, like claudin, occludin, ZO-1 drops, which may be linked to the effect of IL-6 and mast cells in a yet not clearly understood way. It has been shown that by upregulating MMP-2 and MMP-9, it may contribute to the damage of the integrity of BBB. (33) (34) (35)

Due to the effect of pro-inflammatory cytokines, inactivated microglia get activated, transform to a phagocytic state, and increase the production of reactive oxygen species (ROS). Astrocytes may produce amyloid proteins, thus contributing to the neuronal damage. (33) (36) Neuroinflammation downregulates brain-derived neurotrophic factor (BDNF) and its receptor TrkB, which are important elements of neurogenesis, synaptogenesis, regulating neuronal plasticity, learning, and memory. (33) (36)

The level of danger-associated molecular patterns (DAMPs) increases. They adhere to those pattern recognition receptors (PRRs), which are present in the BBB endothelium. Interaction between the DAMPs and their receptors generates further recruitment of pro-inflammatory pathways, strengthening microglial activation and the migration of macrophages into the brain. (33)

Besides these pathological actions, the role of hemodynamic, pharmacologic, hematological, and frailty factors and the role of intra- and postoperative complications have arisen over the decades of investigation.

In a 1955 published article, the role of premedications, potent analgesic and narcotic drugs, blood pressure, and haemoglobin concentration was highlighted as risk factors for postoperative cognitive decline. (37)

More than three decades later, an international, multicentre study, the ISPOCD-1 study, found that early POCD was associated with increasing age, low education, postoperative infections or respiratory complications, and the duration of anesthesia, and only age proved to be a risk factor for late POCD. (31)

The role of low education, presented as low preoperative MMSE scores and the duration of anesthesia, was strengthened by another trial in the development of PNCD. (38)

As major surgeries are always accompanied by anesthesia, the impact or the contribution of this profession to the development of postoperative cognitive dysfunction was the subject of several trials, mentioned hereinafter.

From the anesthesiological side, the effect of the anesthetic agent arose first. (39) Trials comparing the type of anesthesia – general anesthesia vs. non-general anesthesia have shown insufficient data to recommend regional techniques as a suitable method to prevent PNCD. (40)

There are controversial data in the literature on whether the depth of anesthesia has an impact on PNCD. (41) (42) (43) (44) (45)

In a trial comparing light and deep anesthesia in patients undergoing total knee replacement, patients with lower BIS values had lower scores in the MoCA in the immediate postoperative period; however, this difference disappeared on the later cognitive assessments. (46.)

Another research group has come to the same conclusion, finding no connection between the depth of anesthesia and the occurrence of cognitive decline one month after the surgery. (42) (47)

Though its significance with regard to postoperative cognitive function is uncertain, in 2018, EEG-based depth of anesthesia monitoring was among the recommendations of the Fifth International Perioperative Neurotoxicity Working Group for improving perioperative brain health. (48)

1.2.2. Cognitive changes after carotid surgery

Carotid endarterectomy is a reliable method for stroke prevention. (1) (49) Theoretically, removal of a plaque, so eliminating the potential source of emboli and the reason for hypoperfusion, should improve cognitive performance, but at least preserve

the existing cognitive skills; however, the clinical practice does not show this tendency in every case. (50) (51)

This discrepancy may be explained by the presence of both anesthesiological and surgical factors.

Regarding the surgical site, the disturbances of cerebral perfusion may have the most substantial role in the postoperative change of cognitive function. (52)

Postoperative cerebral hyperperfusion is a rare complication after the surgery, but as it may have serious consequences, its relevance cannot be disregarded. (53) It may have an adverse long-term impact on the postoperative change of cognitive function. (54)

On the other hand, cerebral hypoperfusion has great relevance during this type of surgery. As cerebral hypoperfusion is associated with ischemia, it has crucial importance to prevent its development. (55) (56)

The occurrence of cerebral hypoperfusion is most likely during the cross-clamp period of the surgery. The relevance of this part of the surgery has been shown in a meta-analysis, which found that the duration of the cross-clamping period has an impact on the postoperative changes in cognitive function. (52)

The role of cerebral hypoperfusion has been demonstrated by several studies in other fields of medicine. Cerebral blood flow measured by ^{131}Xe clearance was associated with postoperative cognitive performance. (56) Those who had the greatest drop in cerebral blood flow during coronary artery bypass showed the greatest decrease on the postoperative cognitive test.

NIRS is a validated technique to monitor perfusion by continuously tracking cerebral oxygen saturation (rSO2). (57) (58) (59)

Cerebral oxygen saturation and desaturation, as markers of cerebral perfusion, have been linked to postoperative neurocognitive complications, like delirium and cognitive changes. (60) (61) (62)

Avoiding hypotension, so aiming to maintain adequate cerebral perfusion, has highlighted significance in this field of medicine. (63) Adequate blood pressure management, neuromonitoring, if necessary, shunt insertion may help reduce this negative impact, by improving perfusion. (63)

As anesthesia-related risk factors, some of the drugs, relative hypotension, absence of normothermia, and the lack of monitoring the depth of anesthesia, so not accurate titration of anesthetics, may be mentioned. (63)

Referring to the type of anesthetic technique, the conclusions from the trials are not in absolute accordance. Although many of the studies and meta-analyses demonstrated the superiority of locoregional techniques regarding mortality and postoperative complications, like stroke and TIA, the results are premature to come to a conclusion. (64) (65) (66) (67) With regards to the postoperative cognitive function, the majority of clinical trials have not found difference referring to this outcome between the two techniques. (68)

Final conclusion from the recent literature is that the choice of anesthetic techniques should depend on the preferences of the medical team, considering the patients' condition and the equipment of the hospital. (66) (67)

1.2.3. Cognitive Assessment Tools

As in the early phases cognitive impairment may have treatable components, prompt detection has a highlighted importance. (69) (70) The heterogeneity of the disease and the possibility of the presence of influencing factors may make the diagnosis challenging. (70)

Ideally, comprehensive cognitive tests should be reliable, user friendly, able to assess most of the cognitive domains, should not take too much time to complete, and their result should be easy to interpret.

Various neuropsychological tests have been developed to assess cognitive changes, and all of them have their own advantages and disadvantages. MMSE and MoCA are frequently used screening tools as well as in clinical practice and in research.

MMSE was introduced in 1975. (71) (72) Originally, it was designed for psychiatric patients, aiming to discriminate between organic and functional disorders. (71) Since then, it has been the most widely used instrument for the evaluation of cognitive function worldwide and is used as a general cognitive screening tool for various patients in various settings. (72)

It is an 11- item, 30-point brief questionnaire, assessing cognitive domains of orientation, memory, attention, visuospatial skills, and language. (73)
The cut-off score for determining cognitive deficit is 24 points. (74)
It has limited ability for assessing executive functions and has been criticized for ceiling and floor effects. (70) (74) Although, MMSE has been proven to be capable of detecting Alzheimer's disease, it showed low sensitivity for mild impairment. (75)
Mild cognitive impairment (MCI) covers those cognitive declines, which are more severe than expected for one's age and education, but do not interfere with everyday activities. (75) The explanation of this limitation is that MMSE focuses on language-related abilities, which are seldom the first signs of cognitive impairment. (76)

The MoCA test was designed to detect mild changes in cognitive function. It was introduced in 1995 by Dr. Ziad Nasreddine. It is a 30-point survey, assessing a broad spectrum of cognitive domains, like short-term memory, visuospatial abilities, executive functioning, attention, concentration, working memory, language, and orientation to time and place. (71) (76)
Due to its additional aim for evaluating visuospatial skills, executive function, attention, calculation, and delayed memory more accurately, and since it is less focused on verbal ability, it proved to be more sensitive for mild changes of cognitive function. (76)
The cut-off value is 26 points to filter out those who have cognitive decline. (76)
The average score for mild impairment is 22, which ranges between 19 and 25 points. (77) To moderate the influencing effect of education, one point is added to the total score if the patient did not complete 12 years of education. (71)
Interpreting the results requires specific training. (70) (77)

A subscore of the MoCA is MIS, the memory index score. It is a recall task, embedded in the MoCA test. Free and cued recall is evaluated in this part of the test, which is typically affected in early stages of AD. (78)
Based on the MIS score, amnestic mild cognitive impairment can be differentiated from normal cognition, and its newfound decline may be a predictor of conversion to Alzheimer's disease. (78) (79) The threshold is 7 points from the maximum 15 points, but this result should be interpreted together with the total score of the MoCA test. (79)

1.3. Neuromonitoring

Carotid endarterectomy is an effective way to treat significant carotid artery stenosis, so preventing future stroke. (1) (49) As cross-clamping of the three branches of the carotid artery leads to perfusion changes intraoperatively, hypoperfusion may cause neurophysiologic dysfunction, potentially cell death, leading to the deterioration of postoperative neurocognitive condition. (80) Therefore, cerebral monitoring has a great relevance during the operation, with its primary aim is detecting ischemia, especially during the cross-clamp period. (80) Intraoperative neuromonitoring may detect a critical degree of ischemia, guiding surgeons and anesthesiologists to take measures to improve it.

Cerebral neurophysiology can be observed using electroencephalography, evoked potentials, transcranial Doppler ultrasonography, and near-infrared spectroscopy. (80) (81)

EEG has been widely used during carotid surgeries to detect changes in cortical electrical activity that may indicate cerebral ischemia, so guiding shunt placement. (80.) EEG provides a continuous, real-time assessment of brain function, and it has been criticized for the low sensitivity for detecting ischemia in the subcortical regions and the potential impact of anesthesiological drugs on the EEG changes. (80.) (82.)

A processed EEG signal, the bispectral index (BIS) is used for monitoring the depth of anesthesia. A sudden drop of BIS values during the cross-clamp period may indicate ischemia. (80)

Somatosensory evoked potential (SSEP) assesses the functional integrity of the sensory pathways by stimulating peripheral nerves, typically the median nerve, and recording responses from the somatosensory cortex. (80) Significant changes in the waveforms, a decrease in the amplitude or an increase in the latency may indicate compromised cerebral perfusion. (83) These changes proved to be predictors for the occurrence of perioperative stroke following carotid surgeries. (83)

Transcranial Doppler Monitoring (TCD) provides real-time information on cerebral hemodynamics. It uses ultrasound to evaluate cerebral blood flow in the major intracranial arteries, most frequently in the middle cerebral artery. (80) (81) Sudden changes in the flow or the appearance of microembolic signals indicate potential complications. (82)

Limitations of the technique are the absence of an acoustic window in approximately 10-20% of the patients and that its implementation requires experience. The assay may impede the operator, as the investigated area is relatively near to the surgical site. (82)

Monitoring stump pressure reflects collateral cerebral perfusion via the Circle of Willis (CoW), measuring arterial pressure distal to the carotid cross-clamp. Low stump pressure values (lower than 40-50 mmHg) indicate insufficient perfusion and suggest the need for shunt insertion in order to maintain cerebral circulation. (80) (82) As it means a single measurement, for a more comprehensive assessment it is usually used along with other neuromonitoring techniques.

Surgery under regional anesthesia allows for a continuous neurological assessment during the whole procedure. Verbal contact, checks of the orientation and the ability to perform basic cognitive tasks and demonstrating movements enable direct and real-time neurological monitoring. (80) Disadvantages of the regional anesthesia are the stress patients have to experience and the challenging airway access. (80)

The contribution of operated patients to the monitoring has great relevance, as awake patients under regional anesthesia are the most sensitive and specific method to detect a critical degree of ischemia. (80) (84)

In our trial, we used near-infrared spectroscopy to monitor cerebral perfusion and an Entropy monitor for tracking the depth of anesthesia.

NIRS is a non-invasive monitoring tool, which allows for continuous and real-time tracking of organ oxygenization. (85)

It is an optical technique that applies the principles of optical spectrophotometry, using near-infrared light (700-1400 nm). It is based on the different absorption spectra of the chromophores, which makes their separation possible. (86) Emitted light is absorbed to varying degrees by chromophores (deoxy- and oxyhemoglobin, bilirubin, cytochrome C oxidase), so their concentration can be defined using the modified Beer-Lambert law. (86) The different absorption spectra of these chromophores allow for their differentiation. (86) (87) The absorption spectra of oxyhemoglobin and deoxyhemoglobin are maximally separated between 700 and 850 nm. (87) To this NIR light, skin, bones, and connective tissues, the superficial layers are mostly transparent. (86)

As NIRS is a user-friendly device, the data are easy to interpret, and it has been accepted in several fields of medicine. It is a reliable way of neuromonitoring during cardiac,

thoracic, neurovascular, and orthopedic surgery, but it is often used for monitoring tissue oxygenization in septic patients. (88) (89) (90) (91) (92) (93) (94) (95)

NIRS is a frequently used diagnostic tool in neonatal care. It serves not only as a neuromonitor, but it has also been proven reliable for the early diagnosis of NEC. (96) (97) (98) (99)

Monitoring the depth of anesthesia allows the anesthesiologist to maintain the most adequate level of anesthesia. These monitors may operate based on EEG or evoked response analysis. (100) (101) The Entropy monitor belongs to the former group, measuring wave irregularity. (102) Although EEG changes associated with deepening the level of anesthesia have been studied in detail, broadly speaking, the electrical activity's amplitude increases while its frequency decreases, forming a more regular pattern. (100) (103)

Analyzing EEG waves alone only measures the hypnotic effects of drugs and does not provide insight into the potential arousal effects of sudden pain. Entropy monitoring complements EEG-based monitoring with EMG monitoring, which reflects muscle responses to pain, thereby providing information on the degree of the analgesic effect. The EMG signals are obtained from the frontalis muscle (FEMG), which shows activity even with a mild reduction in muscle relaxant effect. EEG and FEMG signals are processed using frequency spectrum analysis and a Fourier transform-based algorithm, resulting in two values that accurately reflect the depth of anesthesia. (101) (104)

The two parameters are "State Entropy (SE)" and "Response Entropy (RE)." (102)

"State Entropy" is derived from EEG signal processing and reflects the hypnotic effect of the administered drugs. SE is the slower-varying component, with a measurement range of 0.8 Hz to 32 Hz. (105)

The "Response Entropy" component is based on EMG signal processing. It is characterized by a fast response time (<2 seconds) and also provides information about muscle responses to external painful stimuli. Its measurement range is slightly higher, from 0.8 Hz to 47 Hz. (105)

State Entropy values range from 0 to 91, and they are equal to or lower than Response Entropy values, which range from 0 to 100. (102) (105)

During surgery, appropriate anesthesia depth corresponds to values between 40 and 60. Lower values indicate overly deep anesthesia, while higher values suggest an increased likelihood of awakening. (102)
An increasing difference (>10) between the two values indicates muscle activity and may be an early sign of arousal. (103)
Its use improves patient safety and helps tailor drug titration to individual needs. (106) (107)

In summary, so far, studies comparing the effectiveness of monitoring techniques to identify the most accurate method for evaluating cerebral perfusion, have not resulted in an obvious answer. The chosen technique should be based on the expertise and preference of the medical team, considering institutional equipment. (80) (82)

1.4. Diabetes mellitus

The prevalence of diabetes has quadrupled in the previous 20 years, from 151 million in 2000 to 537 million in 2021. Without intervention, this number will not stop increasing, which outlines a huge medical and financial burden globally. (108) (109)
As it is a systemic disease, almost all organ systems may be affected, so cerebral function and cognition, too.

The pathophysiology of cognitive impairment in diabetes is complex, neuroinflammation, insulin resistance in the brain, impaired iron metabolism, and accumulation of tau protein may all play a role in the formation of cognitive deficit. (110)
This topic is explained in Discussion B in detail.
From the cognitive domains, attention, visuoconstruction, mental flexibility, psychomotor efficiency, and information processing are the most affected areas in patients with T1DM, while executive function, memory, and psychomotor speed are predominantly involved in T2DM patients. (108)
Among others, the risk factors for cognitive impairment include age, the duration of diabetes, poor glycemic control, unhealthy diet, dyslipidemia, uncontrolled hypertension, and physical inactivity. (111)

Though the prognosis of dementia in a diabetic patient depends to a large extent on the pathology of the disorder leading to cognitive impairment, from this listing it is clear that there are many factors that can be influenced. Optimal diabetes management, management of comorbidities, proper lifestyle and diet may improve outcomes. (111) This implies the significance of careful preparation and medical check-up preoperatively and raises the importance of the optimization of intraoperative hemodynamic parameters, the conscious management of anesthesia in preventing complications. (112) (113) (114) So knowing precisely the predisposing risk factors for postoperative morbidity and mortality and the trends of intraoperative hemodynamic changes characteristic of diabetes could improve outcomes.

As the number of patients affected by these comorbidities is growing, the importance of this knowledge cannot be disregarded.

2. Objectives

2.1. The connection between postoperative cognitive changes and cerebral regional tissue saturation during the cross-clamp period (Study A)

In this study, we focused on the cognitive consequences of regional cerebral tissue saturation values and their changes during the cross-clamp period. The primary endpoint was the postoperative change of cognitive status.

The hypotheses and aims were as follows:

A/1. There is a connection between cerebral tissue saturation measured during the cross-clamp period and the postoperative alteration of cognitive function.

A/2.1. The change of rSO_2 during the cross-clamp period has a more determining role in the formation of cognitive changes than absolute rSO_2 values have.

A/2.2. Determining the thresholds of rSO_2 values and their changes for definitive alterations of cognitive status

A/3. Pre- and intraoperative factors and comorbidities may be associated with postoperative cognitive changes.

A/4. Age has a negative impact on postoperative cognitive outcome.

A/5. Lower absolute cerebral tissue saturation values and major desaturation are correlated with worse postoperative survival and higher rates of complications.

2.2. The comparison of diabetic and nondiabetic patients in relation to postoperative cognitive changes and survival (Study B)

The difference in postoperative outcomes between diabetic and nondiabetic patients was the focus during this part of the study. The primary endpoint was the comparison of postoperative cognitive changes in the two groups; the secondary endpoint was the analysis of survival in the two groups. Besides these, we evaluated the intraoperative physiological changes characteristic of diabetic patients.

The aims and hypotheses were as follows:

B/1. Diabetic patients are at risk for worse postoperative cognitive performance.

B/2. Diabetic patients experience worse outcomes in a long-term follow-up.

B/3. Diabetic patients are more vulnerable during carotid surgeries.

3. Methods

3.1. Study design and participants

This thesis presents a single-center, prospective, observational clinical research. Following the approval of the Ethics Committee of Semmelweis University (Semmelweis University Regional and Institutional Committee of Science and Research Ethics, 17/2019, 02/15/2019) and registration on ClinicalTrials.gov (NCT03907943), patients scheduled for elective carotid endarterectomy at Városmajor Heart and Vascular Center, Semmelweis University in Budapest were recruited for the study. All participants received detailed information and subsequently provided written informed consent.

Between May 2019 and November 2021 (05/13/2019 – 11/04/2021), 129 patients were enrolled. All patients were asymptomatic, with carotid stenosis greater than 70%, as determined by the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria. The type of procedure (eversion endarterectomy – EEA or thromboendarterectomy – TEA), as well as the decision to use a shunt, was at the discretion of the operating surgeons.

Exclusion criteria included symptomatic carotid stenosis, atrial fibrillation, pre-existing dementia (preoperative MMSE score below 24), and absence of consent.

Three individuals were excluded due to MMSE scores below 24 and were not subjected to further testing. In 11 cases, complete anesthesiological monitoring, including NIRS, could not be accurately recorded. One patient passed away from SARS-COVID pneumonia before the first follow-up, and 11 others did not attend the follow-up visit, the three-month postoperative assessment, leaving cognitive data for 103 patients. As their data were missing at random, there was no selection bias, so they were excluded from further analysis.

Out of these 103 patients, comprehensive hemodynamic and cerebral monitoring data were successfully obtained for 76 patients.

A flowchart detailing enrollment and follow-up procedures is presented in Figure 1.

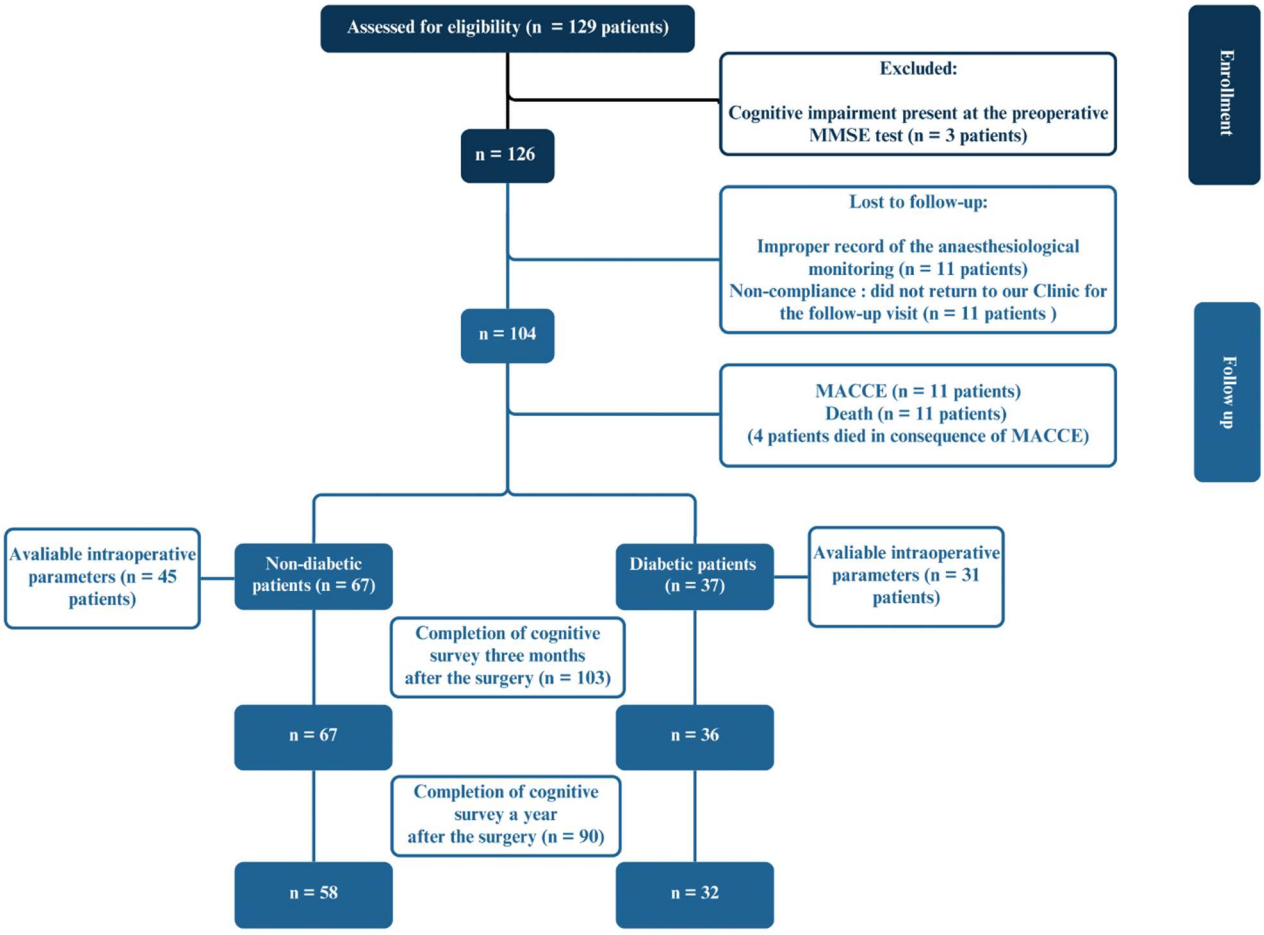

Figure 1. Consort flow diagram of the enrollment and follow-up

Patients were followed up for two years, and the follow-up period ended in November 2023.

In addition to intraoperative vital parameters, the occurrence of adverse cardio- and cerebrovascular events were registered both in the perioperative and during the follow-up period, defined as myocardial infarction, new onset of arrhythmia, hemodynamic instability, cardiac failure, cardiac arrest, death due to cardiac causes, pulmonary embolism, intracerebral hemorrhage, TIA (transient ischemic attack), or stroke.

During the process of data analysis, patients were divided into two groups based on the presence of diabetes mellitus. To define diabetes, we used the definition established by the WHO. (115)

The management of antidiabetic medications and blood glucose controls happened according to the guidelines of the Academy of Medical Royal Colleges. (116)
For predicting postoperative outcomes, we used a recently published score by Blecha. (117) The score was designed using the data of patients with symptomatic carotid stenosis and applied those factors that had a significant association with mortality, weighted based on their beta coefficients.

3.1.1. Study settings

In this work, the findings of two original articles are presented. The research settings and results described in the articles are marked with A and B, as follows:

A: The impact of regional cerebral tissue saturation values on the change of postoperative cognitive function

B: The difference between diabetic and non-diabetic patients regarding the postoperative change of cognitive function, survival rates, and intraoperative physiological change

3.2. Intraoperative management

All patients received general anesthesia using the GE Aisys CS2 system. Induction was achieved with propofol and fentanyl, and anesthesia was maintained with either sevoflurane or isoflurane. Target MAC values ranged from 1.4 to 1.9 for sevoflurane and 0.9 to 1.2 for isoflurane, and values were strictly maintained within these ranges. Atracurium or rocuronium was administered to achieve muscle relaxation.
Following intubation, patients were ventilated with 40–50% oxygen, and end-tidal CO_2 was kept between 33–40 mmHg.
Standard monitoring (ECG, intra-arterial blood pressure, pulse oximetry, capnography) was supplemented with near-infrared spectroscopy (NIRS) and Entropy monitor. Cerebral oxygenation was continuously monitored using the INVOS^{TM} 5100 C oximeter (Somanetics Corp., Troy, MI, USA) throughout the surgery. The sampling frequency was 0.166 Hz. The Somanetics INVOS^{TM} 5100c cerebral/somatic oximeter, uses near-infrared light at two wavelengths: 730 and 810 nanometers. (88) (89)

Desaturation during clamping was assessed using the median rSO_2 value over two minutes before clamping as the baseline, as in this period, we managed to provide similar conditions for the patients. The lowest saturation was determined as the median over the lowest 30-second period during the clamping period.

The percentage reduction from baseline was calculated using: $(rSO_{2preclamp} - rSO_{2lowestclamp}) / rSO_{2preclamp} \times 100$.

The depth of anesthesia was monitored with a GE Entropy monitor, aiming to keep entropy values between 40–60. (43)

Patients' foreheads were cleaned with alcohol pads before neuromonitoring sensors were attached. The neuromonitors we used are demonstrated in Figure 2.

Hemodynamic stability was prioritized, maintaining MAP within ±20% of the preoperative baseline. During clamping, MAP was kept at +0–20% of the baseline.

To prevent hypotension, norepinephrine was administered at 0.03 µg/kg/min, with adjustments in 0.02 µg/kg/min increments.

Lidocaine infiltration was used locally in cases of bradycardia tendency.

All patients received 100 IU/kg of heparin prior to internal carotid artery (ICA) clamping, which was reversed with protamine after the procedure.

The surgery was divided into three phases for trend analysis of monitored vital parameters: preclamping period, clamping period, and postclamping period.

The preclamping phase began after intubation and ended with common carotid artery (CCA) clamping.

The clamping phase covered CCA and ICA occlusion till the complete removal of the clamp.

The postclamping phase extended from clamp removal to extubation.

Monitoring data were saved as .asc and Excel files. Surgical and anesthetic interventions were carefully documented in these files.

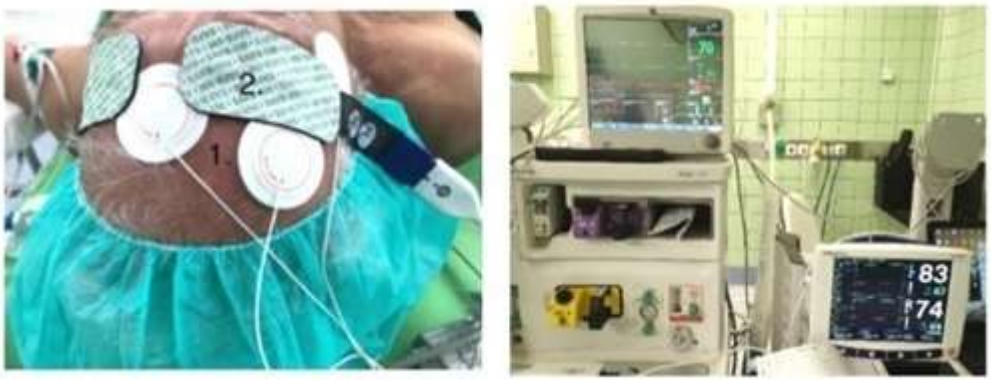

Figure 2. Neuromonitors (NIRS and Entropy monitor) we applied during our study

(In the left panel, the sensors of the Entropy monitor (round, white; 1.) and the sensors of the NIRS monitor (2) are shown. The right panel displays the monitors: the NIRS (INVOS™ 5100 C) monitor is positioned in the right bottom, while the GE monitor can be seen in the upper left corner.)

3.3. Cognitive evaluation

For the assessment of cognitive function, we used the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) tests. Testing was scheduled a day before surgery and three months and a year after it. The completion of the tests was carried out by the same physician (SA- HU710556625-01).

The examination started with MMSE, in order to filter out those who suffered from dementia. Patients who were not able to reach 24 points on the MMSE were excluded. (118) Besides the well-known ability of the MoCA test for detecting subtle changes in cognitive function, which has been proven in several studies, we found a strong correlation between cerebral tissue desaturation and the change of the MoCA test, so we based our calculations on these outcomes in order to determine the definitive changes of cognitive function.

Postoperative cognitive change was considered if the results of the postoperative tests differed from the preoperative scores with a minimum of the standard deviation of the results of the preoperative tests or more (MMSE: 1.79, MoCA: 2.28). (119)

3.4. Statistical analysis

For statistical analysis and for the figures, SPSS software (IBM SPSS Statistics Version 20) and GraphPAD Prism (GraphPAD Prism version 10.0.0., Boston, Massachusetts, USA) were used.

The distribution of data was determined by the Kolmogorov-Smirnov test. According to these results, data were presented as mean and standard deviation in the case of normal distribution and as median and interquartile range in the case of non-normal distribution. Categorical variables were presented as numbers and percentages.

We used the Mann-Whitney U test for comparing groups when the data were non-normally distributed and the Student T-test when the data were normally distributed.

Discrete data were compared using Pearson's chi-squared test, whereas a low number of cases were analyzed using Fisher's exact test. In case of more than two groups, we used the Kruskal-Wallis test for comparison.

The correlation between the rSO_2 values, the degree of desaturation during the cross-clamp period, and the change in the scores of the cognitive test was evaluated with Spearman correlation analysis.

The optimal cutoff for rSO_2 decrease for the detection of intraoperative hypoperfusion causing changes in cognitive performance was analyzed by receiver operating characteristic (ROC) curves.

Linear regression analyses were used to determine the associations between pre- and intraoperative factors and postoperative MoCA changes.

Cox regression analysis was used to determine the association between pre- and intraoperative factors and postoperative complications. All of the risk factors with a p value less than or equal to 0.1 were entered into the multivariable logistic regression model. Kaplan-Meier analysis and log-rank test were used to compare the survival between the investigated groups. A p-value of < 0.05 was considered statistically significant.

3.5. Outcome variables

Cognitive changes represented the primary outcome of the study; the secondary outcome involved the occurrence of major adverse cardiovascular and cerebrovascular events and mortality. In a further analysis, the intraoperative changes of vital parameters characteristic of diabetes mellitus were evaluated.

4. Results

4.1. The impact of cerebral tissue saturation during the cross-clamp period on cognitive changes after carotid endarterectomy (Study A)

4.1.1. Descriptive and outcome data

We included 103 patients in the final analysis regarding short-term cognitive changes. A total of 57.28% of the patients were male, with a mean age of 70.49 years (SD±7.17). Seventy-four (71.84%) of our patients underwent eversion endarterectomy, while 29 (28.15%) had thromboendarterectomy. The median of the cross-clamp period was 27 minutes (IQR:23-33.25 minutes). No patient died within 30 days after the surgery. We observed no cerebral hyperperfusion syndrome.

The median of the desaturation during the cross-clamp period (rSO_{2desat}) was 14.45% (IQR: 9.85%- 23.37%), and the median of the lowest cerebral tissue saturation (rSO_{2low}) value was 59% (IQR: 51%-66%). The baseline characteristics of the patients are shown in Table 1.

Table 1. Baseline characteristics and intraoperative parameters (N= 103 patients)
BMI: body mass index, EEA: eversion endarterectomy, IQR: interquartile range, MAP: mean arterial pressure, rSO_2: regional oxygen saturation, SD: standard deviation, Vascular POSSUM: Vascular-Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity

Parameters	**Mean, median, or number Standard deviation, interquartile range and percentage**
Age (y, mean, SD)	70.49 (7.17)
Male (N, %)	59 (57.28)
Vascular POSSUM (median, IQR)	18 (16-21.25)
BMI (kg/m^2, median, IQR)	28.34 (25.39-30.44)
Smoker (current) (N, %)	31 (30.09)
Alcohol (N, %)	12 (11.65)

Parameters	Mean, median, or number Standard deviation, interquartile range and percentage
Hypertension (N, %)	95 (92.23)
Ischemic Heart Disease (N, %)	34 (33)
Previous stroke (N, %)	23 (22.33)
Diabetes mellitus type 1 (N, %)	11 (10.67)
Diabetes mellitus type 2 (N, %)	28 (27.18)
Chronic Obstructive lung disease (N, %)	20 (19.41)
Hyperlipidemia (N, %)	53 (51.45)
Thyroid dysfunction (N, %)	16 (15.53)
Peripheral arterial disease (N, %)	22 (21.35)
Type of the surgery (EEA) (N, %)	74 (71.84)
Operated side (Left) (N, %)	50 (48.54)
Shunt use (N, %)	29 (28.15)
Time of the shunted period (min, median, IQR)	33 (25-39.5)
Time of the clamping period (min, median, IQR)	27 (23-33.25)
Median of the preclamp. rSO_2 values (%, median, IQR)	70.64 (61.02-82.26)
Lowest rSO_2 values during clamping period (%, median, IQR)	59 (51-66)
Median of the degree of desaturation (%, median, IQR)	14.45 (9.85-23.37)
Mean of MAP during the clamping period (mmHg, mean, SD)	87.54 (9.91)
Vasopressor use during the clamping period (N, %)	73 (70.87)

4.1.2. MMSE

The median preoperative MMSE score was 29 (IQR: 27-29), the postoperative value was 29 (IQR: 28-30). The standard deviation of the MMSE was 1.79.

Based on this, cognitive decline proven by the MMSE test was observable in the case of 9 (8.73%) patients, whereas improvement in the case of 19 (18.44%) patients.

Using the Spearman correlation test, there was a borderline significant correlation (p= 0.051, R= -0.193) with the ratio of desaturation and the change in the MMSE scores at three months, but the change in the MMSE score showed no significant relation with the lowest saturation value (R = -0.070, p= 0.483).

4.1.3. MoCA

In case of the MoCA test, the median of the preoperative and postoperative test scores were 27 (IQR: 26-29) and 27 (IQR: 25-28), respectively. The standard deviation of the MoCA was 2.28.

At three months, we noticed considerable deterioration of the MoCA scores in the case of 37 (35.92%) patients, whereas improvement in 18 (17.47%) patients.

Analyzing the relation between the degree of cerebral desaturation compared to the preclamping values and the change in the MoCA scores, there was a strong, statistically significant, negative correlation (p= 0.001, R= -0.707). The result is illustrated in Figure 3. Between the lowest rSO_2 values and the cognitive change proven by the MoCA test, we obtained similar but less convincing results. It showed significant correlation (p= 0.001) but with a less strong R value (R= 0.529).

Due to these statistically significant results, we based our further analysis on the results of the MoCA tests.

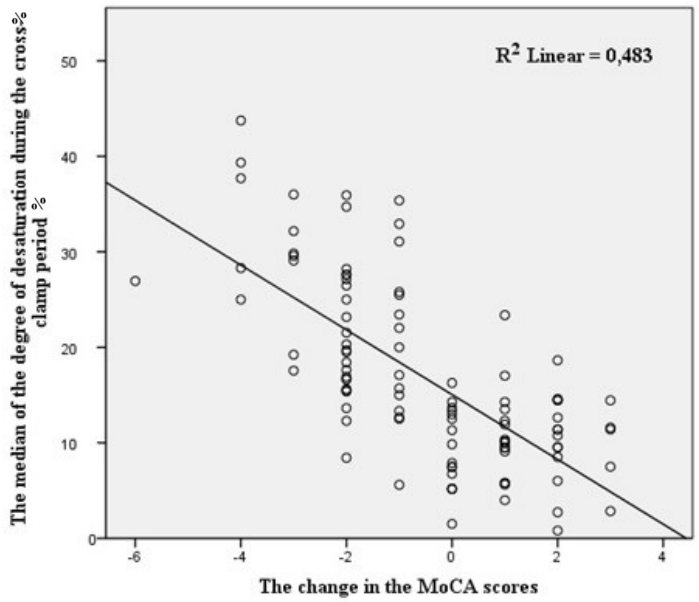

Figure 3. The correlation of the change in the MoCA scores (from preoperative to the 3 months) and the degree of desaturation during the cross-clamp period

4.1.4. Postoperative cognitive impairment based on the change of the MoCA score

As cerebral tissue desaturation showed a strong correlation with the change of MoCA scores, in order to find the potentially harmful degree of desaturation regarding cognitive function, we performed a ROC analysis. According to this, we identified a cut-off of 15.5% decrease of regional cerebral tissue saturation as a threshold with a sensitivity of 86.5%, specificity of 78.8%, positive predictive value of 69.6%, and negative predictive value of 91.2%, AUC=0.876, p= 0.001. The ROC curve is shown in Figure 4.
To confirm this connection, we calculated the cumulative duration of time spent below this level of desaturation (≥15.5%). It differed significantly between the groups (Kruskal Wallis test, p= 0.001).

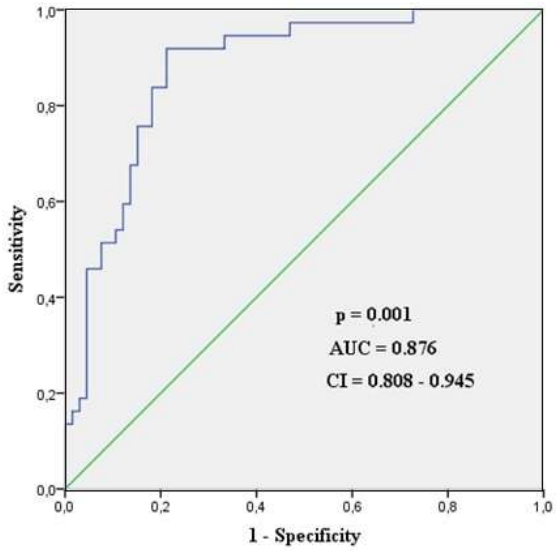

Figure 4. ROC curve of rSO_2 desaturation for detecting postoperative cognitive decline proven by the MoCA test
AUC: area under the curve, CI: confidence interval

Regarding the lowest cerebral rSO_2 values, a ROC analysis gave a significant result (AUC: 0.794, p= 0.001), but the critical value had a weaker connection with the postoperative cognitive decline. Using a 57.5% rSO_2 value as a threshold, it had a sensitivity of 75.7%, a specificity of 69.7%, a positive predictive value of 58.3% and a negative predictive value of 83.6%.

4.1.5. Postoperative cognitive improvement based on the change of the MoCA score

On the same basis, we tried to identify the threshold below which an improvement in cognitive function may be observed. Testing first the connection of the degree of cerebral desaturation and the later experienced cognitive improvement proven by the MoCA test, we found a significant outcome with an AUC= 0.728, p= 0.002.

Desaturation equal to or less than 12.65% had a sensitivity of 72.2%, a specificity of 67.1%, a positive predictive value of 31.7%, and a negative predictive value of 91.9%. The ROC curve is shown in Figure 5.

Regarding potential cognitive improvement and the lowest rSO_2 values, there was a significant but weaker connection between them (AUC=0.653, p= 0.042).

We chose rSO_2 60.75% as the optimal limit, below which rSO_2 values should not fall, with a sensitivity of 66.7%, a specificity of 61.2%, a positive predictive value of 26.7 %, and a negative predictive value of 89.7%.

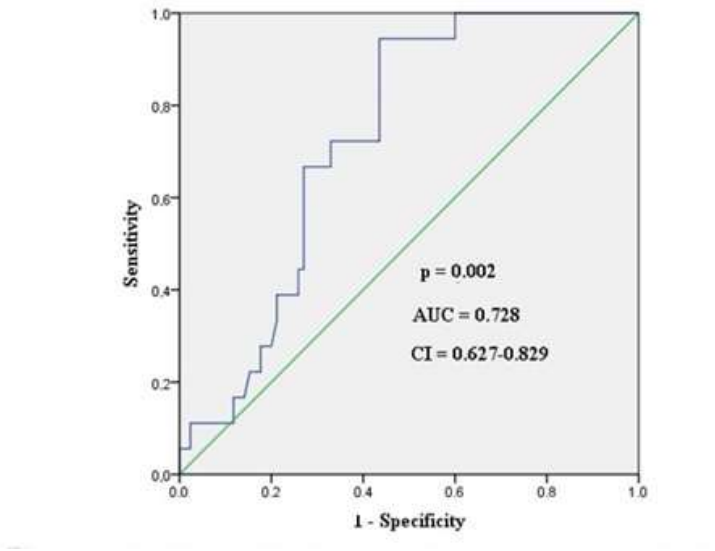

Figure 5. ROC curve of rSO_2 desaturation for detecting postoperative cognitive improvement proven by the MoCA test
AUC: area under the curve, CI: confidence interval

4.1.6. Factors associated with MOCA score decline and improvement

Building on the postoperative change of the MoCA test, we created three groups: patients suffering postoperative cognitive decline (PNCD group), patients with postoperative cognitive improvement (POCI group), and patients with no change in cognitive status (NCCF group). We found cognitive decline in 37 patients (35.92%), improvement in 18 patients (17.47%), and no change in the cognitive function of 48 patients (46.6%). The comparison of the three groups is summarized in Table 2.

Table 2. Comparison of demographic and clinical factors between the three groups created based on the changes in the MoCA scores

BMI: body mass index, CoW: circle of Willis, EEA: eversion endarterectomy, HDL cholesterol: cholesterol: high-density lipoprotein cholesterol, ICA: internal carotid artery, IQR: interquartile range, LDL cholesterol: low-density lipoprotein cholesterol, MAP: mean arterial pressure, MMSE: Mini Mental State Examination, MoCA: Montreal Cognitive Assessment, NCCF group: patients with no change in postoperative cognitive status proven by the MoCA, PNCD group: patients with postoperative cognitive decline confirmed by the MoCA, POCI group: patients with postoperative cognitive improvement confirmed by the MoCA rSO_2: regional oxygen saturation, SD: standard deviation, Vascular POSSUM: Vascular-Physiological and Operative Severity Score for the enUmeration of Mortality *and Morbidity*

Parameters	**NCCF group (48 patients, 46.6%)**	**PNCD group (37 patients, 35.92%)**	**POCI group (18 patients, 17.47%)**	**p value**
Age (y, mean, SD)	69.29 (7.64)	71.31 (6.76)	72 (6.49)	0.274
Male (N, %)	33 (68.80)	14 (37.83)	12 (66.66)	0.011
Vascular POSSUM (median, IQR)	18 (15.25-21)	19 (17-23)	18 (16-22.25)	0.344
BMI (kg/m^2, median, IQR)	27.61 (24-30.46)	28.39 (26.67-30.54)	28.5 (26.07-29.75)	0.622
Smoker (N, %)	18 (37.5)	11 (29.72)	2 (11.11)	0.114
Alcohol (N, %)	7 (14.58)	2 (5.4)	3 (16.66)	0.326
Hypertension (N, %)	44 (91.66)	34 (91.89)	17 (94.44)	0.928
Systolic blood pressure (mmHg, mean, SD)	145.95 (21.47)	147.13 (24.52)	148.53 (19.41)	0.924
Diastolic blood pressure (mmHg, mean, SD)	78.52 (12.87)	80.63 (13.87)	84 (9.16)	0.205
Mean arterial pressure (mmHg, mean, SD)	101 (13.48)	102.80 (15.87)	105.51 (11.54)	0.563

Parameters	NCCF group (48 patients, 46.6%)	PNCD group (37 patients, 35.92%)	POCI group (18 patients, 17.47%)	p value
Ischemic Heart Disease (N, %)	17 (35.41)	12 (32.43)	5 (27.77)	0.838
Previous stroke (N, %)	11 (22.91)	8 (21.62)	4 (22.22)	0.99
Diabetes mellitus type 1+ type 2 (N, %)	16 (33.33)	17 (45.94)	3 (16.66)	0.097
Chronic Obstructive lung disease (N, %)	10 (20.83)	8 (21.62)	2 (11.11)	0.616
Hyperlipidemia (N, %)	22 (45.83)	22 (59.45)	9 (50)	0.456
Cholesterol level (mmol/l, median, IQR)	4.2 (3.45-5.15)	4.25 (3.5-5.27)	4.4 (3.75-5.65)	0.864
Triglyceride level (mmol/l, median, IQR)	1.48 (1.13-2.09)	1.42 (1.06-1.91)	1.77 (0.86-2.32)	0.907
HDL cholesterol level (mmol/l, median, IQR)	1.21 (1.07-1.72)	1.27 (1.12-1.52)	1.24 (1.15-1.30)	0.944
LDL cholesterol level (mmol/l, median, IQR)	2.01 (1.78-3.02)	2.10 (1.64-3.14)	2.46 2.05-2.92	0.768
Statin use (N, %)	28 (58.33)	22 (59.45)	11 (61.11)	0.839
Thyroid dysfunction (N, %)	9 (18.75)	6 (16.21)	1 (5.55)	0.415
Peripheral arterial disease (N, %)	6 (12.5)	10 (27.02)	6 (33.33)	0.106
Operated side (LEFT) (N, %)	22 (45.83)	21 (56.75)	7 (38.88)	0.404
Degree of ICA stenosis (median, IQR)	80 (80-90)	80 (80-90)	80 (80-90)	0.985
Degree of the contralateral ICA stenosis (median, IQR)	40 (40-67.5)	40 (10-60)	42.5 (0-70)	0.968
Anatomy of CoW (complete, N, %)	18 (37.5)	8 (21.62)	6 (33.33)	0.224
Shunt use (N, %)	11 (22.91)	14 (37.83)	4 (22.22)	0.262
Time of the shunted period (min, median, IQR)	34 (25-40)	30.5 (22.5-38)	37.5 (29.25-47.25)	0.405
Time of the clamping period (min, median, IQR)	24 (16-32.5)	30 (23-35)	23 (16.75-26.25)	0.606
Median of the preclamp. rSO_2 values (%, median, IQR)	72 (62.25-77)	68 (61-75.5)	69.75 (62.62-80)	0.19
Lowest rSO_2 values during clamping period (%, median, IQR)	62.5 (56-69)	51 (42-58.5)	62.5 (57.75-70.25)	0.001

Parameters	NCCF group (48 patients, 46.6%)	PNCD group (37 patients, 35.92%)	POCI group (18 patients, 17.47%)	p value
Median of the degree of desaturation (%, median, IQR)	12.41 (7.47-16.13)	25 (17.24-29.33)	11.39 (8.25-14.44)	0.001
Mean of MAP during clamping period (mean, SD)	88.12 (10.65)	87.73 (9.83)	85.61 (8.09)	0.655
Vasopressor use during the clamping period (N, %)	35 (72.91)	25 (67.56)	13 (72.2)	0.857
State Entropy median (median, IQR)	48.25 (44-53.75)	48 (43-56.25)	47 (42-57.25)	0.901
Response Entropy median (median, IQR)	50.25 (47-56)	50.50 (46.75-58.5)	52 (45.37-59.12)	0.904
Education (y, median, IQR)	12 (11-15.75)	12 (11-15)	11.5 (11-14.5)	0.742
MMSE test scores preoperatively (median, IQR)	29 (27.25-30)	29 (27-29)	28 (26.75-29)	0.143
MoCA test scores preoperatively (median, IQR)	28 (26-29)	28 (27-29)	25.5 (22.75-26.25)	0.001
Median time spent below 15.5% rSO_2 reduction calculated from the baseline (median, IQR)	0 (0-58.5)	570 (137-1214)	0 (0-0)	0.001
Type of surgery (EEA, N, %)	37 (77.08)	23 (62.16)	14 (77.77)	0.219

Analyzing the differences, we found a higher proportion of women among those who suffered postoperative cognitive decline based on the postoperative cognitive assessment using the MoCA test (p= 0.011).

The degree of desaturation was significantly greater in the POCD group (p= 0.001), and the lowest rSO_2 values were also found in this group, showing a significant difference compared with the other two groups (p= 0.001). The latter two differences are demonstrated in Figures 6 and 7.

The preoperative results of the MoCA test were significantly lower in the POCI group (p= 0.001).

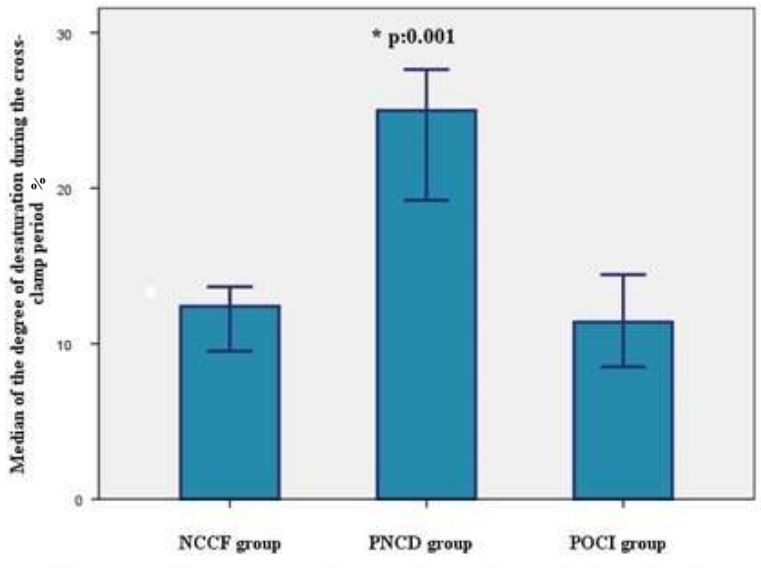

Figure 6. Comparison of the degree of desaturation between patients with different directions of cognitive change proven by the MoCA test

NCCF group: patients with no change in cognitive status proven by the MoCA,
PNCD group: patients with postoperative cognitive decline confirmed by the MoCA test,
POCI group: patients with postoperative cognitive improvement confirmed by the MoCA test

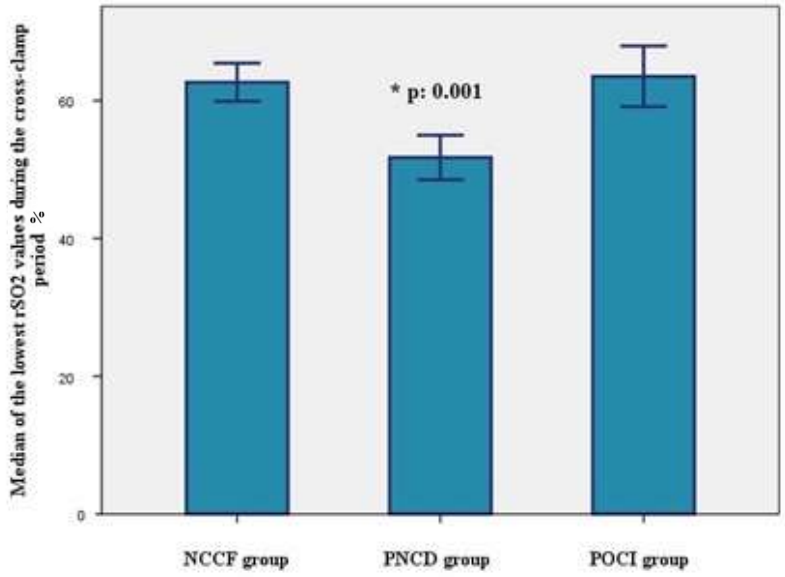

Figure 7. Comparison of the lowest rSO_2 values between patients with different directions of cognitive change proven by the MoCA test

NCCF group: patients with no change in cognitive status proven by the MoCA,
PNCD group: patients with postoperative cognitive decline confirmed by the MoCA test,
POCI group: patients with postoperative cognitive improvement confirmed by the MoCA test

Using univariate regression analysis, a significant association was found between the deterioration of cognitive function proven by the MoCA test with the female sex (p= 0.003), with the degree of desaturation during the clamping period (p= 0.001), and with the lowest rSO_2 values (p= 0.001). Regarding the improvement proven by the same test, we found significant connection in the case of the latter two and diabetes mellitus type 2. However, the odds ratio indicates a negative association in relation to diabetes and the degree of desaturation. The exact data of the univariable regression analysis are shown in Table 3.

Table 3. Results of the univariate logistic regression analysis for all variable
ASA score: American Society of Anesthesiologists physical status classification, BMI: body mass index, C.I.: confidence interval, COPD: Chronic obstructive pulmonary disease, MAP: mean arterial pressure, OR: odds ratio, Vascular POSSUM: Vascular-Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity

Parameters	**PNCD group**				**POCI group**			
	AOR	95% C.I		Sig.	AOR	95% C.I		Sig.
		Lower	Upper			Lower	Upper	
Age	1.025	0.969	1.086	0.389	1.037	0.964	1.115	0.324
Sex	3.520	1.516	8.174	0.003	0.618	0.212	1.081	0.378
Mean of MAP during the clamping period	1.003	0.963	1.045	0.884	0.976	0.926	1.029	0.363
Use of vasopressor	0.781	0.325	1.876	0.581	1.083	0.349	3.360	0.890
Median of the lowest rSO2	0.881	0.833	0.932	0.001	1.052	1.000	1.106	0.050
Median of the desaturation	1.199	1.117	1.288	0.001	0.883	0.811	0.962	0.004
ASA score	1.107	0.496	2.470	0.804	1.189	0.429	3.301	0.739
VascularPossum score	1.099	0.986	1.225	0.088	1.023	0.896	1.168	0.736
Hypertension	0.929	0.209	4.128	0.923	1.526	0.176	13.229	0.701
Ischemic heart disease	0.960	0.407	2.263	0.926	0.743	0.241	2.287	0.604
COPD	1.241	0.456	3.381	0.672	0.465	0.098	2.213	0.336

Parameters	PNCD group				POCI group			
	AOR	95% C.I		Sig.	AOR	95% C.I		Sig.
		Lower	Upper			Lower	Upper	
Diabetes mellitus type 2	2.261	0.930	5.498	0.072	0.126	0.016	0.999	0.050
Diabetes mellitus type1	2.361	0.668	8.350	0.183	1.056	0.208	5.357	0.948
Diabetes mellitus (type 1 + type 2)	2.103	0.910	4.860	0.082	0.315	0.085	1.173	0.085
Neurological disorder	0.793	0.291	2.165	0.651	0.406	0.086	1.920	0.256
Previous stroke	0.938	0.355	2.478	0.897	0.992	0.292	3.371	0.990
Hyperlipidemia	1.656	0.733	3.741	0.225	0.932	0.337	2.577	0.892
Thyroid gland disorder	1.084	0.360	3.266	0.886	0.275	0.034	2.225	0.226
Peripheral arterial disease	1.667	0.639	4.344	0.296	2.156	0.703	6.614	0.179
Smoking (current)	0.973	0.404	2.344	0.951	0.386	0.103	1.443	0.157
Alcohol consumption	0.320	0.066	1.547	0.156	1.689	0.409	6.981	0.469
BMI	1.046	0.957	1.143	0.318	1.001	0.895	1.119	0.989
Education (yrs)	1.087	0.924	1.278	0.313	0.934	0.756	1.154	0.527
Time of the cross clamp	1.033	0.975	1.094	0.267	0.982	0.939	1.027	0.420
Shunt use	2.070	0.859	4.985	0.105	0.686	0.205	2.288	0.539
Operated side	0.597	0.265	1.345	0.213	1.609	0.569	4.546	0.370
Degree of the stenosis on the operated side	1.016	0.962	1.073	0.568	0.979	0.917	1.045	0.526
Degree of the stenosis on the contralat. side	1.001	0.988	1.013	0.889	0.998	0.983	1.014	0.834
Anatomy of Circle of Willis	2.344	0.750	7.324	0.143	0.653	0.173	2.460	0.529
Preoperative MMSE score	1.017	0.792	1.304	0.897	0.768	0.574	1.028	0.076
Preoperative MoCA score	1.355	1.084	1.692	0.078	0.587	0.450	0.767	0.001

According to the results of multivariate logistic regression, the degree of desaturation (p= 0.001), diabetes mellitus type 2 (p= 0.027), and female sex (p= 0.034) were significant predictors for PNCD.

The degree of desaturation (p= 0.046) was independently associated with the postoperative improvement of cognition, besides the results of preoperative MoCA assessment (p= 0.001). The summarized results of the multivariable analysis are in Table 4.

Table 4. The results of the multivariable logistic regression analysis
C.I.: confidence interval, MoCA: Montreal Cognitive Assessment, OR: odds ratio PNCD group: patients with postoperative cognitive decline confirmed by the MoCA, POCI group: patients with postoperative cognitive improvement confirmed by the MoCA, Vascular POSSUM: Vascular-Physiological and Operative Severity Score for the enUmeration of Mortality *and Morbidity*

Parameters	**PNCD group**				**POCI group**			
	AOR	95% C.I.		p value	AOR	95% C.I.		p value
		Lower	Upper			Lower	Upper	
Sex	3.438	1.096	10.779	0.034	-			
Diabetes mellitus type 2	3.809	1.168	12.422	0.027	-			
Median of the degree of desaturation	1.184	1.070	1.310	0.001	0.896	0.804	0.998	0.046
Preoperative MoCA score	-				0.588	0.426	0.814	0.001

4.1.7. Analysis of the deteriorating tendency of cognitive status in female patients

We have not found any statistically significant difference between the sexes referring to the pre- and postoperative test scores (males preoperative MMSE: 28 (27-30), females preoperative MMSE: 29 (28-29), p= 0.494; males postoperative MMSE: 29 (27-30), female postoperative MMSE: 29 (28-30), p= 0.552; males preoperative MocA: 27 (25-29), female preoperative MoCA: 28 (26-29), p= 0.056; male postoperative MoCA: 27 (25-28), female postoperative MoCA: 26.5 (24.25-28), p= 0.806). Comparing the groups in relation to the change of the test scores, we observed that female patients tended to lose more points postoperatively on the MoCA test (change in the MoCA scores: 0 (-

1-1), -2 (-2-0.75) in males and females, respectively. This meant a statistically significant difference (p= 0.008).

To understand the sex difference, we compared them, finding a significant difference between them regarding the occurrence of thyroid gland disorders (p= 0.001) and the degree of desaturation (p= 0.050). Female patients experienced significantly greater desaturation (median of rSO_{2desat}:17.67% IQR: 10.46%- 28.05%) and had significantly lower cerebral tissue saturation values (median of rSO_{2low}: 55.5% IQR: 48.5%-60.75%) than male patients (median of rSO_{2desat}: 13.63% IQR: 9.52%-17.64%, p= 0.05, median of rSO_{2low}: 62% IQR: 55.5%-69%. p= 0.002).

Despite the tendency for more substantial desaturation, we found no difference between females and males regarding the anatomy of CoW (complete/incomplete, p= 0.836), the extent of the carotid stenosis of both the operated (p= 0.695), and the contralateral side (p= 0.919).

In relation to the well-known risk factors for cognitive impairment, we did not find such condition, which could account for this finding. There was no difference between the sexes regarding age (p= 0.226), education level (p= 0.615), preoperative cognitive status (preoperative MoCA test p= 0.056), the presence of hypertension (p= 0.239), hyperlipidemia (p= 0.588), depression or mood disorders (p= 0.226), smoking (p= 0.231), or diabetes (p= 0.320). Moreover, the presence of previous stroke in the anamnesis was higher among male patients (p= 0.021).

4.1.8. Impact of age on cerebral tissue saturation and on the change of cognitive function

In order to analyze the impact of age on our cognitive results we divided our patients into four groups, based on their age: Group I – 7 patients (5.9%), younger than 60 years, Group II – 43 patients (36.4%), aged 60-69 years, Group III – 42 patients (35.6%), aged 70-79, Group IV – 11 patients (9.3%), older than or equal to 80 years.

We found no significant differences between the groups regarding cerebral tissue saturation values and changes in cognitive test scores. However, older patients gained lower scores on the preoperative and postoperative cognitive tests. The impact of education on these results was excluded.

The analysis of the groups in terms of comorbidities showed that smoking (p= 0.008) was more frequent among younger patients, and they had higher BMI values (p= 0.030) as well. The occurrence of COPD (chronic obstructive pulmonary disease) was higher in the oldest group (p= 0.039).

Though we observed only a trend (p= 0.062), the incidence of hyperlipidemia was numerically highest among the youngest patients. To get a more accurate view, we analyzed the levels of all the lipid parameters of our patients. Although it did not reach the level of significance (p= 0.056), triglyceride levels were substantially higher in Group I, in the group of our youngest patients. We found a statistically significant difference regarding the levels of cholesterol (p= 0.042), which showed a decreasing tendency with ageing. The comparison of the groups is summarized in Table 5.

Table 5. Comparison of clinical factors between the four groups created based on the classification of ages
BMI: body mass index, HDL cholesterol: high-density lipoprotein cholesterol, IQR: interquartile range, LDL cholesterol: low-density lipoprotein cholesterol, MMSE: Mini Mental State Examination, MoCA: Montreal Cognitive Assessment, rSO_2: regional oxygen saturation, SD: standard deviation

Characteristic/ Parameters	**Group I. (≤ 59 years) 7 patients (5.9%)**	**Group II. (60-69 years) 43 patients (36.4%)**	**Group III. (70-79 years) 42 patients (35.6%)**	**Group IV. (≥ 80 years) 11 patients (9.3%)**	**p-value**
MMSE test scores preoperatively (median, IQR)	29 (28-30)	29 (28-30)	28 (27-29)	27 (27-29)	0.040
MoCA test scores preoperatively (median, IQR)	29 (26-30)	28 (26-29)	28 (25-28)	25 (24-26)	0.001
MMSE test scores postoperatively (median, IQR)	29 (28-30)	29 (28-30)	29 (28-30)	27 (25-29)	0.003
MoCA test scores postoperatively (median, IQR)	28 (27-29)	27 (25-28)	26.5 (24-28)	24 (24-26)	0.002
Change in the MMSE scores (median, IQR)	0 (-1 – 0)	0 (0 – 1)	0 (0-2)	0 (-2 – 1)	0.312
Change in the MoCA scores (median, IQR)	0 (-2 – 1)	-1 (-2 – 1)	-0.5 (-2 - 1.25)	0 (-2 – 1)	0.975

Characteristic/ Parameters	Group I. (≤ 59 years) 7 patients (5.9%)	Group II. (60-69 years) 43 patients (36.4%)	Group III. (70-79 years) 42 patients (35.6%)	Group IV. (≥ 80 years) 11 patients (9.3%)	p-value
Education (y, median, IQR)	11 (11-12)	12 (11-16)	12 (11-16)	12 (10-16)	0.951
Median of the preclamp. rSO_2 values (%, median, IQR)	74 (64-86)	70 (60-77)	71 (65.5– 77)	65 (64-75)	0.590
Lowest rSO_2 values during clamping period (%, median, IQR)	67 (54-72)	60 (50-67)	57 (51– 64.62)	57 (51-66)	0.552
Median of the degree of desaturation (%, median, IQR)	13.51 (11.39-16.27)	14.28 (9.85-22.03)	15.04 (9.41-26.59)	13.66 (11.33- 18.42)	0.836
Chronic Obstructive lung disease (N, %)	0 (0)	10 (23.25)	5 (11.9%)	5 (45.45)	0.039
BMI (median, IQR)	28.4 (23.33-31.6)	29.06 (27.04-30.86)	27.22 (23.95-29.21)	26.72 (22.22-29.01)	0.030
Smoker (N, %)	3 (42.85)	20 (46.51)	6 (14.28)	2 (18.18)	0.008
Hyperlipidemia (N, %)	5 (71.42)	26 (60.46)	15 (35.71)	7 (63.63)	0.062
Statin use (N, %)	3 (42.85)	22 (51.16)	28 (66.66)	10 (90.90)	0.059
Cholesterol (mmol/l, median, IQR)	5.1 (4.77-6.75)	3.95 (3.28-5.22)	4.4 (3.7 – 5.5)	4.1 (3.6-4.3)	0.042
Triglycerides (mmol/l, median, IQR)	2.85 (1.25-3.15)	1.5 (1.21-2.42)	1.4 (1- 1.90)	1.25 (0.83-1.7)	0.056
HDL cholesterol (mmol/l, median, IQR)	1.3 (1.05-1.78)	1.20 (1.01-1.39)	1.31 (1.2-1.73)	1.14 (0.94-1.5)	0.207
LDL cholesterol (mmol/l, median, IQR)	3.3 (2.52-4.35)	1.95 (1.59-3.02)	2.28 (1.92-3.12)	1.96 (1.69-2.61)	0.092

4.1.9. The impact of cerebral tissue saturation on postoperative outcomes

Neither the lowest rSO_2 levels (p= 0.675), nor the degree of desaturation (p= 0.366) showed any significant association with perioperative complications.

With regards to long-term complications, the lowest rSO_2 had a significant connection (p= 0.009) with this outcome.

Using an ROC curve (p= 0.009, AUC: 0.743), the most optimal threshold of the lowest rSO_2 values for predicting the occurrence of long-term complications was 54.5%, with a sensitivity of 81.8%, specificity of 73.1%, and with a negative predictive value of 97.1% and a positive predictive value of 26.5%. We did not find a significant association in terms of the degree of desaturation (p= 0.071) and the occurrence of long-term complications.

The connections between long-term mortality and the two cerebral tissue saturation parameters were not significant: absolute saturation values - p= 0.085, degree of desaturation p= 0.145.

4.2. Comparison of diabetic and non-diabetic patients (Study B)

4.2.1. Participants and descriptive data

In this part of the study, the data of 104 patients were analyzed. Thirty-seven patients (35.7% of the population) had diabetes, 25 (67.56%) of whom received oral hypoglycemic medications, and 12 patients (32.43%) received insulin alone or in combination with oral hypoglycemic medications. Diabetes medications are summarized in Table 6.

Table 6. Summary of diabetic medications in the diabetic group

Diabetes medication	**Number of patients (N)**	**Percentage of patients (%)**
One oral antidiabetic active substance/hypoglycemic agent medication	20	54.05
Two or more oral antidiabetic active substances	8	21.62
Oral antidiabetic medication + insulin	4	10.81
Insulin	5	13.51

In Table 7, the applied hypoglycemic agents are summarized.

Table 7. The applied hypoglycemic agents and their frequencies
DPP-4 inhibitors: dipeptidyl peptidase 4 inhibitors, GLP-1 agonists: glucagon-like peptide-1 receptor agonists
SGLT2 inhibitors: sodium-glucose cotransporter-2 (SGLT2) inhibitors

Hypoglycemic agent	**Number of diabetic patients using the agent**	**Percentage of diabetic patients using the agent (%)**
Biguanides	25	67.56
Sulfonylureas	8	21.62
DPP-4 Inhibitors	4	10.81
SGLT2 Inhibitors	2	5.40
GLP-1 Agonists	2	5.40

The trend of HbA1c levels is summarized in Table 8.

Table 8. HbA1c levels of diabetic patients
HbA1c: Hemoglobin A1c

Parameters	**Median of HbA1c**	**IQR**
Preoperative HbA1c level (%)	6.38	5.83-7.6
Preoperative HbA1c level (mmol/mol)	47	41-58.32
HbA1c level one year after the surgery (%)	6.5	5.94-7.6
HbA1c level one year after the surgery (mmol/mol)	45.4	39.49-59.5
HbA1c level two years after the surgery (%)	6.55	5.92-7.24
HbA1c level two years after the surgery (mmol/mol)	48	39.68-57.16

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

In relation to coexisting diseases, there was no difference between diabetic and non-diabetic patients, apart from intervention due to peripheral arterial disease (p= 0.017)

in anamnesis, and the occurrence of renal insufficiency (p= 0.012) based on the preoperative creatinine level. Diabetic patients had higher fasting blood glucose levels (p= 0.001), while preoperative cholesterol levels were lower in the diabetic group than in the control group (p= 0.009). The comparison is shown in Table 9.

Table 9. Baseline characteristics of the two groups
Variables with normal distribution are presented as the means and standard deviations, and nonnormally distributed data are presented as medians and interquartile ranges. Categorical data are presented as numbers and percentages.
BMI: body mass index, CEA: carotid endarterectomy, Vascular-POSSUM: Vascular-Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity.

Characteristics/Parameters	**Patients without diabetes mellitus (67 patients, 64.42%)**	**Patients with diabetes mellitus (37 patients, 35.57%)**	**p value**
Age (y, mean, SD)	70.81 (7.42)	69.89 (6.73)	0.539
Male (N, %)	36 (53.7)	23 (62.16)	0.320
ASA	3 (2-3)	3 (2-3)	0.657
Vascular-POSSUM (median, IQR)	18.82 (3.73)	19.81 (3.86)	0.210
BMI (kg/ m^2, median, IQR)	28.40 (24.69–29.38)	27.96(25.65–30.94)	0.318
Smoker (current) (N, %)	21 (31.34)	10 (27.02)	0.645
Alcohol (N, %)	6 (8.95)	6 (16.21)	0.245
Preoperative fasting blood glucose (mmol/l)	5.7 (5.15–6.1)	7.1 (6.27–7.92)	**0.001**
Anemia (N, %)	2 (2.98)	0 (0)	0.537
Hypertension (N, %)	61 (91.04)	34 (91.89)	0.539
Ischemic Heart Disease (N, %)	18 (26.86)	16 (43.24)	0.070
Previous stroke (N, %)	16 (23.9)	7 (18.91)	0.606
Chronic Obstructive Pulmonary disease (N, %)	12 (17.91)	9 (24.32)	0.435
Hyperlipidemia (N, %)	35 (52.23)	18 (48.64)	0.828
Cholesterol level (mmol/l)	4.55 (3.7–5.52)	3.8 (3.21–4.65)	**0.009**
Triglyceride level (mmol/l)	1.41 (1.04–2.00)	1.78 (1.16–2.45)	0.224
Statin use (N, %)	41 (61.2)	23 (62.16)	0.993
Chronic renal insufficiency ** (N, %)	1 (1.5)	5 (13.5)	**0.012**

Characteristics/Parameters	Patients without diabetes mellitus (67 patients, 64.42%)	Patients with diabetes mellitus (37 patients, 35.57%)	p value
Peripheral arterial disease (PAD) (N, %)	14 (20.89)	12 (32.43)	0.193
Preoperative PAD intervention (N, %)	4 (5.97)	8 (21.62)	**0.017**
Previous CEA or stent (N, %)	2 (2.98)	4 (10.81)	0.101
Major lower extremity amputation (N, %)	0 (0)	2 (5.40)	0.124
Education (school years)	12.46 (2.43)	13.05 (2.58)	0.251
Low financial state (N, %)	2 (2.98)	2 (5.40)	0.539
Risk score of Blecha et al.	2 (1–4)	5 (3–7)	**0.001**

** Based on the definition of Blecha et al., preoperative hemoglobin <10 mg/dl.*

*** Based on the definition of Blecha et al., preoperative creatinine ≥1.3 mg/dl, no patient on dialysis.*

As in diabetic patients, the pathology of the cerebral arteries was characterized by more severe stenosis of the contralateral carotid artery, a higher proportion of diabetic patients underwent thromboendarterectomy, and shunt insertion was more frequently used among them. These data are presented in Table 10.

Table 10. Intraoperative parameters

Nonnormally distributed data are presented as medians and interquartile ranges, and normally distributed data are presented as the means and standard deviations. Categorical data are presented as numbers and percentages. CoW: Circle of Willis.

Characteristics/ Parameters	Patients without diabetes mellitus (67 patients)	Patients with diabetes mellitus (37 patients)	p value
Operated side (left) (N, %)	30 (44.8)	20 (54.05)	0.297
Eversion endarterectomy (EEA) (N, %)	56 (83.58)	18 (48.65)	**<0.001**
Thromboendarterectomy (TEA) (N, %)	11 (16.41)	19 (51.35)	**<0.001**
Ipsilateral stenosis (%) (median, IQR)	80 (80–90)	80 (80–90)	0.125
Contralateral stenosis (%) (median, IQR)	40 (0–50)	55 (22.5–78.75)	**0.012**
Completeness of CoW (N, %)	20 (29.9)	10 (27.02)	0.734
Shunt use (N, %)	12 (17.9)	17 (45.94)	**0.002**
Shunt time (min, median, IQR)	30.5 (20–41)	34 (28–39.5)	0.347
Clamp time (min, median, IQR)	27.5 (22-35)	29 (26.25-37.75)	0.177

4.2.2. Cognitive evaluation

Three months after the surgery, cognitive function was assessed in case of 103 patients, and 36 patients (34.95%) had diabetes. The preoperative MMSE (p= 0.941) and MoCA (p= 0.265) scores did not differ between the groups.

We have not found a statistically significant difference in the change of the MMSE scores three months after the surgery (p= 0.936) between non-diabetic and diabetic patients, while this difference was significant with regard to the change of the MoCA scores (p= 0.028). Though diabetic patients tended to lose more points postoperatively, this outcome did not mean a statistically significant difference in the direction of the change in cognitive function between the groups: cognitive improvement - p= 0.073, cognitive impairment – p= 0.080, unchanged cognitive function – p= 0.748.
Compared with those at baseline, individual declines in the MIS scores were significantly higher in the diabetic group than in the nondiabetic group at three months after surgery (p= 0.035).

One year after the surgery, we had the data of 90 patients, 32 (35.55%) of whom had diabetes. A similar tendency was observable in the change of the test scores one year after the surgery. There was no significant difference between our groups regarding the change of the MMSE scores (p= 0.921), while it proved to be significant in relation to the change of the MoCA scores (p= 0.042). Based on the change of the MoCA scores, we found a significantly lower tendency for cognitive improvement among diabetic patients (p= 0.029). Similarly, the MIS scores differed significantly at the 12th month assessment between diabetic and nondiabetic patients (p= 0.040), and the improvement based on the MIS scores was significantly greater in the nondiabetic group (p= 0.002) one year after the surgery. The data are shown in Figure 8 and Figure 9.

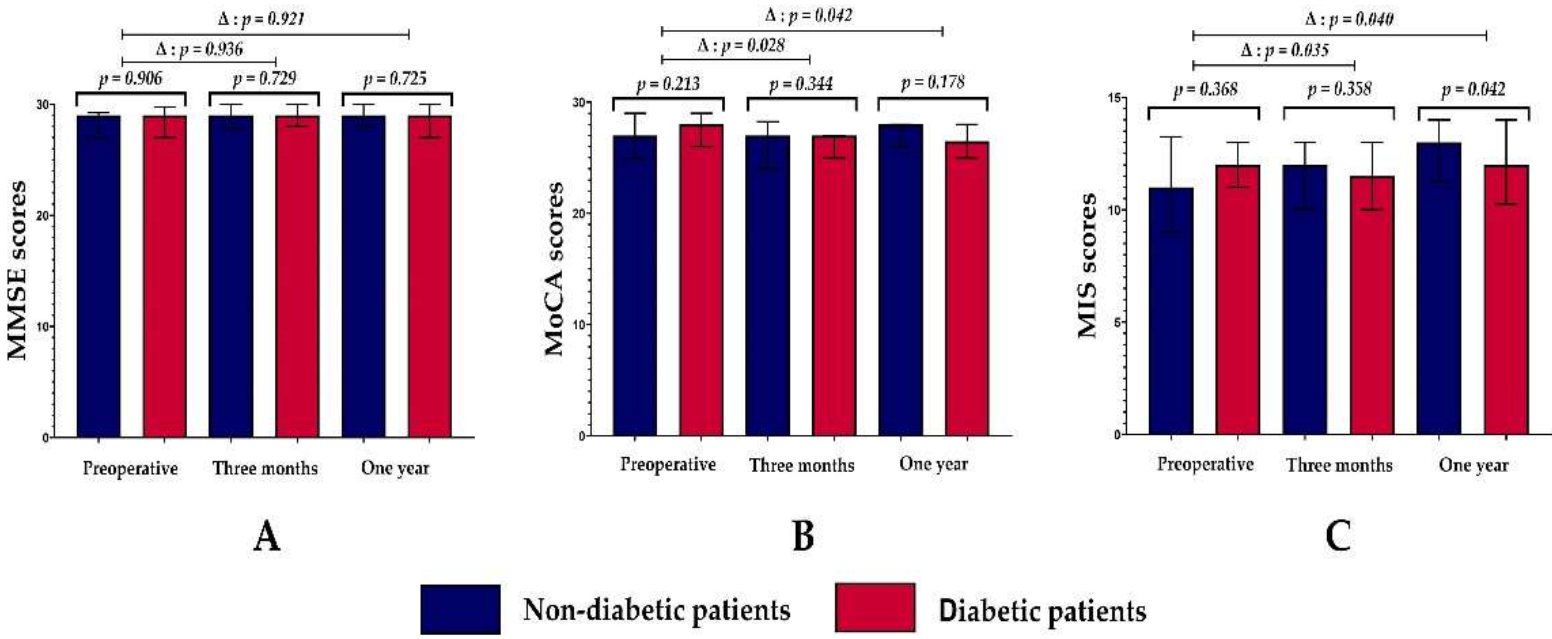

Figure 8. The results of the cognitive tests (A: MMSE, B: MoCA, C: MIS), the statistical significance of the difference between the groups and of the change from the preoperative level

MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive Assessment, MIS: Memory Index Score

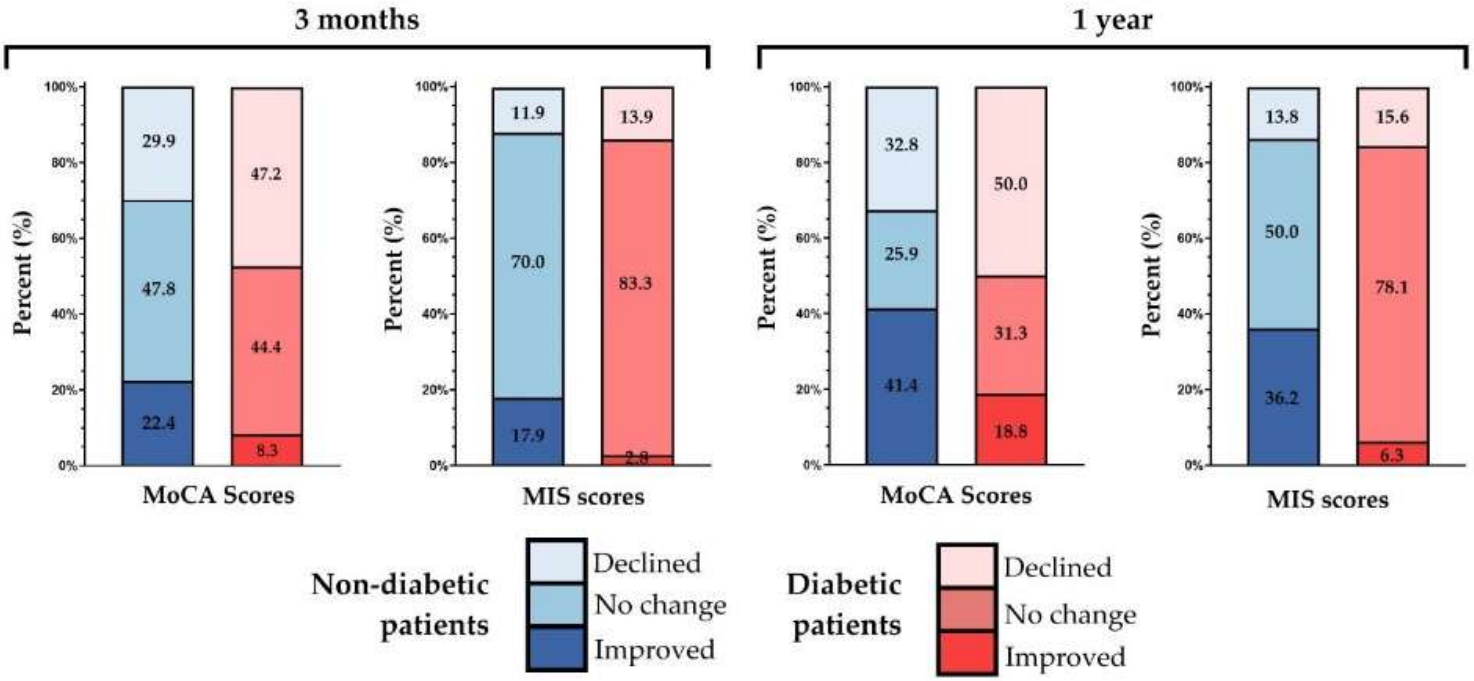

Figure 9. The proportion of the direction of cognitive changes based on the MoCA scores and MIS scores 3 months and a year after the surgery
MoCA: Montreal Cognitive Assessment, MIS: Memory Index Score

4.2.3. Risk assessment

No patient died within 30 days after the surgery. In the perioperative period, complications occurred in case of 4 patients, three of whom had diabetes. We observed TIA-s in two patients *(*cerebral ischemia and other intracranial disorders were ruled out), one myocardial infarction, and severe hemodynamic instability in one patient. Statistically, it did not mean a significant difference between diabetic and non-diabetic patients (p= 0.087).

Eleven patients passed away during the whole follow-up period, four of them experienced a MACCE-related event. The causes of death were SARS-Covid pneumonia in case of one patient, multi-organ dysfunction after vascular surgery, lung tumor/ malignancy, myocardial infarction leading to death, cardiac failure leading to death, acute peritonitis, intracerebral hemorrhage in case of two patients, and three patients died of natural causes.

Seven of them had diabetes, so all-cause mortality was significantly higher in the diabetic group (p= 0.040). The Kaplan-Meier curves for mortality and diabetes are shown in Figure 10.

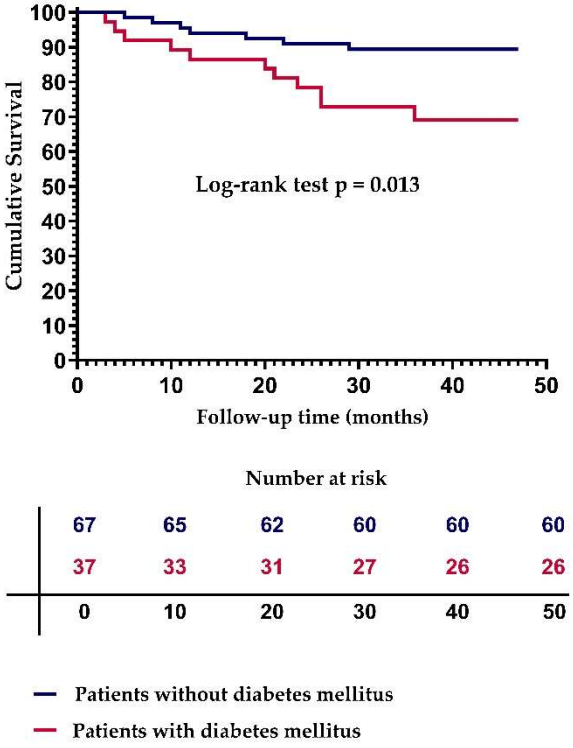

Figure 10. Kaplan-Meier curve for unfavorable postoperative outcome in diabetic and nondiabetic patients.

During the 37-month average follow-up period, eleven patients experienced MACCEs. Seven of them had diabetes. This meant a statistically significant difference between the groups (p= 0.040).

Univariate Cox regression showed female gender (p= 0.003), postoperative cognitive decline as measured with the MoCA (p= 0.003), the median of the lowest rSO2 during the cross-clamping period (p= 0.025), diabetes mellitus (p= 0.016), and Blecha score (p= 0.001) as factors significantly associated with long-term mortality and cardiovascular and cerebrovascular complications.

In the multivariate Cox regression, postoperative cognitive decline as measured with the MoCA (p= 0.034), and the risk score reported by Blecha et al. (p= 0.021) were independently associated with mortality and MACCEs. Stratification according to

diabetes status did not affect these relationships. The results of the multivariate analysis are summarized in Table 11.

Table 11. Multivariate Cox regression analysis for two-year mortality and major cardiovascular and cerebrovascular events
PNCD: perioperative neurocognitive disorder based on the postoperative change of MoCA.

Parameters	**AOR**	**95% C.I.**		**p value**
		Lower	Upper	
PNCD	4.477	1.289	15.550	**0.018**
Diabetes mellitus	1.351	0.489	3.738	0.562
Carotid severity score by Blecha et al.	1.435	1.165	1.767	**0.001**
Median of the lowest rSO_2 value during the cross-clamp period	1.039	0.977	1.105	0.226

4.2.4. Intraoperative parameters

We have the complete intraoperative anesthesiological monitoring registration of 76 patients.

The mean of systolic arterial blood pressure (SAP) values were significantly higher across all three surgical periods in the diabetic group than in the nondiabetic group (preclamping (p= 0.036), cross-clamping (p < 0.001), and postclamping (p= 0.034) periods). Diabetic patients also had higher mean arterial pressure (MAP) during the cross-clamping period (p= 0.001).

Analyzing vasopressor use, the frequencies of vasopressor use at preclamping and postclamping periods (p= 0.001 and p= 0.023, respectively) were significantly higher in the diabetic group, whereas the total applied doses were significantly higher in that group in all three phases of the operation (preclamp.: p= 0.005; cross-clamp.: p= 0.003; postclamp.: p= 0.033).

We observed significant differences regarding cerebral tissue oxygenation.

In the preclamping period, diabetic patients had lower median ipsilateral rSO2 values (67.4% vs. 74.6%, p= 0.011), and the minimum values of regional cerebral tissue saturation were also lower among them during the clamping (54.4% vs. 60.0%, p= 0.052) and preclamping (61.1% vs. 68.3%, p= 0.033) periods.

Using 65% as a threshold, a median regional cerebral tissue saturation value of less than 65% was observed in 38.70% of diabetic patients and in only 15.55% of nondiabetic patients during the preclamping period. This proved to be a significant difference (p= 0.022).

The SE difference (mean–minimum) was significantly greater in diabetic patients than in nondiabetic patients in the postclamping period (p= 0.009), and minimum state entropy (SE) was significantly lower in the postclamping period among diabetic patients (29.1 vs. 37.6, p= 0.003). These may raise the role of a deeper anesthetic effect or altered brain activity in diabetic patients.

We suggest that as part of the overall observed increased hemodynamic lability, diabetic patients had a higher heart rate during the postclamping period than nondiabetic patients (71.8 vs. 64.6, p= 0.035).

All of the intraoperative parameter comparisons are presented in Table 12.

Table 12. Comparison of intraoperative parameters between the groups.
$EtCO_2$: end-tidal carbon dioxide, DAP: diastolic blood pressure, HR: heart rate, MAP: mean arterial pressure, rSO_2: regional cerebral tissue saturation, SAP: systolic arterial pressure, SE: state entropy, SE difference: difference between the mean and minimum values of SE.

Parameters	**Preclamp period**			**Cross-clamp period**			**Postclamp period**		
	Diabetic group	Nondiabetic group	**p value**	Diabetic group	Nondiabetic group	**p value**	Diabetic group	Nondiabetic group	**p value**
HR	67.6 (7.8)	64.6 (9.9)	0.118	70.4 (18.2)	62.4 (17.6)	0.125	71.8 (14.2)	64.6 (12.5)	0.**035**
rSO_2 Ipsilateral mean	67.4 (10.4)	74.6 (7.9)	**0.011**	59.6 (11.9)	64.4 (12.8)	0.133	67.4 (10.8)	72.4 (14.9)	0.169
rSO_2 Contralateral Mean	71.1 (8.3)	76.3 (13.8)	0.076	70.1 (6.9)	75.0 (14.9)	0.186	70.2 (8.1)	74.6 (12.5)	0.205
rSO_2 Ipsilateral minimum	61.1 (9.9)	68.3 (13.1)	**0.033**	54.4 (14.5)	60.0 (15.7)	0.052	60.0 (10.1)	64.5 (15.3)	0.241
$ETCO_2$ difference	2.4 (1.7)	2.9 (2.1)	0.425	1.7 (0.7)	1.3 (0.7)	**0.018**	4.5 (3.9)	4.1 (2.4)	0.315
SE difference	10.4 (8.7)	12.4 (7.3)	0.648	6.0 (7.4)	5.5 (5.1)	0.442	16.7 (13.6)	11.4 (8.3)	**0.009**
SE minimum	37.5 (9.1)	34.9 (12.8)	0.901	31.8 (18.4)	40.9 (20.1)	0.292	29.1 (17.5)	37.6 (17.9)	**0.003**

Parameters	Preclamp period			Cross-clamp period			Postclamp period		
	Diabetic group	Nondiabetic group	**p value**	Diabetic group	Nondiabetic group	**p value**	Diabetic group	Nondiabetic group	**p value**
DAP mean	59.7 (12.6)	58.1 (10.7)	0.173	69.7 (11.9)	62.2 (10.6)	**0.021**	60.5 (15.6)	60.1 (10.4)	0.258
DAP minimum	43.5 (10.1)	41.4 (11.0)	0.104	59.8 (12.7)	53.2 (12.4)	**0.037**	46.7 (11.1)	45.9 (11.0)	0.208
SAP mean	128.7 (19.2)	119.5 (17.0)	**0.036**	145.8 (20.8)	131.3 (22.8)	**0.000**	134.8 (28.5)	125.6 (19.4)	**0.034**
SAP minimum	91.8 (20.6)	86.2 (16.9)	0.123	120.0 (22.1)	107.6 (28.5)	**0.002**	93.8 (18.4)	92.0 (17.2)	0.272
MAP mean	85.9 (16.7)	80.5 (10.4)	0.099	97.9 (12.5)	86.7 (15.4)	**0.001**	85.9 (15.9)	82.5 (11.7)	0.089
MAP minimum	61.4 (11.9)	56.0 (11.9)	0.125	84.0 (13.5)	72.4 (15.6)	**0.013**	61.1 (13.8)	61.7 (13.2)	0.286
vasopressor use (%)	29 (78.37)	26 (38.80)	**0.001**	29 (78.37)	36 (53.73)	0.099	25 (67.56)	25 (37.31)	**0.023**
vasopressor (ug)	13.32 (5.24–25.45)	5 (0–14.16)	**0.005**	141.56 (42.44–222.93)	38.08 (5–89.37)	**0.003**	14.16 (2.18–29.16)	8.33 (0–15.83)	**0.033**

5. Discussion

5.1. Study A

In our prospective study, we aimed to analyze the relation between the absolute values of cerebral tissue saturation and desaturation during the cross-clamp period of carotid endarterectomies and postoperative cognitive function.

We have found a strong, significant correlation between the change in the MoCA scores compared to preoperative values and cerebral tissue oxygen desaturation, whereas there was no significant connection with regard to the change of MMSE scores.

Similarly, the correlation between the lowest rSO_2 values and the change in the MoCA tests was significant, while it failed to show any significant result in the case of the MMSE tests. Therefore, NIRS proved to be a reliable way of neuromonitoring, as the use of MoCA test for assessing cognitive function in the perioperative setting.

There are many screening tools for cognitive function, and all have their own advantages and disadvantages. In our analysis, we chose the MMSE and MoCA tests for assessing our patients' cognition in order to have two tests with different abilities and for getting an accurate view of the cognitive status. Both tests are widely used in the clinical setting, and they have been proven to be capable in detecting AD. (75) (120) MMSE has been used to detect dementia and severe neuropsychiatric disorders, but it has a low sensitivity in the detection of mild cognitive changes. (75) (120) (121) (122)

Detecting subtle changes in cognition is the MoCA test's own, as it is able to reveal early signs of cognitive impairment. (120) (121) (122)

Our findings reflect these properties, as in our study, MMSE failed to show significant correlation with either the ratio of desaturation, or the lowest saturation value, while MoCA showed a good correlation with both of them, as it was able to detect subtle changes in cognition. Therefore, the use of MoCA can be more accurate and advantageous in the perioperative setting.

We have found that the percentage drop of the cerebral tissue oxygen saturation was a better predictor for the change in cognitive performance, compared to the absolute lowest value.

The baseline value of cerebral tissue saturation shows significant individual differences due to biological variations of the cerebral arterial/venous ratio and to the effects of age

and sex on cerebral tissue saturation. (123) (124) However, in a recent trial, the normal value of average cerebral tissue saturation was determined at 67.6%, the lowest threshold of 56% being measured in healthy volunteers. (125)

From these facts it follows that the value of near-infrared spectroscopy lies in the monitoring of the tendency of the changes in cerebral rSO_2. (126) (127) (128)

As in our study the degree of cerebral tissue desaturation has a higher predictive value for postoperative cognitive changes than the absolute value of cerebral tissue oxygen saturation, our results support the rationale of trend monitoring.

Though the literature is not coherent in the aspect of the impact of cerebral tissue saturation on postoperative cognitive performance, several research groups have come to the same conclusion, namely, that significant cerebral desaturation is a risk factor for postoperative cognitive decline. (60) (90) (91) (93) (129) (130) (131) (132) (133) The majority of the trials confirmed the influence of cerebral tissue oxygenation and desaturation on postoperative cognitive function, though they were performed in other fields of medicine. Orthopedic surgery, cardiac surgery with cardiopulmonary bypass, and thoracic surgery are the most frequently investigated areas besides carotid surgeries. (60) (91) (130) (131) (132) (133)

Despite the notable number of trials, the exact extent of potentially harmful changes in cerebral tissue saturation with regard to cognition is still uncertain.

Based on the literature, the threshold of critical cerebral tissue desaturation varies between a drop of 10-20%. (57) (58) (134)

A twenty percent decrease in cerebral tissue saturation caused an 8-fold increase for developing cognitive disorders in a trial investigating the risk of cerebral complications after carotid endarterectomy. (135)

This was strengthened by another research group. According to them, the 20 % drop from baseline allowed did not reduce the occurrence of PNCD. They recommended a higher absolute value in order to prevent this outcome. (136)

The cutoff value of the maximum decrease of rSO_2 was set at 11%, as a potential predictor of postoperative cognitive decline in another study. (133)

Similarly to this result, using a 10% decrease as a threshold had a significant correlation with postoperative cognitive function in geriatric orthopedic patients. (60)

In awake patients, using 10% as a threshold for desaturation, there was a good correlation with cerebral ischemia during carotid endarterectomy in a few-year-old study. (134)
Seeking the critical threshold for cerebral hypoperfusion using NIRS and somatosensory evoked potentials, the threshold was set at 16% of desaturation. (137)
A quite similar limit of 15% showed excellent clinical outcomes when used as a guide in selective shunting in a study published in 2019. (138)
These findings are very close to ours, as we determined a cut-off value for consecutive mental deterioration at 15.5% with a specificity of 78.8% and sensitivity 86.5%. Preventing such a degree of desaturation may have a beneficial impact on postoperative cognitive functions.

Though there is still some uncertainty regarding rSO_2 desaturation, absolute cerebral tissue saturation values are an even less charted field of science.
We found 57.5% to be the optimal threshold for predicting postoperative cognitive decline, while 54.5% was the threshold for prognosing long-term complications. These results are in acceptable agreement with the results of earlier trials, defining the cut-off value for cerebral ischemia at 59% or recommending a higher limit than 55% of rSO_2 as a threshold, as it did not reduce the onset of PNCD after cardiopulmonary bypass. (136) (139)
These values are not precisely defined thresholds. Due to biological differences and the impact of influencing conditions, the exact limit of potentially harmful cerebral tissue saturation level may not be determined precisely. (123) (124)
It should be evaluated together with the relative saturation drop and the patient's condition.

Aiming for maintaining an adequate level of cerebral saturation values, thereby keeping cerebral perfusion in suitable ranges, allowing only tolerable decreases in rSO_2 values may result not only in better outcomes with regard to the cognitive functions, but may prevent the occurrence of long-term complications. (135) Our results have strengthened these beneficial impacts, as the lowest saturation values showed a significant connection with long-term outcomes.

To our knowledge, the relation between the improvement of cognitive performance and cerebral tissue saturation values has not been examined extensively.

The role of stable perioperative hemodynamic parameters in the postoperative development of cognitive performance was demonstrated in a Japanese study. (140)
Preventing a significant drop in cerebral rSO_2 values may have a beneficial impact on postoperative cognitive performance, as higher rSO_2 values proved to predict developing POCI. (141)
Based on our study, setting the absolute value of minimum rSO_2 at 60.75% as a limit for postoperative cognitive improvement seems to be a reliable threshold and is in acceptable accordance with previous studies. (139)

Searching for risk factors, there was a significant association between female gender and postoperative cognitive decline. Women experienced significant desaturation more frequently, though there was no difference between the sexes in the aspects of the anatomy of the circle of Willis and the degree of stenosis.
Generally, women were found to have greater vulnerability regarding cognitive decline: the prevalence of mild cognitive impairment is higher among women and in most cases the progression of the decline is also faster. (142) (143) (144)
The difference in brain and cognitive reserve may explain this phenomenon, as they might influence the tolerance to hemodynamic changes and to the surgical strain. (145) (146) (147)
The connection between diabetes and cognitive dysfunction is also well-known.
The explanation of the higher occurrence of cognitive decline - based on the MoCA test - among diabetic patients might be that hyperglycemia promotes the deterioration of atherosclerotic changes of small and medium-sized arteries, and it might make diabetic patients more vulnerable to the surgical stress and the hemodynamic changes accompanying it. (148) (149) (150) Furthermore, it might even act as a risk factor for cerebrovascular complications, though there are conflicting data about the risk of a diabetic patient developing cardio- or cerebrovascular complications after carotid interventions. (151) (152) (153) (154)
On the other hand, lower preoperative MoCA scores were associated with the improvement of cognitive performance postoperatively. This result is in agreement with a similar study, which demonstrated that younger age and lower MoCA scores preoperatively were strong predictors of improving cognitive performance postoperatively. (155)

As aging has an emphasized relevance in the daily clinical care, we aimed to analyze the impact of age on cerebral tissue saturation and, consequently, cognitive performance and function.

Based on our results, apart from the fact that older patients gained lower scores on the cognitive assessment, independently of education, there was no difference between the age groups regarding these aspects. This finding, the lower performance of older patients, is not a novelty. Changes in white matter, a decrease in white and grey matter volume, and changes in neurotransmitter levels are all part of normal cognitive aging and may explain age-associated cognitive decline. (156)

The lack of any significant difference between the age groups regarding postoperative cognitive changes and cerebral tissue saturation values led us to analyze the groups from other aspects too.

The higher frequency of smoking, significantly higher BMI, and higher cholesterol levels found among our youngest patients may help in the interpretation of the former uncommon, surprising finding, as all these parameters are well-known risk factors for cardiovascular morbidity.

In a recent study, lipid parameters showed a strong correlation with increased PWV (pulse wave velocity). Besides increased PWV being associated with cardiovascular morbidity, it is a marker of arterial stiffness, which is a reliable predictor of early vascular aging. This connection was confirmed by another study. (157) (158)

Smoking is a major risk factor for atherosclerotic vascular disease. It promotes the early onset of cardiovascular aging. (159) (160)

Similarly to this, obesity increases not only the risk of cardiovascular diseases but also leads to an earlier occurrence of cardiovascular morbidity. (161)

In conclusion, the condition of the cardiovascular system and the extent of its functional deterioration is highly variable among individuals of the same chronological age. Elevated lipid levels, obesity, and smoking may contribute to the impairment of the cardiovascular system in the case of our “younger” patients.

We assume that our “younger” patients were more vulnerable to surgical stress, to the impact of the change in cerebral tissue saturation levels, as their cardiovascular system may have been more damaged than could be expected at their chronological age.

This outcome underlines the importance of early vascular ageing.

5.2. Study B

In this part of our trial, we aimed to evaluate the postoperative cognitive changes, the postoperative risk accompanying diabetes mellitus, and the intraoperative physiological changes characteristic of the disease.

In our analysis, there was no significant difference between diabetic and non-diabetic patients with regard to the pre- and postoperative MMSE and MoCA test scores, and we have not found any statistically significant difference between them concerning the change of MMSE scores. In relation to the MoCA test, there was a significant difference: diabetic patients lost more points on both of the postoperative cognitive assessments.

The major difference between the groups regarding the definitive postoperative cognitive change was the significantly lower occurrence of cognitive improvement among diabetic patients one year after the operation. Preservation of cognitive skills, or ideally postoperative cognitive improvement, is one of the most desired alterations after carotid surgery for the patients.

In our analysis, patients in the diabetic group experienced a greater decline in the MoCA test subscore, in the MIS as well. The rate of improvement fell behind in the diabetic group at both assessment times.

Besides the fact that impairment of memory penetrates the whole life as it makes every situation more difficult, a new onset of MIS decline may increase the chance of conversion from mild cognitive impairment to Alzheimer's disease. (162)

In contrast with postoperative cognitive impairment, the connection between cerebral tissue saturation values or a change in them, and postoperative cognitive development is less established. Higher rSO2 levels proved to be able to predict this positive change in cognitive function. (141) Despite the pharmacological and surgical efforts, diabetic patients exhibited lower rSO_2 values than non-diabetic ones in all three phases of the operation. As discussed in section "Study A", these trends may have a negative influence on postoperative changes of cognitive abilities.

In addition to lower cerebral tissue saturation values observed among diabetic patients, glycemic status may also have an impact on the condition of postoperative cognition. Chronic hyperglycemia may also contribute to the poor cognitive performance of diabetic patients. (163) (164) Elevated glucose levels are associated with oxidative stress and exert

their damaging effect through numerous different cellular and biochemical pathways, contributing to the activation of proinflammatory cytokines, so increasing vascular permeability and platelet activation, and to the impairment of leukocyte function, including abnormalities of monocyte and polymorphonuclear neutrophil function and increasing the amount of circulating prothrombin fragments. (165) (166) (167) (168) The disease may impair the integrity of the blood-brain barrier, thus increasing permeability. (169) (170) By diminishing nitric oxide availability and compromising astrocytic gap junctional communication, the greater Aß accumulation may contribute to the decline. (171) (172)

Diabetes seemed to be poorly controlled in our diabetic patients, as glycated hemoglobin was elevated in a considerable part of them (70%). Inadequate glycemic control may obviously worsen the cognitive outcome and status of our diabetic patients.

Comparing the groups in relation to outcome, we observed significantly higher long-term mortality and cardio- and cerebrovascular complications among diabetic patients.

Analyzing cerebral tissue saturation from the point of view of postoperative morbidity, the threshold of rSO_2 carrying an elevated risk was determined at 65% or lower cerebral tissue saturation values. (173) This condition occurred in 15% of non-diabetic patients, while it was present in 39% of the diabetic ones. As previously mentioned, the normal value of cerebral tissue saturation was set at 67.6%, with the lowest of 56%. (125) In our patients, the median of rSO_2 values in the preclamping period was 67.4% in diabetic patients, while it was 74.6% in non-diabetic ones. Regarding the lowest values measured during the cross-clamp period, these numbers were 54.4% and 60% in diabetic and non-diabetic patients, respectively. Despite the efforts for maintaining adequate hemodynamic conditions, diabetic patients underperformed regarding both of the thresholds, which may indicate pathological circumstances and contribute to worse outcomes. (174)

We found a higher degree of stenosis of the contralateral carotid artery and higher fasting glucose levels in the diabetic group, which could have contributed to this unfavorable trend of cerebral tissue saturation.

The damaging impact of hyperglycemia has been proven in several clinical trials and has been discussed previously. (175) (176) (177)

It has been suggested that, in diabetic patients, identifying and optimizing the potential risk factors and optimizing the metabolic state and the carbohydrate condition might reduce the perioperative risk. (153) (178) (179) In relation to the carbohydrate household of our diabetic patients, this claim might be rightful, as preoperative HbA1c levels were elevated in 70% of our diabetic patients and did not show any significant improvement through the years of our follow-up time.

Better-controlled blood glucose levels might have had a beneficial effect on the less favorable outcomes experienced in the case of our diabetic patients.

Besides the carbohydrate condition of our patients, the higher degree of stenosis of the contralateral carotid artery observed in the diabetic group may have had an impact on the higher mortality rates among diabetic patients. The stenosis of the contralateral carotid artery is also associated with poor outcomes after carotid surgeries. It may contribute to the undesirable hemodynamic changes detected during the operation and thus to the adverse cardiovascular events postoperatively. (180) (181) (182)

With regards to the intraoperative hemodynamic trends, the diabetic group was characterized by hypertonic tendency. Behind this hypertonic tendency, the higher vasopressor necessity of diabetic patients may be the explanation. These trends found in our diabetic patients, the greater degree of vasopressor necessity, and the fluctuation of the trend regarding blood pressure values can all be part of a complication of diabetes, namely cardiovascular autonomic neuropathy. This phenomenon is a microangiopathic complication of diabetes, affecting parasympathetic and sympathetic fibers innervating the respiratory and cardiovascular systems. (183) (184) The reported prevalence of CAN is quite wide, as it depends on the criteria used to define it and on the studied population of diabetic patients. There are several risk factors influencing the development of CAN, among others, such as duration of diabetes, the quality of glycemic control, smoking, age, and obesity. (185) This dysfunction ends in abnormalities regarding the regulation of heart rate and blood pressure regulation, and consecutive intra- and perioperative cardiovascular instability. (185) (186) (187)

The interaction of anesthesia and CAN may help the interpretation of the fluctuating, major changes of blood pressure that can result in unexpected and severe hemodynamic instability, a greater amount of vasopressor required, higher long-term mortality, and an

elevated risk for long-term cardio- and cerebrovascular complications, experienced among our diabetic patients.

Our results underline the undeniable necessity of accurate preoperative examination, a well-treated metabolic status, careful anaesthesiological management and close monitoring, including neuromonitoring in diabetic patients.

5.3. Significance of the studies

Analyzing the impact of cerebral tissue saturation on postoperative cognitive function, as well as the effect of diabetes mellitus on cerebral tissue saturation and on perioperative outcomes, has led to an improvement of the quality of patient care and increased patients' safety in the field of anesthesiology. As a new aspect of neuromonitoring during carotid surgeries, aiming to prevent a significant drop in cerebral tissue saturation presumably will have a beneficial effect on patients' cognitive status postoperatively, so contributing to the overall well-being of our patients.

Neuromonitoring received greater emphasis in carotid surgeries, leading to a wide range of benefits in everyday practice, while the outstanding role of adequate perioperative control of carbohydrate metabolism had been strengthened.

5.3.1. Strengths of this study

Our study contributed to a yet unanswered question whether cerebral tissue saturation would have an adverse effect on postoperative cognitive function. As intact cognition is a key element of a happy, independent, and healthy life, and the population requiring surgery ages, this question has increasing relevance day by day.

5.4. Limitations

Despite our efforts to enroll a considerable number of patients, the relatively small sample size should be mentioned as limitation, as well as the single-center design of the study. Based on the HbA1c levels of our diabetic patients, their metabolic status was poorly controlled.

Though cognitive evaluation occurred during a stable phase, for the sake of completeness, it must be mentioned that these changes may alter over time.

The data from the repeated assessments are under publication. The COVID epidemic had a negative effect on the less effective follow-up.

6. Conclusions

The main purpose of this research work was to investigate the connection between cerebral tissue saturation during carotid surgeries and the postoperative status of cognitive function. To analyze this topic accurately, we investigated the potential thresholds of rSO_2 values carrying risk for cognitive decline, and the factors that may influence this outcome.

In Study A, after careful analysis, we found a strong connection between the alterations of cerebral tissue saturation during the cross-clamp period of carotid surgeries and the postoperative changes of the MoCA scores reflecting cognitive status.

Thus, the following conclusions were drawn.

A/1. Based on our results, regional cerebral tissue saturation has an impact on the postoperative changes in cognitive function as proven by the MoCA test.

A/2.1. The relative change from baseline has a more determining effect on this outcome than absolute saturation values.

A/2.2. We identified 15.5% as the relative change and 57.5% as the absolute value as reliable thresholds in terms of an impairment of cognitive function. Concerning postoperative improvement in cognition, 12.65% and 60.75% were these limits, with respect to the degree of desaturation and absolute value, respectively.

A/3. Among the preoperative factors, female gender and non-insulin dependent diabetes mellitus exerted a negative influence on cognitive outcomes, while the degree of desaturation had a significant role in both directions of cognitive changes. Lower preoperative MoCA scores had a role in predicting improvement of cognition.

A/4 In our analysis, we did not find a statistically significant connection between age, neither in relation to the trend of cerebral tissue saturation, nor in relation of cognitive changes postoperatively.

A/5. According to our analysis, only the lowest rSO_2 values showed a significant connection to the occurrence of long-term complications.

These findings underline the importance of proper neuromonitoring during carotid surgeries, as these changes, these subtle alterations in cerebral perfusion, potentially carrying an elevated risk for worse outcome, cannot be detected from the monitoring of "traditional" physiological parameters during general anesthesia. The worth of intact cognition cannot be disregarded. Using cognitive changes as an endpoint is a very sensitive marker of a successful surgery.

In Study B, we analyzed the difference between diabetic and nondiabetic patients regarding the postoperative changes of cognitive function, survival and complication rates, as well as intraoperative physiological changes. The increasing number of diabetic patients requiring surgery necessitates this knowledge in order to achieve high-level management of the affected patients. We have come to the following conclusions:

B/1. Diabetic patients experienced a greater decline in their scores on the cognitive assessment using the MoCA test. With regard to the definitive change of cognition, the tendency of cognitive improvement was less pronounced in the diabetic group.

B/2. Similarly to the results of cognitive evaluation, diabetic patients were at greater risk of mortality and MACCE during the follow-up period.

B/3. During the surgeries, diabetic patients required more doses of vasopressor therapy and more often, leading to higher blood pressure values. Despite this hypertonic tendency, the absolute values of cerebral tissue saturation were generally lower in the diabetic group.

7. Summary

The aim of my research was to investigate the impact of cerebral tissue saturation and its change during the cross-clamp period on the patients' cognitive status. Cognitive function did not receive much interest, however, in the past few years it has gained more and more attention. So far, the evaluation of cognitive function, as well as preservation of cognitive skills, has not been in the focus of perioperative assessment and management. In our aging population, the relevance of mental health is getting more emphasis. With the decreasing rates of complications, we can contribute to the success of a carotid surgery, that is, the maintenance and ideally the improvement of cognitive status.

In this thesis, I have explained the connection between cerebral tissue saturation measured via NIRS and postoperative cognitive function assessed with the MoCA test. As the change in rSO_2 has a more determining role in the trend of postoperative mental status, preventing a significant drop in cerebral tissue saturation has an emphasized role during the intervention. In a subanalysis, the lowest cerebral tissue saturation values showed a significant association with the occurrence of long-term complications.
These results confirm the usefulness of NIRS monitoring during carotid surgeries, the need for neuromonitoring during these surgeries, and the eligibility of the MoCA test for assessing cognitive function in the perioperative period.

The increasing number of diabetic patients raised the necessity of our second research question, analyzing diabetic patients with respect to postoperative cognitive status, survival, and intraoperative trends of hemodynamic and cerebral parameters. The elevated risk for worse outcomes (higher risk for mortality and MACCE) and lower postoperative cognitive performance strengthened the relevance of the third point, the relevance of the change of physiologic parameters. The aim was to investigate the physiologic changes characteristic of this comorbidity in order to achieve a more professional management, thereby improving the outcomes of the affected patients. Diabetic patients proved to be more sensitive to anesthesiological and surgical stress, so in their cases the role of thorough preoperative assessment, as well as careful management and neuromonitoring must be highlighted.

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