TECHNISCHE UNIVERSITÄT MÜNCHEN

TUM School of Medicine and Health

Prädiktive Relevanz des intraoperativen Neuromonitorings bei der elektiven operativen Behandlung intrakranieller Aneurysmen

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INTRODUCTION

Unruptured intracranial aneurysms (UIAs) are surgically clipped in order to reduce the risk of rupture and subsequent subarachnoid hemorrhage (SAH) or, in rare cases, a mass effect, both of which might result in fatal results. [1–7]

Despite recent improvements in microsurgical methods, surgery for cerebral aneurysms still has a high rate of morbidity.[8] Ischemia of eloquent brain areas and subsequently impaired neurological function can be caused by a variety of intraoperative circumstances or occurrences. In many situations, examination alone is insufficient to detect imminent ischemia, and it must be supplemented with additional approaches better suited for such monitoring purposes.[8] As there is a 0.25%-1% annual risk of spontaneous rupture of an aneurysm, with subsequent subarachnoid hemorrhage, the morbidity rate after elective aneurysm clipping should be lower than that to justify the preventive treatment. [1,5,6,9,10]

In today's brain vascular surgery, intraoperative neuromonitoring (IOM) of motor and somatosensory evoked potentials is a well-established approach for reducing postoperative neurologic morbidity [1,11–15]

IOM encompasses a plethora of technological systems and electrophysiological modalities, resulting in a diverse set of potential application domains. IOM gives real-time feedback of patient’s motor and sensitive function. It is utilized to detect the eventual shift in nerve conduction caused by decreased blood flow and structural injury, in the reversible phase, to prevent lasting neurologic impairments.[1,9]

As the technology has become increasingly popular and still grows, IOM is being used more frequently in neurosurgical procedures as it became an essential part of the neurosurgical armamentarium. [11]

Nevertheless, the predictive value and sensitivity of IOM in the microsurgical clipping of UIAs is still under discussion and remains elusive [16–19]. It is further important to note that false-negative monitoring has a detrimental impact on the surgeon's trust in IOM. [19,20]

The aim of this study was to define the predictive value of IOM in the elective surgical treatment of UIAs and to assess its subjective intraoperative value for the surgeon.

1.1. Intracranial Aneurysms

1.1.1. Epidemiology

Intracranial aneurysms are focal abnormal dilatations in the wall of the cerebral arteries. There are four primary types of intracranial aneurysms: saccular, dissecting, fusiform, and micotic. The saccular type accounts for approximately 90% of intracranial aneurysms. Saccular intracranial aneurysms occur in about 1.0 - 2.0 % of the population. [21] Further imaging studies

with MRI and arteriography show that 0.5 to 3.0% of the population carries an unruptured intracranial aneurysm. A European prevalence study found the prevalence of saccular intracranial aneurysms to be 1.8% in adults.[21]

These vascular alterations are not congenital but rather acquired as a result of several factors. The origin, as well as the influencing factors, have not been determined conclusively.[5,22] Nevertheless, genetic, and detrimental non-genetic variables that contribute to the development of intracranial aneurysms can be distinguished.

The following major risk variables have been agreed upon in recent investigations. [3,23,24]

First, hemodynamic plays an important role in the development and growth of intracranial aneurysms.

Common vascular risk factors, particularly hypertension, lipid accumulation, and atherosclerosis, cause hemodynamic stress in the vessels.

Thus, higher wall shear stresses caused by pressure fluctuations lead to significant changes in the vessel wall that favor the development and growth of intracranial aneurysms. [3,23,24]

In addition to the vascular risk factors mentioned above, cigarette smoking and alcohol abuse can lead to a reduction in vascular stability and oxygenation, promoting progressive increase of aneurysm size and even favoring rupture of the aneurysm. [3,23,24] Smokers, for example, are three times more likely than non-smokers to develop an intracranial aneurysm. [3]

Certain genetic variables have been linked to an increased risk of intracranial aneurysms. Hereditary collagenous connective tissue disorder is thought to be positively correlated to the presence of intracranial aneurysms. When compared to reference populations, those with a first-degree family diagnosed with an intracranial aneurysm or SAH (prevalence ratio (PR) 3.4, 95 %, CI 1.9–5.9) or autosomal dominant polycystic kidney disease (PR 6.9, 95 % CI 3.5–14.0) have a higher risk of UIA. [3]

Several studies have revealed a female predominance among patients with UIA. [3,25]

Patients with a history of SAH, have an 11 times higher relative risk of rupture, as compared with patients without previous hemorrhage. [26]

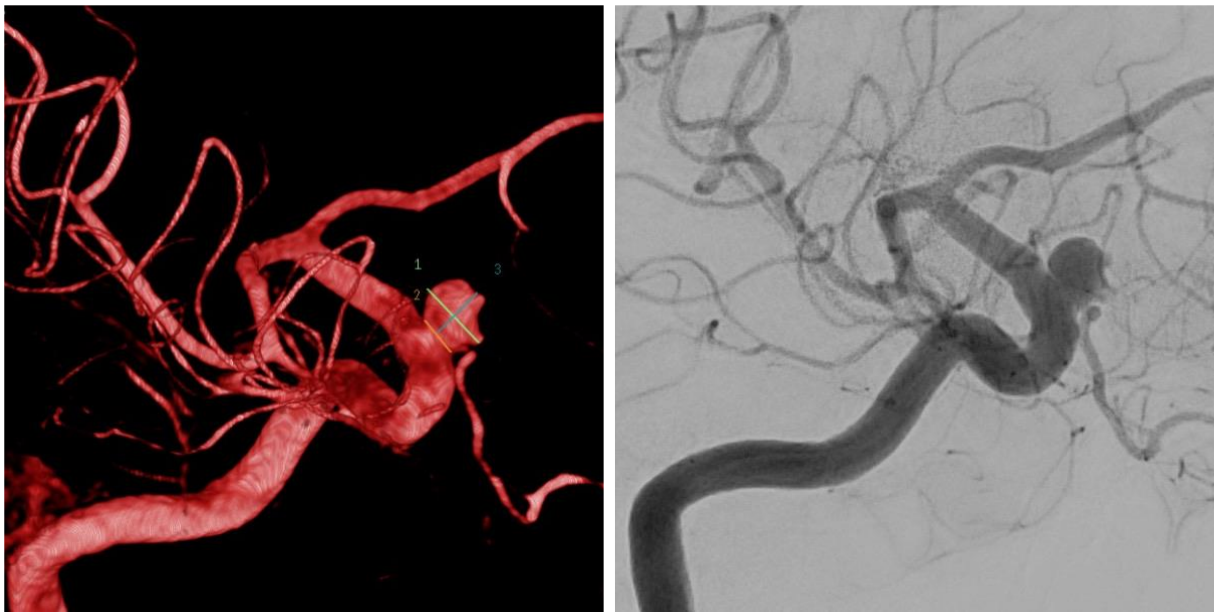

Figure 1: Paraophtalmic ICA Aneurysm, Preoperative Angiography, Digital Subtraction Angiography (right) and three-dimensional reconstruction (left)

IAs affect about 3% of the german population, implying that over 2 million Germans have an UIA.

Due to the increasing frequency of brain imaging, the number of incidentally discovered aneurysms is increasing.[27,28]

Eighty-five percent of the saccular aneurysms originate from the arteries of the circle of Willis. The internal carotid artery (ICA), the anterior and middle cerebral arteries (ACA, MCA), and their branches harbor 80–90 percent of all cerebral aneurysms, whereas just 10–20 percent are located in the posterior circulation (the vertebral (VA), basilar (BA), and posterior cerebral arteries (PCA) and their branches). Multiple aneurysms are found in 30% of the patients. [22]

Table 1: Most common locations of intracranial aneurysms and their frequencies in percent.

Location	**Frequency (%)**
Anterior communicating artery	35
Internal carotid artery	30
Middle cerebral artery	22

Most UIAs are diagnosed incidentally during a routine examination in the absence of neurological symptoms. Neurological impairments owing to local mass impact, such as palsies of the cranial nerves feeding the ocular muscles (ptosis, mydriasis, or diplopia), are less common clinical correlates of larger UIAs [2] Other clinical manifestations include a stroke or a

seizure. [25]It can be presumed, these aneurysms that lead to the above-mentioned symptoms within just a few days or weeks are growing more rapidly, are generally larger, and therefore carry a much higher risk of rupturing with them. [2]

As a consequence of increasing diagnostic, clinicians are more frequently faced with a dilemma, regarding the appropriate clinical management, namely, preventive treatments with inherent complications, or conservative management with or without follow-up imaging, which leaves patients at small but definite risk of aneurysm rupture. [3]

A rupture of an intracranial aneurysm (IA) results in a subarachnoid hemorrhage, a life-threatening clinical event.

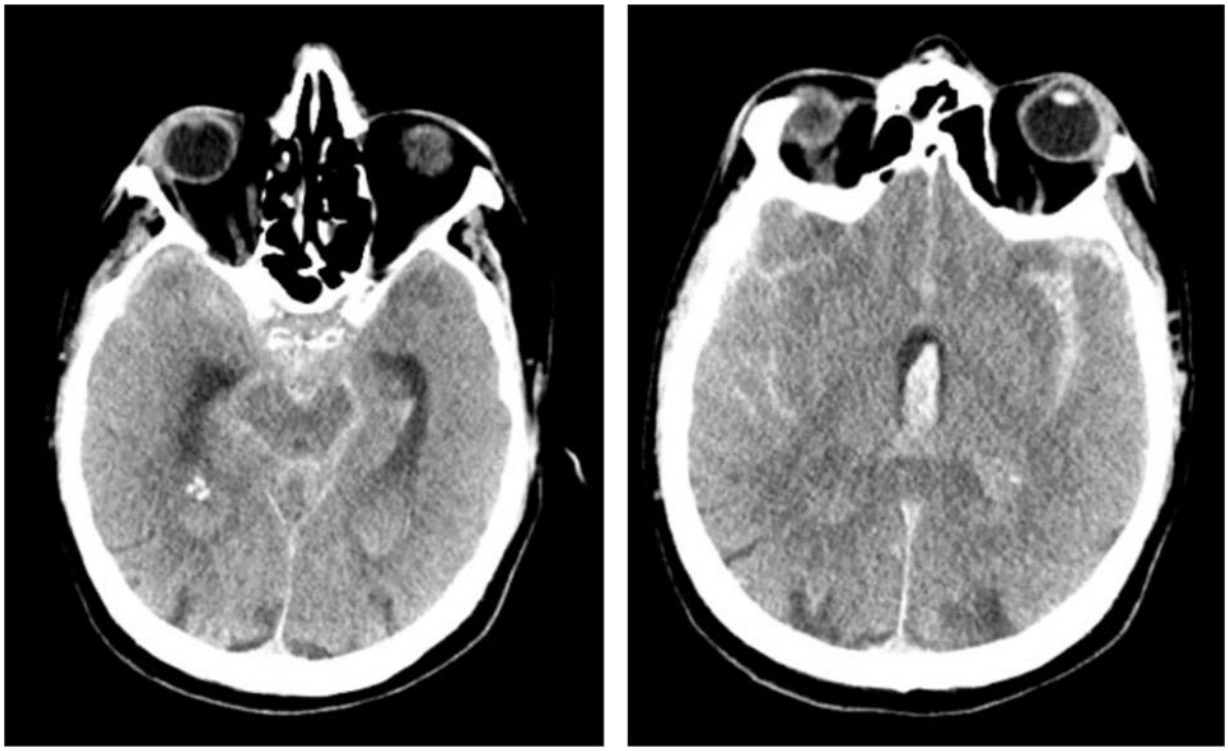

Figure 2: Cranial computed tomography of a patient with a SAH Hunt and Hess °IV due to a ruptured intracranial aneurysm of the basilar artery. The basal cisterns and the subarachnoid spaces are filled with blood. Furthermore, the computed tomography shows an intraventricular hemorrhage.

Several studies have outlined factors that increase the risk of rupture of IAs.

The PHASES Score is often utilized in clinical practice. It is the result of a meta-analysis of six prospective cohort studies with 8382 patients and 29166 patient-years of follow-up.[27]

It combines patient origin (the risk of rupture was found to be 2-8 times higher in the Finnish and Japanese populations.), age, hypertension, aneurysm size, aneurysm location, and previous SAH.

Table 2: PHASES aneurysm risk score. It combines patients' origin, age, hypertension, aneurysm size, aneurysm location and previous subarachnoid hemorrhage. SAH = subarachnoid haemorrhage, ICA= internal carotic artery, ACA=anterior cerebral arteries (including the anterior cerebral artery, pericallosal artery, anterior communicating artery), MCA=middle cerebral artery, Pcom=posterior communicating artery, posterior=posterior circulation (including vertrebral artery, basilar artery, cerebellar arteries, posterior cerebral artery). (Greving et al. 2014)

PHASES aneurysm risk score	**Points**
(P) Population	
North American, European (other than Finnish)	0
Japanese	3
Finnish	5
(H) Hypertension	
No	0
Yes	1
(A) Age	
< 70 years	0
≥ 70 years	1
(S) Size of aneurysm	
< 7.0 mm	0
7.0 – 9.9 mm	3
10.0 – 19.9 mm	6
≥ 20 mm	10
(E) Earlier SAH from another aneurysm	
No	0
Yes	1
(S) Site of aneurysm	
ICA	0
MCA	2
ACA/Pcom/posterior	4

The resulting score predicts a patient's risk of aneurysm rupture within the next five years. [27] The management and treatment of UIAs is discussed controversially.

It is complicated by several variables. The risk of rupture assumes special importance when deciding which aneurysm to treat. [6,21,26]The natural history hazards of site, size, and group should be compared to the location, size, and age-specific risks of repair for each patient.[6] **(Figure 3)**

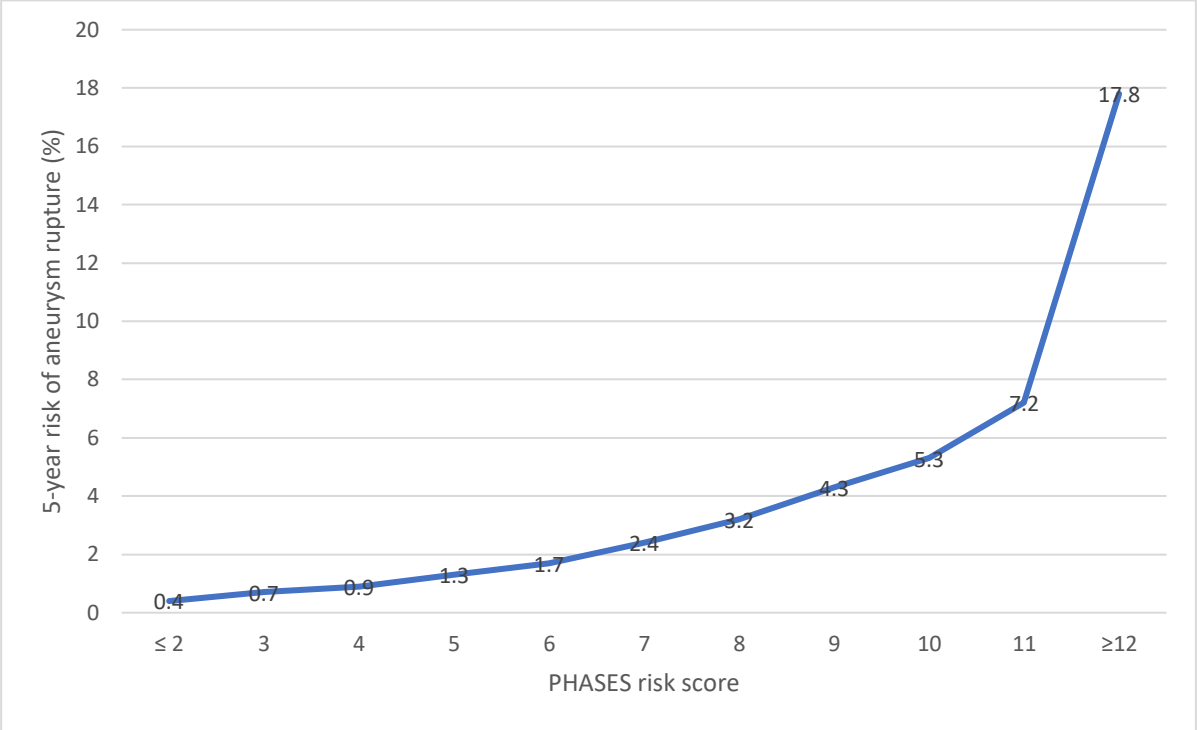

Figure 3: Calculated five-year risk of aneurysm rupture. It combines patients' origin, age, hypertension, aneurysm size, aneurysm location and previous subarachnoid hemorrhage. (Greving et al. 2014)

1.1.2. Diagnostic approach

The present high number of imaging examinations used in the diagnosis of neurological and neurosurgical diseases and the increasingly rapid access to high-quality, non-invasive imaging procedures have led to intracranial aneurysms being detected more frequently as asymptomatic incidental findings. [3,29]

The common modalities for delineation of size and morphology of IAs are computed tomography (CT), magnetic resonance imaging (MRI), and digital subtraction catheter angiography (DSA).

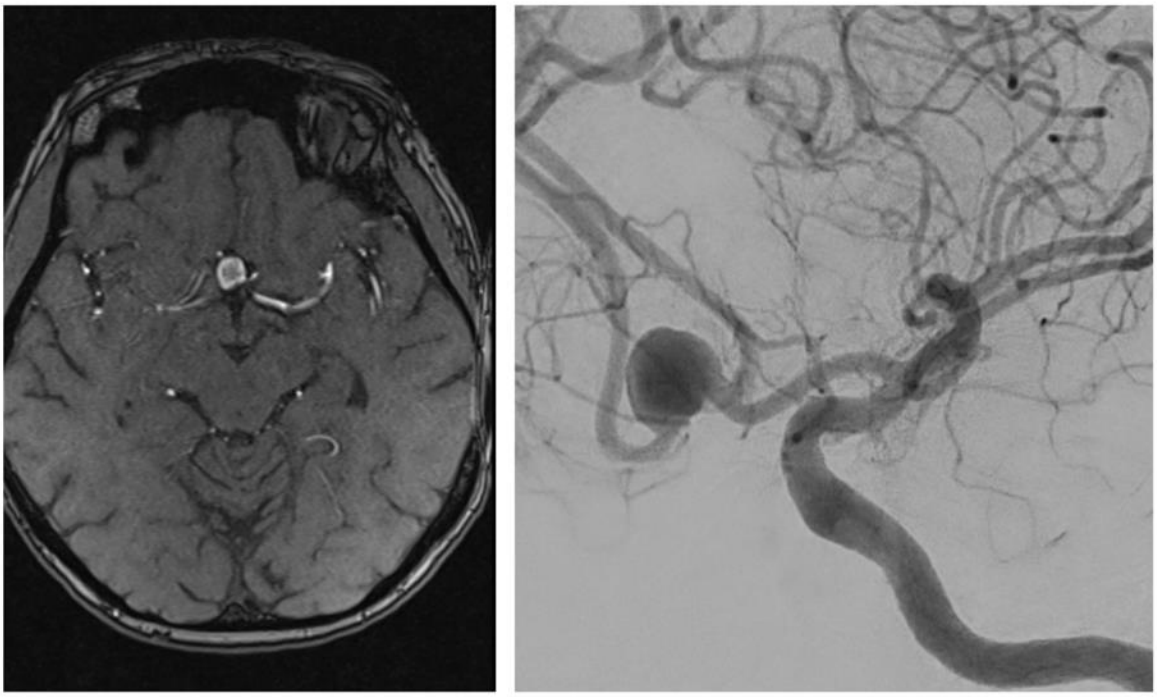

Figure 4: AcomA Aneurysm (8mm, PHASES Score 8: 5-year rupture risk: 3,2%), MRI with gadolinium contrast media on the left. Preoperative Angiography: Digital Subtraction Angiography on the right.

As the sensitivity of CT and MRI is lower, compared to DSA, the DSA is considered the gold standard technique for diagnosis of aneurysms or other vascular abnormalities. Additionally, depending on the clinical course, DSA offers the opportunity of direct endovascular treatment of the aneurysm.

CT together with its adjunct techniques CT angiography (CTA) and CT perfusion, is able to image the aneurysm, the feeding vessels, and the cerebral status of blood flow.

CTA shows brain arteries in three-dimensional views using thin-section contrast-enhanced CT and software-generated images. These reconstructed images can be obtained in a matter of minutes and enable for the evaluation of the vasculature in close proximity to the brain and the bones of the skull base, aiding surgical planning. [30]

However, sensitivity of CTA is significantly lower (83% for small aneurysms <4mm) compared to DSA [30]. Both, CTA and DSA are associated with radiation exposure and possible allergy to iodinated contrast agent.

MRA is another non-invasive technique with a high sensitivity of 95% for detecting intracranial aneurysms. It does not involve radiation exposure, which makes it ideal for a screening setting and for long-term follow-up of patients with treated and untreated IAs. [31]

Accordingly, catheter angiography remains the gold standard for the diagnosis of IAs, providing a comprehensive assessment of the aneurysm and its relationship to adjacent vessels, which is critical for optimal treatment.

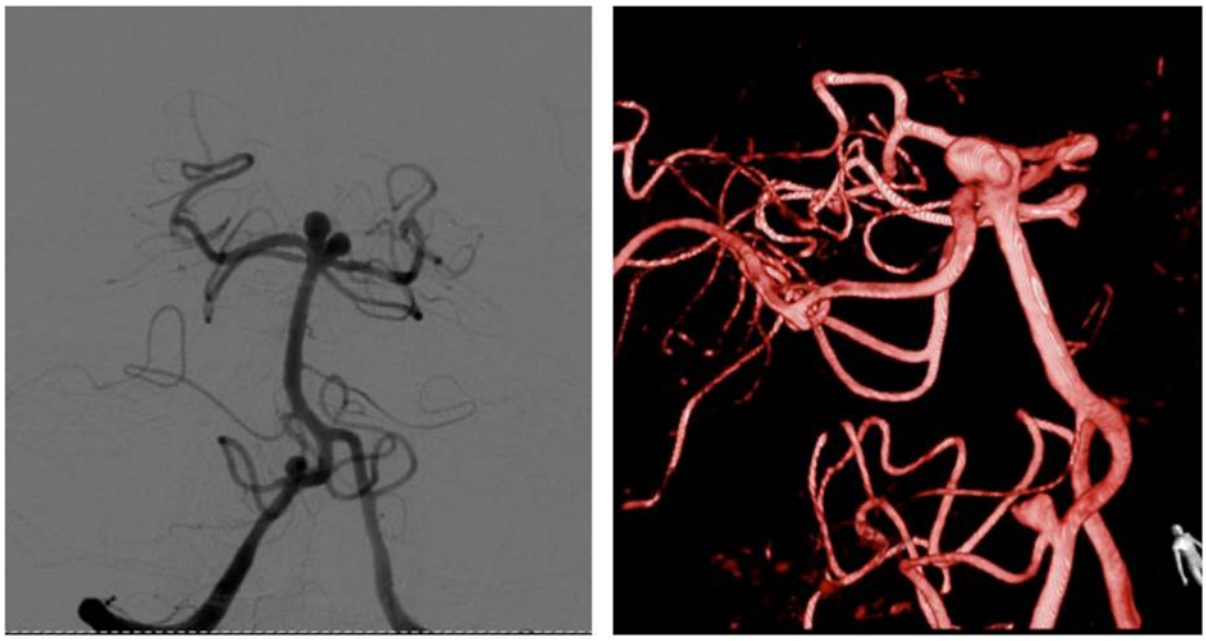

Figure 5: Preoperative Angiography of a patient with an intracranial aneurysm of the right posterior inferior cerebellar artery (PICA) and an aneurysm of the basilar artery (BA). Digital Subtraction Angiography (left) and three-dimensional reconstruction (right).

1.1.3. Clinical aspects of intracranial aneurysms

The majority of UIA remain asymptomatic for many years[2], as the prevalence of small aneurysms is significantly higher, than the prevalence of large symptomatic UIA, having a local mass effect on the brain or compressing the cranial nerves, resulting in focal neurologic deficits [24,2]

Even though the incidence of aneurysmal rupture and subsequent SAH (10 cases per 100.000 persons per year) is low[26,32,33], the high case fatality rate and morbidity of subarachnoid hemorrhage underlines the importance of preventive management in each case. Ten to twenty-five percent of people with acute SAH die soon after the hemorrhage or before reaching the hospital.[22]

A SAH is a type of intracranial extra-axial hemorrhage and characterized by blood within the subarachnoid space, between the arachnoid membrane and the pia mater.

Patients typically present with thunderclap headache, described as a sudden-onset headache that is the most severe headache of their lives. Focal neurological deficits often occur simultaneously with or shortly after the headache. It is often associated with photophobia and meningism.[32]

Patients can be classified into five groups based on their clinical appearance using the internationally employed Hunt and Hess grading system, which is a predictor of survival [32,34].

Depending on the severity, symptoms range from a mild headache, vomiting, and dizziness to seizures and coma. [22,34]

The number of years of potential life lost as a result of acute SAH (aSAH) is comparable to that lost because of ischemic stroke and intracerebral haemorrhage.[29] This kind of bleeding has a high case fatality and morbidity rate, and it is a common subtype of stroke. [35]

Beyond this, the SAH bears a significant financial burden.[29]

When compared to those who have other stroke subtypes, many people with ruptured cerebral aneurysms are young, having an average age of around 55 years.[36]

The young age of onset, as indicated above, and the poor outcome are the key causes for the massive impact of SAH.[37]

Compared to the general population, there is evidence that patients who have had an initial SAH from an aneurysm are more likely to develop a new aneurysm and have another SAH.

mortality after survival from aSAH was actually higher compared to healthy people of the same age and sex.[36]

Despite the fact that two-thirds of aSAH survivors regain functional independence, half of them have cognitive deficits, half are dissatisfied with their lives, and just a third return to the same job they had before the event of SAH.[4,22]

Given these circumstances, it is apparent that minimizing the risk of rupture, as well as optimizing the therapy of IAs, is significantly important.

1.1.4. Therapeutic options for intracranial aneurysms

The variety of treatment options for aneurysms necessitates careful examination of the strategy on an individual basis. It should be emphasized that surgical and endovascular techniques are complementary rather than competitive; the procedures are suitable for different circumstances. [33,38–40]

No matter, which modality was used in the diagnostic, there are several parameters, that must be documented, in relation to the right treatment for the patient. The choice is primarily based on the shape of the aneurysm, but the condition and age of the patient must also be considered.

1.1.4.1.Surgical Clipping

Clipping is an open microsurgical procedure, that seals off the aneurysm's neck, preventing the blood from entering the aneurysm. By placing a titanium clip across the base or neck, the IA is completely excluded from the normal blood circulation, without blocking of any small perforating vessels nearby. Under general anesthesia, a craniotomy is performed to open the skull and access the aneurysm. In most cases, a pterional approach is used depending on the location of the aneurysm. After dural opening, the brain is gently retracted to locate the aneurysm and to explore vascular supply. The clip is placed with optimal protection of the surrounding vessels.

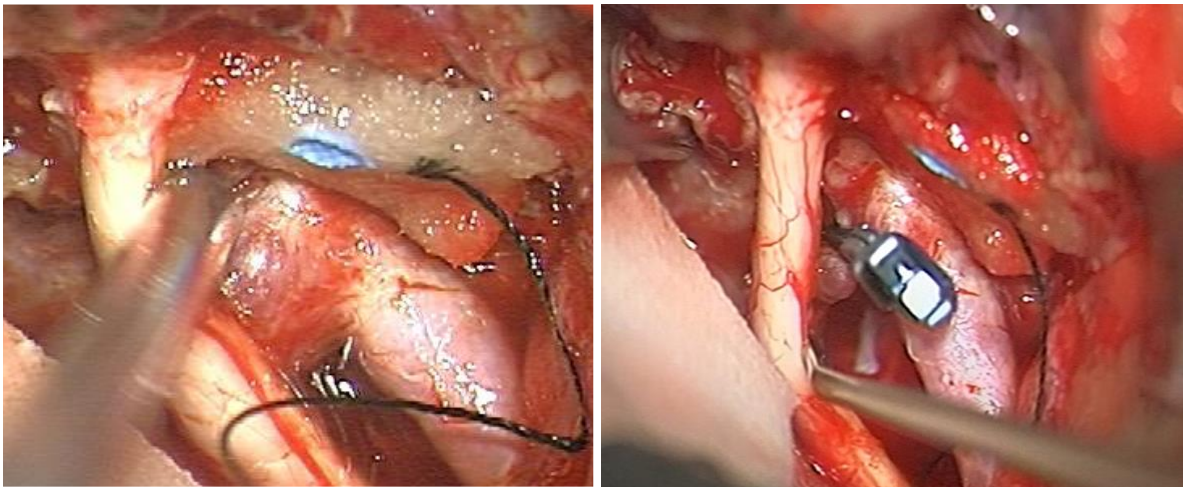

Figure 6:Intraoperative view. Paraophtalmic aneurysm protruding to right optic nerve (left). After placement of the titanium clip (right)

Technical equipment such as IOM, Indocyanide-Green angiography (ICG angiography) and microvascular Doppler systems are utilized to ensure the highest level of safety during the procedure and to achieve the best possible outcome. [8]

Due to low rebleeding rates and good long-term follow-ups, microsurgical clipping of IAs has become the gold standard surgical therapy.

Additionally, surgical treatment is associated with the best angiographic outcome, as endovascular treatment has the crucial issue of incomplete closure, as well as the uncertainty about the long-term durability of aneurysm-occlusion. [38]

However, surgical treatment is associated with higher perioperative mortality (1.2-3.5% for surgical clipping and 0.5-1.7% for endovascular coiling) because it is more invasive than endovascular treatment. [33,38]

1.1.4.2.Endovascular Coiling

The use of detachable coils for intra-aneurysmal occlusion is based on two electrochemical principles: electro thrombosis and electrolysis. This causes intra-aneurysmal thrombosis and the development of clots. [41] In the 1990s the Guglielmi detachable coil (GDC; Boston

Scientific/Target Therapeutics, Freemont, CA, USA) was firstly established in the USA.[33,41] The coils are placed into the aneurysm via microcatheter that is entered through the femoral or radial artery and advanced into the brain. It allows the endovascular treatment of IA, without the need of craniotomy. Thus, compared to open surgery, the operative trauma is reduced, and the procedure is, therefore, more gentle.

In recent decades, endovascular treatment of IA has become increasingly popular as expertise grows, and techniques evolve. (20.5% endovascular coiling in 1998, 54% in 2009) [9]

The approach is particularly useful for saccular aneurysms with a narrow neck and a typical configuration. Aneurysms that can't be reached with a traditional surgical method may nevertheless be able to be treated endovascularly.

1.1.4.3.Current evidence on Surgical Clipping vs. Endovascular Coiling

The management of IAs, especially UIAs, is contentious due to lack of understanding of the natural history of IAs and risk of repairing them. [6,26]

As it is crucial to choose the optimal therapy for the patient to determine which treatment provides the best possible clinical outcome, several studies comparing these two treatment options have been conducted in the recent decades.

The International Subarachnoid Aneurysm Trial (ISAT)[33,38] and International Study of Unruptured Intracranial Aneurysms (ISUIA)[6,26] have strongly influenced the management of IAs, as they were conducted to compare the safety and efficacy of endovascular coiling with microsurgical clipping (ISAT) and to determine the risk of rupture and the risks associated with the treatment of UIAs (ISUIA).

Comparing the two treatment modalities, studies have outlined, that when a patient's clinical grade is good and the aneurysm anatomy is compatible for endovascular therapy, endovascular coil treatment of ruptured cerebral aneurysms is more likely than neurosurgical treatment to result in independent survival at one year. [33,38] The risk of seizures occurring after surgical clipping is significantly higher compared with endovascular coiling. [38]

However, endovascular treatment harbors a higher risk of aneurysm residual or recurrence of aneurysm after complete closure.[9,28,38]. Incomplete closure of the aneurysm at short-term follow-up is more common in up to 46% of cases than inadequate clipping in about 1.5% of cases. The patients with coiled aneurysms were more likely to require additional hospitalizations for repair procedures (28,1% after endovascular coiling, 9,5% after surgical clipping). [9] Therefore, post-interventional follow-up must be planned for at least 6 months after the procedure. [33,39,42]

In conclusion, the early mortality advantage and superior perioperative outcomes of endovascular coiling over clipping are counterbalanced at long-term follow-up after hospitalization, and it even tends to worsen survival.[9,38] This discrepancy between

perioperative and long-term mortality rates could be attributed to a higher number of subsequent hospitalizations for aneurysm repair procedures after endovascular coiling, as well as patient-related risk factors.[9]

1.2. Intraoperative Neuromonitoring

The above-mentioned hazards of surgical clipping necessitate sophisticated intraoperative monitoring techniques, as minimizing the perioperative risk is crucial for optimal clinical outcome after surgery. IOM encompasses a plethora of technological systems and electrophysiological modalities, resulting in a diverse set of potential application domains.

The use of neurophysiological techniques during surgery enables for accurate identification of the sensorimotor region, which is essential for its anatomical and functional preservation.[43]

IOM is widely established during surgery for IAs, for tumors of the rolandic region, for tumors adjacent to the pyramidal tract, or for intraspinal tumors. [8,11,19,44]

It is not only used in neurosurgical operations but is also becoming increasingly important and valued in thoracic interventions and thyroid surgery.

The IOM's potential applications are constantly expanding, so it will soon be able to help protect patients from post-operative deficits in a wide range of surgical procedures.

This growth ensures that it is not only an essential part of the surgical armamentarium for current operations, but also for future ones.[14]

1.2.1. History of IOM

The history of IOM goes back to the 19th century when Flourens (1842) analyzed and localized cerebral functions physiologically. By removing defined areas of the pigeons' brain, he concluded that certain areas of the brain localize specific functions. In 1870 Hitzig performed the first successful electrical stimulation. [44]

The study published by Penfield and Boldrey in 1937 established intraoperative cortical stimulation as standard method in patients without general anesthesia. To treat epilepsy, they exposed the cortex of conscious patients to electrical impulses intraoperatively and constructed the somatosensory homunculus from the results. They were able to more accurately target particular regions of the brain with this electrical stimulation and improve their patients' postoperative outcomes. [17,43,44]

In 1991, LeRoux et al modified this technique, paving the way for intraoperative electrical stimulation of the cortex in patients under general anesthesia. [43] They were the first ones, using monitoring of evoked potentials in neurosurgery. With the aid of cortical and subcortical stimulation mapping techniques, they performed surgical resection of tumors in the rolandic region of the brain. [45]

1.2.2. Aims of IOM

The central objective of all IOM procedures is to provide real-time or close to real-time feedback to the operative team to prevent or minimize iatrogenic injury to critical neural structures including eloquent areas of the brain, spinal cord, cranial nerves, spinal nerve roots, and peripheral nerves. [14]

IOM prevents lasting neurologic impairments since it is used to detect the eventual shift in nerve conduction caused by decreased blood flow and structural injury in the reversible phase. [1,9]

Several studies confirmed the increased surgical safety when using IOM and also provide evidence of improved outcomes in surgical procedures where eloquent neural structures are at risk. [15,17,43,46] Intraoperative neurophysiologic techniques not only evaluate the functional integrity of the observed system but also provide the surgeon with more confidence while confirming the functional integrity of eloquent structures during surgery.

1.2.3. Types of IOM

IOM incorporates a plethora of technological systems and electrophysiological modalities, resulting in a diverse set of potential application domains. In general, two methods of monitoring can be distinguished.

Somatosensory evoked potentials (SSEP) are electrocortical potentials of brain activity that arise in response to a repetitive specific peripheral stimulus and can be determined as a derivable correlate from general electroencephalogram (EEG) activity. These include auditory evoked potentials (AEP), which are elicited by acoustic signals, visual evoked potentials (VEP), which are evoked by visual stimuli, and SSEPs, which are generated by electrical stimulation of peripheral sensory nerves.

1.2.3.1.Motor evoked potentials

To monitor the motor pathway, motor evoked potentials (MEPs) are used.

Transcranial electric stimulation of the primary motor cortex (M1) causes a distinct response in the motor unit of the corresponding muscle in the form of a transcranial motor-evoked potential (tcMEP). Extremity electromyography is recorded, and the amplitude and latency are assessed. If the blood supply to the cortex is disrupted by an incorrectly placed clip, it leads to a lack of oxygen and consequently an ischemia of the underperfused brain area. If M1 is affected, the ischemia results in a decrease in tcMEP, indicating to the surgeon that the patient's motor integrity is jeopardized.

The tcMEPs are based on neuroanatomical and neurophysiological principles. According to Brodmann, M1 is located in the precentral gyrus and forms the origin of motor function. [44,47,48]

Due to somatotopic organization of the cortex as a sensomotory homunculus, specific motor units can be addressed individually. [44]

The pyramidal tract consists of two distinct pathways, encompassing the corticospinal and the corticonuclear tract. They originate in giant pyramidal cells from layer V in M1 and terminate in alpha motor neurons in the spinal cord (corticospinal) or brainstem (corticonuclear). The axons of the primary motor neurons descend through the internal capsule and synapse on the spinal cord (corticospinal tract) controlling movements in the trunk and limbs or on the cranial nerves (corticonuclear) controlling muscles of the face, neck, and head.

The middle cerebral artery supplies blood to the primary motor cortex for the face and upper extremities, while the anterior cerebral artery supplies blood to M1 for the lower extremities (ACA). A blockage of either of these arteries can cause weakness in the affected limbs. The lenticulostriate arteries (branches of the MCA) perforate the internal capsule The occlusion of these will result in contralateral upper and lower extremity weakness. The basilar artery supplies the tractus further down in the brainstem. A blockage causes a variety of symptoms, including nerve palsies, tetraplegia, failures of the protective reflexes and death.

Using IOM, this anatomic pathway can be induced externally by applying an electric current to the scalp: the membrane potential of adjacent neurons depolarizes and is lifted to threshold, generating an action potential. Following the pyramidal tract and the peripheral nerve, it results in a contraction of the activated muscles, which can be recorded as evoked potentials by electromyography (EMG). [49] The generated EMG potentials then allow the valid mapping of the functional integrity of the motor pathways and core areas, on the basis of their latency and amplitudes. [8,11]

After inducing anesthesia and positioning the patient, stimulation needles are placed subcutaneously at the C3 and C4 positions in accordance with the standardized international ten-twenty (10-20) system (by Jasper et al.). [50] **(Figure 7)**

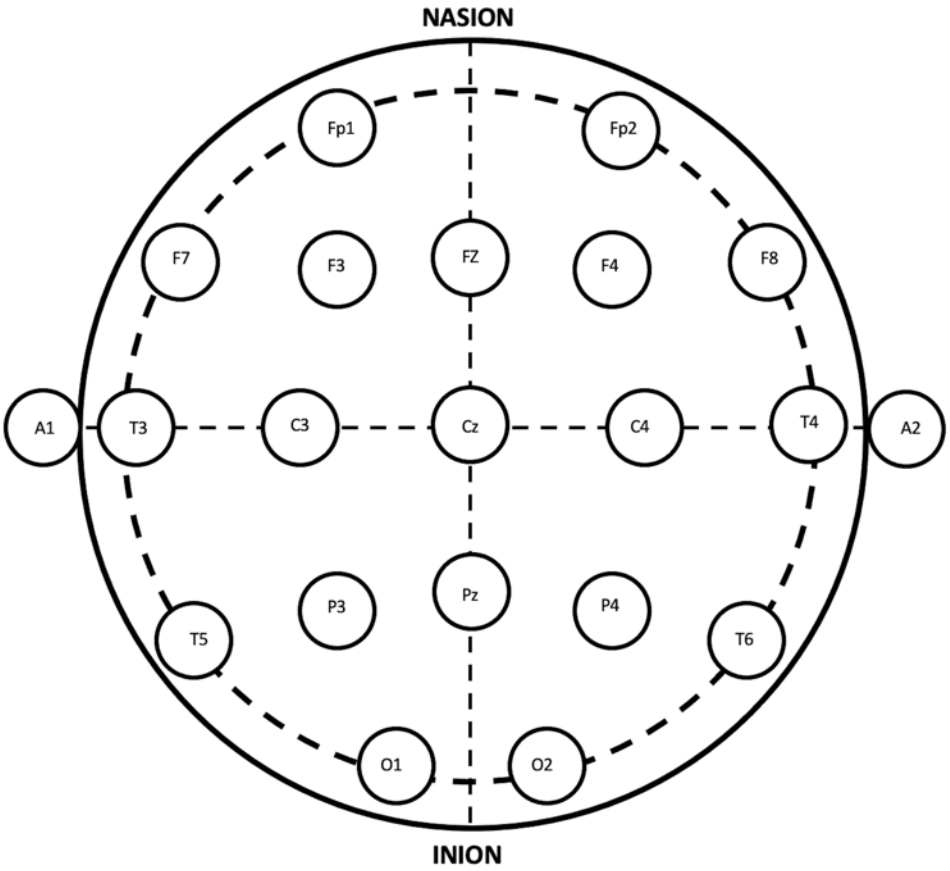

Figure 7: Schematic depiction of the international 10–20 system (By Jasper et al. 1957) and the electrode placements. C3 and C4 correspond to placements over the primary motor cortex.[50]

For detection of compound muscle action potentials (CMAPs) the needle electrodes are placed in a bipolar way with a distance of approximately 10 mm over the thenar (M. abductor pollicis brevis) and brachial biceps for the upper extremity and the anterior tibial muscle and flexor hallucis brevis for the lower limb, contralateral to the side of transcranial stimulation. In order to derive MEPs under general anesthesia, a high-frequency pulse series is necessary for each stimulation. [43,47,49] The most established stimulation technique is a train of five pulses with a high frequency of 300-500 Hz, a pulse duration of 0.2-0.3 msec and an intensity of 1 to 30 mA. Depending on the anesthetic depth and choice of narcotics the parameters differ individually. [19,43,47,51]

1.2.3.2.Somatosensory evoked potentials

SSEPs are electrocortical potentials of brain activity that arise in response to a repetitive specific peripheral stimulus and can be determined as a derivable correlate from general electroencephalogram (EEG) activity. When conducting this type of electrophysiological testing, the pathway for the stimulus to enter must be investigated first, which includes vision,

hearing, and peripheral nerve/spinal cord function. [52] VEPs are applied in certain brain surgeries near the optic chiasm, the visual tracts, or occipital cortices. Pattern reversal stimulus are used to activate the optic nerve and visual pathway The use of SSEPs in Neurosurgery is most standardized in spinal an posterior fossa surgery, frequently in conjunction with the use of AEPs. [52] The latter is also ideal for monitoring interventions near the vestibulocochlear nerve (VIII).
Therefore, the choice of the intraoperative monitoring technique depends on the location and type of pathology that must be treated. In microsurgical clipping of IAs, this is the area of supply that is perforated by the artery carrying the aneurysm.

SSEPs are elicited by electrically stimulating peripheral nerves of the upper (Median nerve) or lower extremity (Posterior tibial nerve). The responses are derived by subdermal needle electrodes located over the contralateral postcentral region, as well as over the spinal cord and peripheral nervous system. The median nerve recording should last 40 msec and the posterior tibial nerve recording should last 60 msec. [52] Recording electrodes are placed at C3' and C4' scalp locations (approximately 20 mm posterior from C3 and C4, respectively), and at Erb's point (EP). The SSEPs assesses the functional integrity of peripheral sensory nerves, spinal ganglia, dorsal columns, medial lemniscus, thalamus, thalamocortical tract and primary somatosensory cortex (S1) in the postcentral gyrus.

1.3. Current evidence on IOM

The IOM techniques that are available, have been increasingly used in the past decades and they are steadily improving. [11] Despite the fact that multiple studies have shown beneficial effects, there is still uncertainty about the predictive value and sensitivity of IOM.
In neurosurgery, IOM serves as a warning criterion for intracranial and spinal operations. Changes in amplitude or latency are signs of a vulnerability that could lead to focal neurological deficits. Decreasing amplitudes and extended latency times need to be addressed with special care. [43] Studies from Szelenyi et al. have shown that the intraoperative utilization of motor and somatosensory evoked potentials is a well-established approach for reducing postoperative neurologic deficiency[11]. MEP showed a significantly good correlation between intraoperative neurophysiological events and postoperative focal neurological deficits. Neuloh et al. were even able to demonstrate the MEP's superiority over the combination of SSEP and microdoppler [8]. In Glioma surgery, the utilization of IOM leads to an improved quality of resection, since the surgeon has a higher sense of security operating according to functional frontiers, due to the given real-time feedback. [19]

1.3.1. Reliability and predictive value of IOM

The correlation of intraoperative neurophysiological alterations with postoperative focal neurological deterioration is a crucial concern of research on IOM. Especially the sensitivity, specificity and predictive values of IOM are extensively under discussion. Even though false negative results are much more detrimental than false positive results, both of them should not occur too often, as they both have a deleterious impact on the surgeon's trust in IOM [20]. With regard to the false negative results, Krieg et al. were able to prove a high sensitivity of IOM in their study on glioma resection. False negative cases were described as patients with deteriorated motor function without showing MEP changes during surgery. In the study the postoperative neurological deficits were due to postoperative complications, such as brain edema, intracerebral hemorrhage, or ischemia (insufficient perfusion over time). Consequently, the cases initially interpreted as false-negative can be adequately explained by a secondary event after surgery, which is very important for the credibility of the IOM.[19]

1.4. Objectives of this thesis

Although the number of IAs being treated, is steadily increasing and microsurgical techniques are improving, the treatment of IAs is still associated with significant morbidity. [8,9]

Ischemic complications after aneurysm clipping are a critical source of postoperative neurological morbidity.

Minimizing perioperative risk and avoiding adverse events is crucial to achieving optimal short- and long-term patient outcomes that justify elective surgical treatment.

In today's brain vascular surgery, IOM of motor and somatosensory evoked potentials is a well-established approach for reducing postoperative neurological deficits. In the reversible phase, the IOM is utilized to detect the eventual shift in nerve conduction caused by decreased blood flow and structural injury and to prevent lasting neurologic impairments.[1,9]

As the technology becomes more popular and constantly grows, IOM is being used in a standardized way in neurosurgical procedures. [11]

Although, several, mainly retrospective, studies were conducted in the recent decades, the predictive value of IOM has not been yet determined.

The impact of IOM on the clinical outcome and the sensitivity of IOM in clipping of UIAs, especially during temporary clipping are still under discussion and lack prospective data. The relation between temporary clipping and amplitude reduction, as well as the maximum duration of temporary clipping without a postoperative focal neurological deficit, is still a matter of controversy. It should also be noted that part of the value and utility of IOM derives from its potential impact on the surgeon's strategy during different surgical procedures, which is mostly unexamined. This aspect needs to be evaluated from the surgeon's point of view. [16–19]

The aim of this study was to determine the predictive validity of IOM for postoperative functional outcome and its perceived added value for intraoperative real-time feedback of functional impairment in the surgical treatment of UIAs.

2. MATERIALS AND METHODS

2.1. Ethics approval

This study was designed and performed in accordance with the Declaration of Helsinki from 1964 and with the ethical standards of Klinikum rechts der Isar, Technical University of Munich (no. 18/19s). All patients received oral and written informed consent before surgery. After the patient's consent, the patient was included in the study. There is no randomization and no comparison between different cohorts of patients, the IOM continues to be applied to each case with a given indication. This does not create any ethically questionable disadvantage for the patients.

2.2. Study design

This is a prospective observational diagnostic study of a cohort of 47 patients with unruptured intracranial aneurysms. The objective of this study was to define the predictive value of IOM in the microsurgical clipping of UIAs, by assessing its positive and negative predictive values in addition to its sensitivity for detecting intraoperative ischemic injury to motor-eloquent territories. The study aimed to create a standardized procedure for the application of the IOM so that a scientifically comparable evaluation can take place It evaluates the clinical relevance of intraoperative neuromonitoring during microsurgical clipping of UIAs. Furthermore, the correlation between intraoperative changes in the evoked potentials and the postoperative neurological condition was investigated.

2.3. Patient population

We screened patients aged 18 years or above undergoing elective microsurgical clipping of UIAs which is routinely performed under IOM at our Department. A cohort of 47 patients with UIAs was enrolled in this study. All patients were scheduled for elective operative treatment of their UIAs at the Department of Neurosurgery, Klinikum rechts der Isar, Munich between February 2019 and February 2021. Inclusion criteria consisted of age above 18 years, written informed consent and an unruptured intracranial aneurysm to be surgically treated. Exclusion criteria was age under 18 years. Patients with a history of aneurysmal SAH of the index aneurysm or prior endovascular treatment of the index aneurysm were also excluded. All baseline characteristics, surgical data and postoperative clinical data of the patients were collected prospectively. A neurological examination was conducted pre- and postoperatively and at day of discharge.

2.4. Preoperative Clinical Evaluation

Indication for microsurgical clipping of the UIA was due to decision of the interdisciplinary neurovascular board, including neurologists, neuroradiologists and neurosurgeons.

When deciding whether or not to treat the aneurysm, the size and location of the it, as well as the 5-year rupture risk (PHASES Score), were all properly considered. The parameters were also used to evaluate if surgical clipping or end-vascular coiling was the preferred option.

Prior to surgery, every patient received diagnostic approach. First, an MRI with angiography or a CTA was requested to assess the location of the aneurysm. In addition to that, every patient received a preoperative DSA to accurately analyze the size and configuration of the aneurysm and to ensure optimal preoperative planning. This DSA with 3D reconstruction also helps the surgeon to work out the ideal approach during surgery to achieve the best possible surgical outcome. With the help of DSA, small vessel branches from the aneurysm can be visualized and the surgeon is able to plan the clipping accordingly without risking a diminished perfusion of eloquent areas. **(Figure 8)**

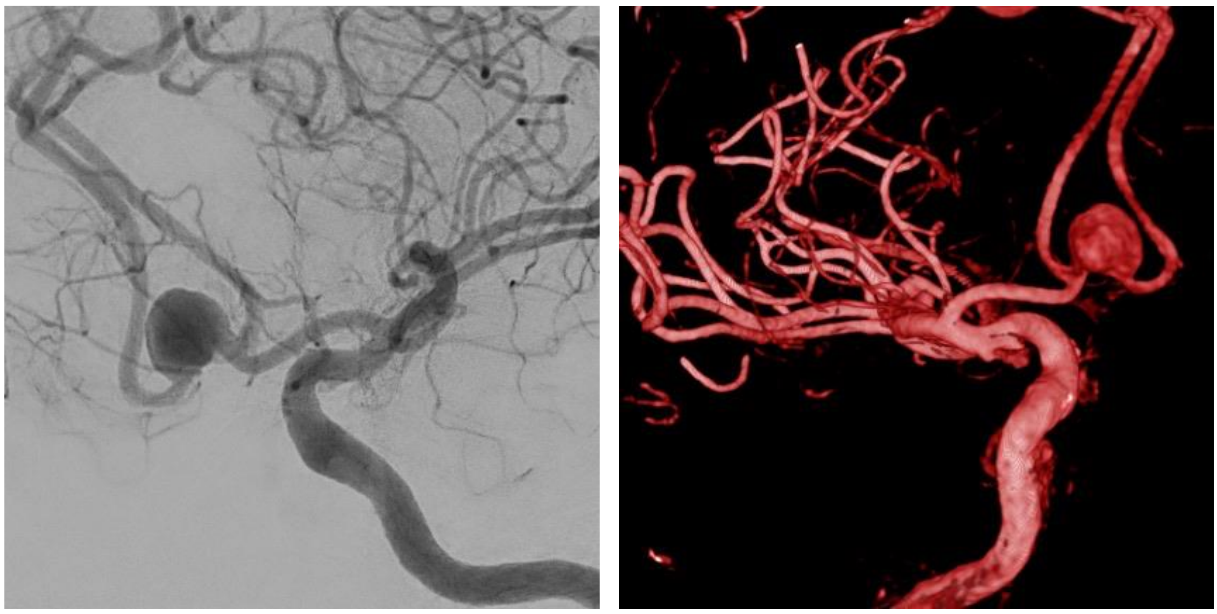

Figure 8: AcomA Aneurysm (8mm, PHASES Score 8: 5-year rupture risk: 3,2%), Preoperative Angiography, Digital Subtraction Angiography (left) and three-dimensional reconstruction (right)

On the day of admission, the preoperative neurological status was assessed. A neurosurgery resident conducted an orienting neurological examination in accordance with a defined procedure, which included testing limb strength, sensory function, neuropsychological symptoms, and cranial nerves. The strength of the extremities is assessed on a scale of 0 to 5. These strength levels according to the "British Medical Research Council Scale (BMRC)" are presented in Table 3. **(Table 3)**

Table 3: British Medical Research Council Muscle Grading System.

Grade	Observation
0	No contraction
1	Flicker or trace contraction
2	Active movement with gravity eliminated
3	Active movement against gravity
4	Active movement against gravity and resistance
5	Normal strength

Regarding the functional status and general condition of the patient, the modified Rankin Scale (mRS), American Society of Anesthesiologists (ASA) Physical Status Classification, and the Glasgow Coma Scale (GCS) were obtained before surgery.

The mRS is a 7-level scale, quantifying the functional outcome of the patient. The scale runs from 0 to 6, running from the optimal health with no symptoms (0) to death (6). **(Table 4)**

Table 4: The Modified Rankin Scale (mRS)

The Modified Rankin Scale (mRS)	
0	No symptoms, perfect health
1	No significant disability. Able to carry out usual activities, despite minimal symptoms
2	Slight disability. Can care for him/herself without assistance but is impaired in everyday life.
3	Moderate disability. Needs help in everyday life but can walk without strangers or with aids.
4	Moderately severe disability. Needs assistance with personal hygiene, cannot walk without help.
5	Severe disability. Bedridden, incontinent, needs constant nursing assistance.
6	Dead.

The ASA Physical Status Classification System assesses a patient's medical co-morbidities, in term of predicting the perioperative risks. ASA PS Classification ranges from ASA I to ASA VI, with "I" indicating a normal healthy patient and "VI" marking a declared brain-dead patient.

Karnofsky performance status scale (KPSS) was also used to classify and quantify the preoperative functional status of the patient. The performance status was rated on a numerical scale ranging from 0-100, representing the patient's ability to conduct normal activity, to undertake active work, and need for assistance with 100 representing full activity and 0 representing death. GCS assessed a patient based on their ability to perform eye movements, speak, and body movement. These 3 parameters (Eye opening, verbal, and motor response) present the elements of the GCS. The scale ranges from 3 (no reaction) to 15 (fully responsive and oriented).

2.5. Anesthesia

Because volatile anesthetics have been demonstrated to adversely interfere with IOM, total intravenous anesthesia was used in all 47 cases, using propofol for induction and maintenance of anesthesia[19,49]. Fentanyl was utilized to achieve intraoperative analgesia. Rocuronium was exclusively used for intubation because, as a depolarizing muscle relaxant, it blocks neuromuscular transmission and makes IOM impossible. [19,49]

2.6. Technique of intraoperative Neuromonitoring

IOM was performed in every microsurgical aneurysm clipping, included in this study.
TcMEPs and SSEPs were used as IOM modalities during aneurysm clipping. For aneurysm clipping of the posterior circulation, auditory evoked potentials (AEP) and facial nerve electromyography (EMG) were performed for aneurysms of the posterior circulation.
For transcranial electric stimulation (TES) and median nerve stimulation an *ISIS stimulator* (Inomed, InomedMedizintechnik, Germany) or Axon stimulator (AxonSystems, Hauppauge, NY) was used. IOM setup, recordings, and analysis were performed by a neurophysiological specialist trained in IOM.
In accordance with the 10-20 system, a pair of transcranial subdermal needle electrodes (Inomed 27-gauge bipolar needle electrode, Inomed Medizintechnik®) were positioned at the C3 and C4 positions and at the C3' and C4' positions. and connected to the Inomed ISIS IOM® system (Inomed Medizintechnik®) or the AxonEpocheXPe neuromonitoring system, (Axon Systems, Hauppauge, NY) via a stimulation headbox after the patient was properly positioned. The "10-20 system" originates from the homogenous spatial sectioning of the patient's cranium: the Cz reference point is acquired by half the distance between the nasion and the inion. C3 on the left and C4 on the right side, represent the respective cortical projections of the hand area of both M1s. They are obtained by dividing the distance from one tragus to the other in 20% steps.

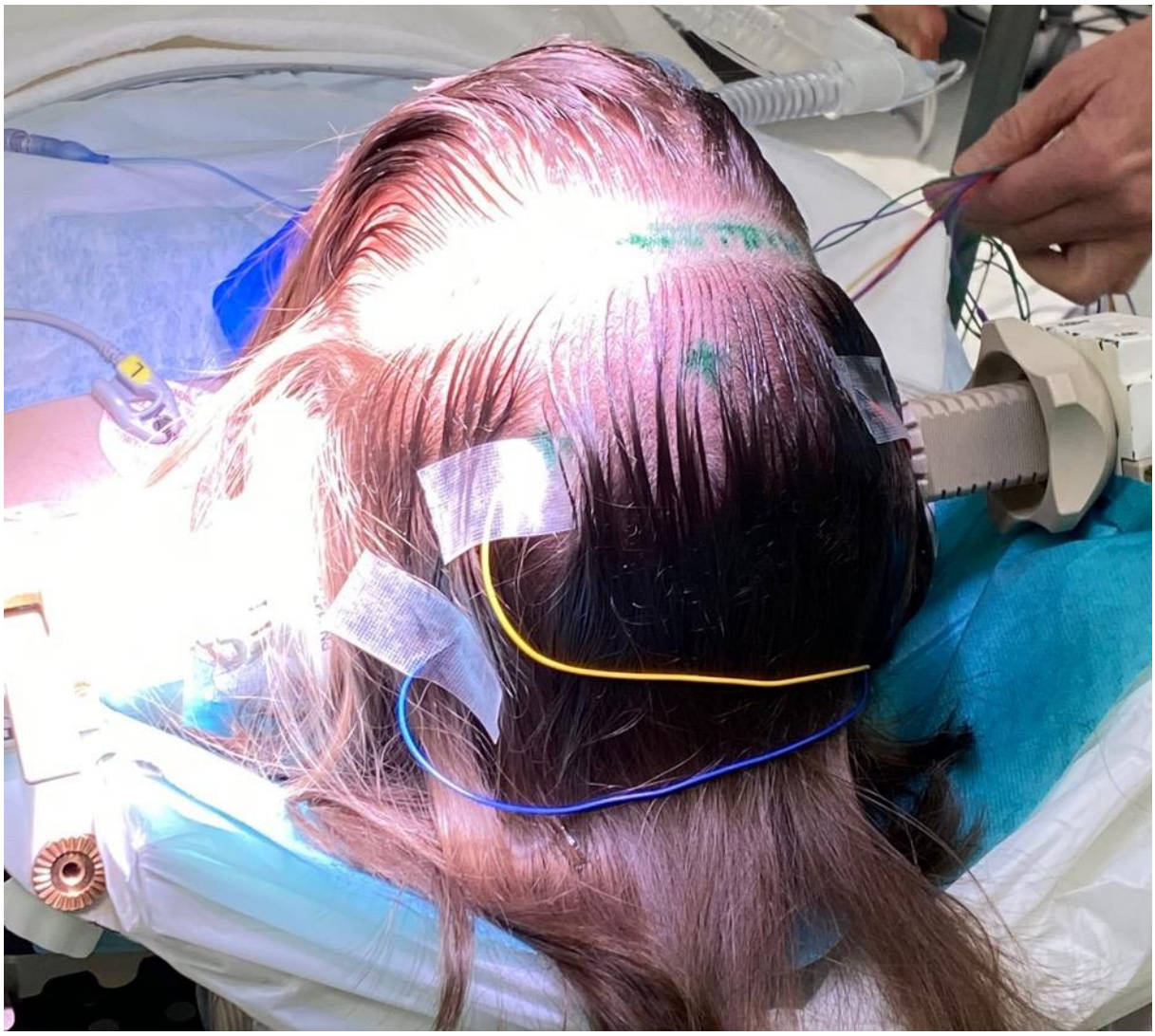

Figure 9: Electrode placement according to the 10-20 system.

Subcutaneous stimulation needles were placed at C3 and C4: a C3-anode/C4-cathode for left hemispheric stimulation and C4-anode/C3-cathode for right hemispheric stimulation. For detection of MEPs, recording electrodes were positioned in a bipolar approach, contralateral to the side of transcranial stimulation, over the thenar (M. abductor pollicis brevis) and brachial biceps for the upper extremities and the anterior tibial muscle and flexor hallucis brevis for the lower limb.

To stimulate the median nerve for SSEPs, anodal square-wave pulses of 200s length were administered at the wrist at minor suprathreshold intensities.

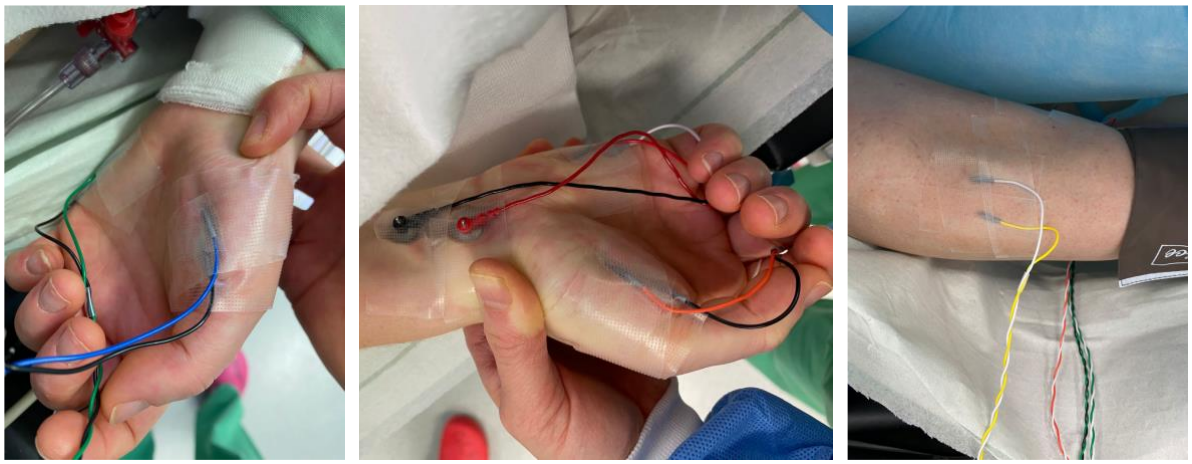

Figure 10: Acquisition of the MEPs by electrodes blaced over the M. abductor pollicis brevis (upper limb, picture on the left and in the middle) and the M. tibialis anterior (lower limb, right picture).

For SSEP detection, the electrodes were placed at C3', C4' (2 cm behind C3 and C4) and Erb's point with reference to Fz, in accordance with the international 10-20 system.

During the application of stimuli, the electrical impedance was constantly monitored. Each patient's initial stimulation settings were predetermined and adjusted based on their individual stimulation threshold. With a constant-current stimulation intensity of 90 mA, a baseline response was initially obtained. The train of five stimulation technique was utilized for TES, using a train of five 300s square-wave anodal pulses.

The stimulus trains were delivered every 10–15 seconds during surgery, depending on the step of microsurgical clipping, alternating between the 10–20 and guided stimulation electrodes. If the initial stimulation settings failed to induce a baseline response, the stimulation intensity was subsequently increased in 10 mA increments until a threshold response was generated.

Similarly, an excessive motor response to a baseline stimulus of 90 mA led to a 10-mA reduction in stimulus intensity until a detectable tcMEP could be recorded without excessively disruptive extremity movements. The intensity of stimulation was adjusted until the amplitude strength of the tcMEPs was between 500 and 2000 V.

Figure 11: Intraoperative Neuromonitoring Unit.

Evoked potentials were continuously recorded during several stages of the surgery, including dural opening, dissection of the arachnoid membrane and aneurysms, application of temporary and permanent clips, and dura closure. In the event of an unforeseen occurrence, such as a vessel incision or aneurysm rupture, the potentials were strictly monitored.

Throughout surgery, the amplitude, latency and duration of the evoked potentials were investigated.

Surgical maneuvers that directly contributed to a change in monitoring parameters were reported. The surgeon noted the reason for the alteration, the location of the manipulation, the countermeasures, and the recovery time. Peak-to-peak differences were used to quantify amplitude, whereas latency was defined as the time between the commencement of stimulation and the first measurable amplitude.

In case of changes in amplitude, the changes were categorized as 1) reversible potential loss or 2) irreversible potential loss. For tcMEP and SSEP monitoring, cut-off criteria for abnormalities were defined as amplitude diminishment over 50% of baseline level, or an increase in latency by more than 50% of the respective baseline records. The baseline level was recorded immediately after opening of the dura mater.

A transient loss was defined as a loss of amplitude that increased back to baseline level during surgery. There was no time limit set, but the time until the recovery of amplitude was documented.

Each case of transient loss of amplitude was documented carefully, as mentioned above. **(Figure 12)**

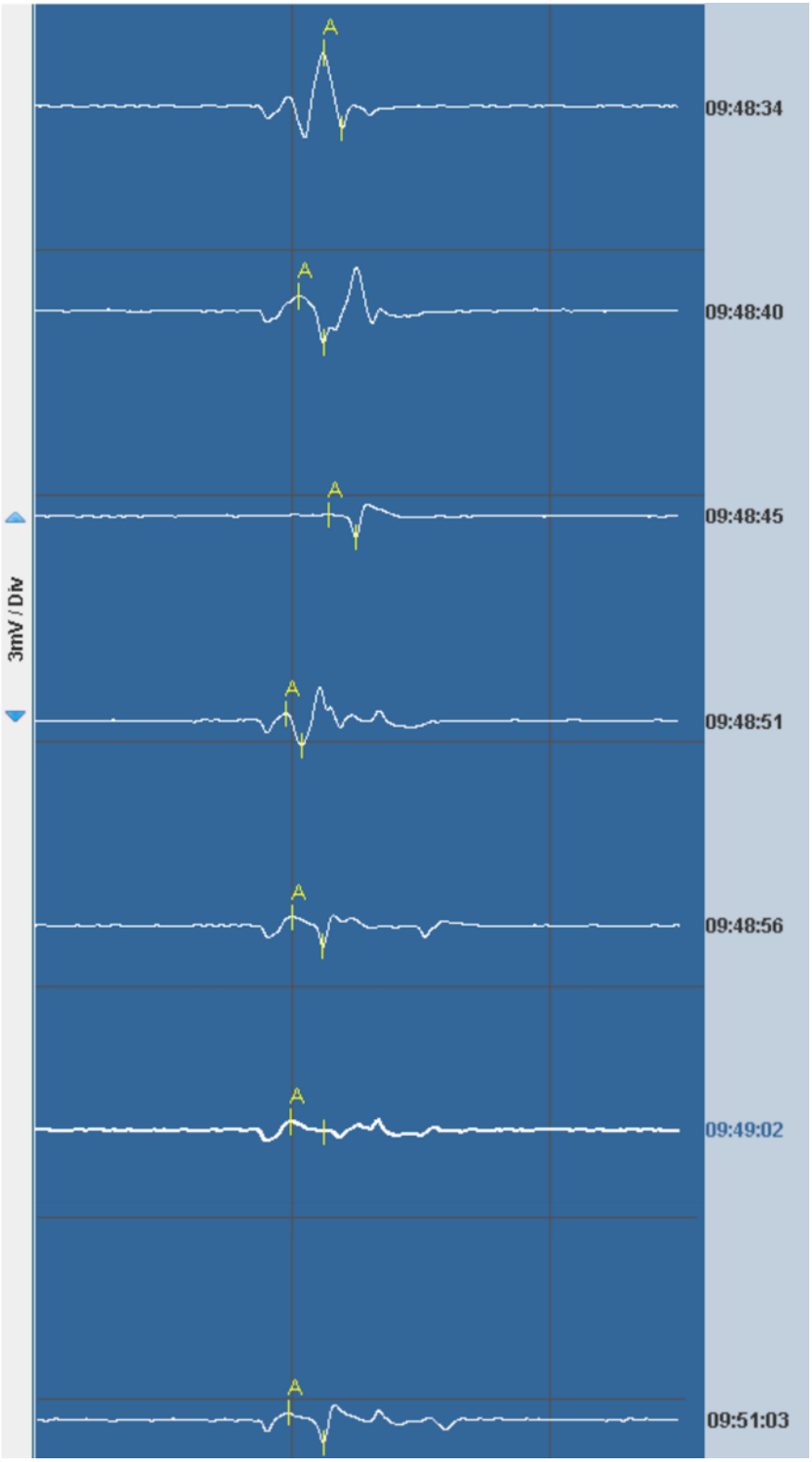

Figure 12: tcMEPs of a patient with an AcomA aneurysm clipping. At 09:48:34 regular MEP amplitude; decline in amplitude of tcMEPs until 09:49:02 (>50% of the baseline amplitude: 0.365 mV - 0.046 mV) 8 min after temporary clipping of the ICA. The temporary clip was subsequently removed at 09:49:02. At 09:51:03 beginning of recovery of tcMEP amplitude 2 min after temporary clip removal.

2.7. Intraoperative Data

Microsurgical clipping of the UIA was performed by an experienced neurosurgeon. Intraoperative data was prospectively collected divided in different subcategories.
Most important, the IOM data was meticulously analyzed, and correlations to postoperative neurological status were reviewed.

Due to IOM data, the patient population was divided into three subgroups:

- 1: stable IOM signal
- 2: reversible decline in amplitude with an increase back to baseline level
- 3: irreversible decline in amplitude

As described in chapter 2.6, cut-off criteria for abnormalities were defined as an amplitude diminishment ≥ 50% of baseline level or an increase in latency by ≥ 50% of the respective baselines recorded immediately after opening of the dura mater.
In every case, where changes in IOM met the cut-off criteria, the surgeon temporarily paused the surgery and explored the cause of evoked potential decline.
If a temporary clip has been applied, it was removed. If a permanent clip was already in place, it was released pro tempore until the evoked potentials returned to baseline. The aneurysm was wrapped and clipped if the decrease in amplitude was caused by aneurysm rupture and accompanying hemorrhage. If the deterioration in amplitude was not due to clip application or accidental bleeding, vital parameters (blood pressure, temperature) and intracranial pressure were measured.
Intraoperative confirmation of correct aneurysm clipping, and blood flow was performed by using ICG angiography and microdoppler.
Intraoperative adverse events were also documented.

2.8. Temporary Clipping

Temporary clipping (TC) as a prophylactic or adjunctive surgical technique was evaluated with respect to the duration and decline of IOM signals during the procedure. The use of temporary clips transiently interrupts blood flow through the UIA, allowing accurate visualization of the in vitro aneurysm configuration for safe and correct clipping.
However, because blood flow is interrupted for a short period of time, TC bears the risk of ischemic injury to eloquent areas distal to the clipped vessel, which is an important target of tcMEP IOM and may manifest as a decrease in amplitude.

In the event of a decrease in amplitude during TC, we examined whether there was a chronological sequence and causal relationship between TC and the onset/termination of the amplitude decrease. The subsequent response of the surgeon was also assessed.
The relationship between the duration of TC and the amplitude decrease of the IOM signals received special attention in this study.

2.9. Questionnaire of the surgeon

To evaluate the surgeon's perspective, a postoperative questionnaire regarding surgery, IOM, and temporary clipping was completed by the operating neurosurgeon. The use and benefits of the IOM were evaluated by the operating surgeons.
In the questionnaire, the operating surgeon responded to questions about the perceived impact of the IOM on the course of the procedure, as well as its added value to surgical and functional outcomes compared to not being able to utilize this modality.
Surgical outcome must be approached from different angles. On the one hand, there is the result of microsurgical aneurysm clipping in terms of complete obliteration of the UIA, no residual flow into the aneurysm and the assured perfusion of brain areas perfused by vessel branches from the aneurysm. On the other hand, there is the neurological outcome of the patient, as a part of surgical outcome. IOM can accomplish in the outcome of surgery as it gives intraoperative real-time feedback of patient’s motor and sensitive function. It detects eventual shifts in nerve conduction in the reversible phase and therefore prevents lasting neurologic impairments. If the IOM indicates an impending focal neurological deficit (decline in amplitude of tcMEP or SSEP) and the surgeon can return the evoked potentials to baseline level through an adapted intervention, the IOM can contribute to an improved surgical outcome.

2.10. Postoperative clinical course

All patients underwent postoperative DSA directly after microsurgical clipping in order to assess the clipping outcome. Experienced neuroradiologists evaluated each DSA individually and determined the correct position of the aneurysm clips. A special emphasis has been placed on vessel patency (clip stenoses) and complete aneurysm exclusion.

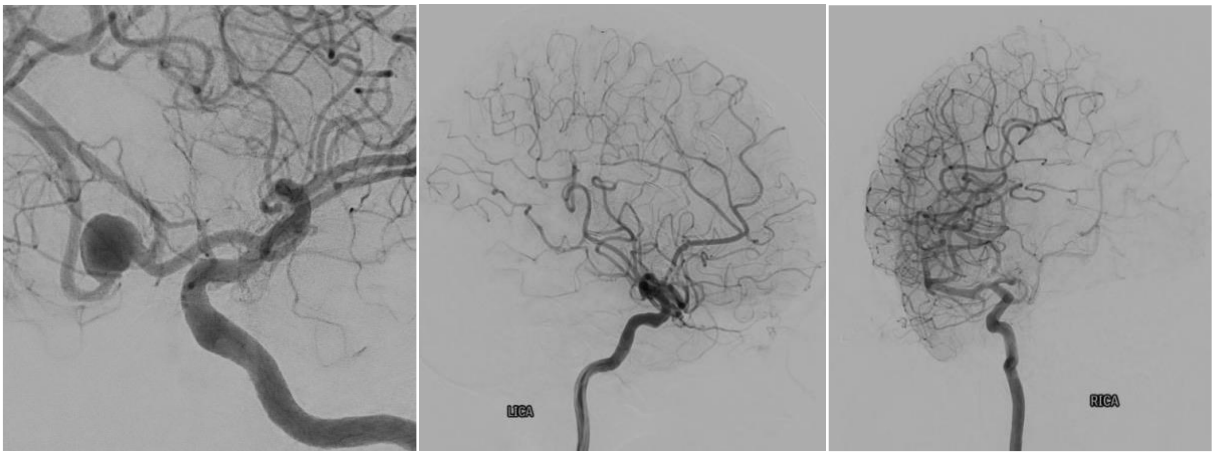

Figure 13: Comparison of pre- and postoperative DSA, after microsurgical clipping of an AcomA Aneurysm. Left picture shows the preoperative DSA, the picture in the middle and on the left show the postoperative DSA, demonstrating a successful clipping, with exclusion of the aneurysm.

Neurological status was evaluated immediately postoperatively in the Peri Anesthesia Care Unit (PACU), at postoperative day (POD) 1, POD 5 and day of discharge (DOD). A postoperative neurological deficit was defined as the presence of either transient (full regression by discharge day) or permanent postoperative neurological symptoms.

Accordingly, on the one hand, we have the surgical outcome in terms of clip location and complete aneurysm closure, including validated perfusion of eloquent brain areas. On the other hand, the surgical outcome comprises the postoperative neurological status of the patient.

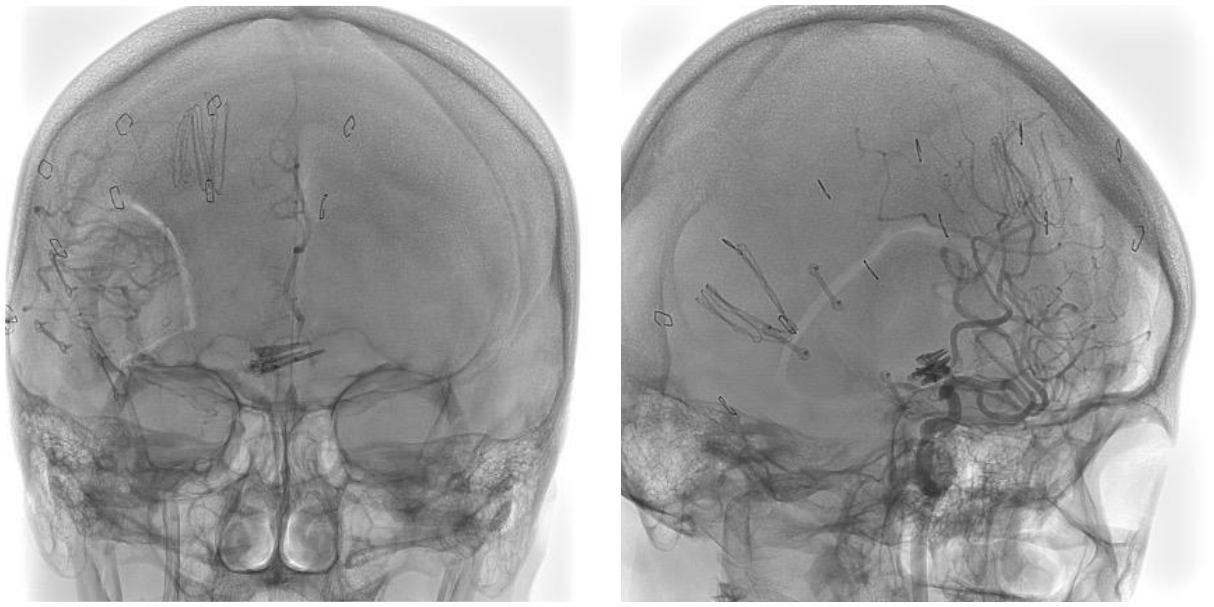

Figure 14: Postoperative X-ray during DSA after clipping of AcomA aneurysm. The applied clips are visible in the postoperative imaging.

The postoperative neurological status was referred to the intraoperative monitoring data.

A true positive case was documented for a patient with a permanent loss or decline of more than 50% of the baseline level of the EPs and a postoperative deterioration of neurological status.

A true negative result of monitoring was observed if evoked potentials remained stable throughout surgery or exhibited a temporary decline of amplitude with recovery until skin suture and the patient presented without new neurological impairment or improved clinically.

A false positive result of monitoring was present when evoked potentials were permanently lost or deteriorated > 50% of baseline level during surgery but the patient had an unchanged or improved postoperative neurological status.

A false negative case was considered if evoked potentials remained stable throughout surgery or exhibited a temporary decline of amplitude with recovery until skin suture, but the patient was clinically worse postoperatively.

In addition, the postoperative mRS at PACU, POD1, POD5 and DOD was compared to the preoperative mRS.

We defined the following as the primary postoperative endpoints:

- Neurological status (postoperative focal neurologic deficit)
- mRS.

They were correlated with IOM abnormalities.

Postoperative complications (unexpected adverse events) and further operations were also documented.

2.11. Statistical analysis

Data that have a normal distribution are expressed as mean/median ± standard deviation (SD), non-normally distributed data as median and range.

The primary endpoint was the correlation of postoperative focal neurological deficits with abnormalities in IOM.

Diagnostic test performance (sensitivity, specificity, negative predictive value, positive predictive value) was calculated with standard formula. The Chi-square test was used to compare baseline characteristics. Differences between groups, stratified by stable vs decline in IOM were tested with the Mann-Whitney-U test for multiple comparisons for independent nominally scaled samples. Intraoperative monitoring data was reviewed and related to the postoperative neurologic status, especially the motor status. A secondary endpoint was defined as the occurrence of amplitude changes of the tcMEP monitoring in relation to the duration of temporary clip occlusion of parent vessels. Calculations were made with IBM SPSS statistics version 28. Values of $p < 0.05$ were considered significant.

3. RESULTS

3.1. General evaluation

From February 2019 to February 2021, 47 patients were scheduled for elective clipping of UIAs. IOM was successful in all 47 cases.

In overall series, 7 of patients had a preoperative motor deficit. After microsurgical clipping none of them had a deterioration of motor function.

Analyzing all modalities of IOM, in 87.2% of all cases (41 patients) IOM (tcMEPs, SSEPs, AEPs, facial nerve EMG) was stable throughout surgery, but 2.4% (1 patient) developed a permanent focal neurological deficit (facial nerve palsy) in the PACU, still present at the DOD. Further investigation revealed that this neurologic deficit was caused by subacute ischemic complications after surgery in the operating field. Thus, a secondary event led to the facial nerve palsy. Therefore, no false negative results were reported. All patients with reversible decline in IOM (12.7%) did not show any postoperative neurological deficits, no matter how long the decline was. All declines in IOM were declines in tcMEPs. In all other cases, tcMEP was stable. Regarding the postoperative neurological motor status, there were no new motor impairments after surgery, when tcMEP were stable or the decline in tcMEP was only temporary, and the amplitude went back to the baseline level at the end of surgery. TC was performed in 12 cases, with a transient decline of tcMEPs in 4 cases (33.3%). Time of TC ranged from 2 minutes to 18 minutes, median duration 6 minutes (±4.1). All declines in amplitude of IOM were reversible and postoperative neurological outcome was uneventful in all cases.

3.2. Patient population

47 patients met the inclusion criteria of UIA and elective microsurgical clipping, consisting of 36 (76.6%) female and 11(23.4%) male patients, who ranged from 26 to 76 years. Median age at surgery was 57 years (IQR 47-67 years). (Table 5)

Concerning cardiovascular risk factors, 19 (40.4%) patients presented with arterial hypertension, 20 (42.6%) of the patients were smokers and 7 (14.9%) former smokers. Four patients (8.5%) had regular alcohol consumption. Five patients (10.6%) had familial aneurysms. Regarding the medical history, 15 patients (31.9%) had suffered from an aneurysmal SAH in the past. Moreover, 7 patients (14.9%) already had a microsurgical clipping of an UIA and 10 patients (21.3%) received an endovascular coiling in the past. Preoperative mRS ranged from 0 to 4. Most commonly was mRS of 0 in 34 (72.3%) of the patients. mRS ≥2 occurred in 4 (8.5%) of the patients. Median postoperative mRS was 0 (IQR 0-1). Baseline characteristics are displayed in table 5. **(Table 5)**

Table 5: Baseline characteristics of all patients, risk factors and medical history.

Demographics	**All patients (n=47) N (%) or median (±SD)**
Sex	F 36 (76.6) M 11 (23.4)
Age	57 (IQR 47-67)
Modified Rankin Scale (mRS)	
Preoperative mRS = 0	34 (72.3)
Preoperative mRS = 1	9 (19.2)
Preoperative mRS ≥ 2	4 (8.5)
Postoperative mRS = 0	33 (70.2)
Postoperative mRS = 1	9 (19.2)
Postoperative mRS ≥ 2	5 (10.6)
Risk factors	
Smoking	20 (42.6)
Former Smoking	7 (14.9)
Hypertension	19 (40.4)
Alcohol consumption (regularly)	4 (8.5)
Familial aneurysms	5 (10.6)
Medical history	
Previous SAH	15 (31.9)
Previous surgical clipping	7 (14.9)
Previous endovascular coiling	10 (21.3)

3.2.1. Aneurysm characteristics

Due to multiple aneurysms, 61 aneurysms were clipped in 47 patients. A single aneurysm was diagnosed in 28 cases (59.6%), 19 patients (40.4%) had multiple aneurysms. Of those, 10 patients (21.3%) had 2 aneurysms, 5 had 3 aneurysms and 4 patients had >3 UIAs. Mean size of the aneurysm was 5.1 mm (±3.7 mm). Thirty-seven aneurysms (55.2%) were smaller than 5 mm and 2 aneurysms (3%) were larger than 20 mm.

Regarding, the aneurysms, that were clipped, in 37 cases only one aneurysm was scheduled for clipping (77.1%). 2 aneurysms were surgically treated in 7 cases (14.7%), 3 IA were clipped in 2 cases (4.3%) and 1 patient had >3 IA treated. **(Table 6)**

Table 6: Aneurysm characteristics regarding number, size, and associated PHASES Score.

PHASES Score	**All patients (n=47) N (%) or median (±SD)**
Median PHASES Score	5 (range: 0-12)
Number of aneurysms	
1	28 (59.6)
2	10 (21.3)
3	5 (10.6)
>3	4 (8.5)
Size of aneurysms	
<5 mm	37 (55.2)
5-9.9 mm	24 (35.8)
10-19.9 mm	4 (6)
>20 mm	2 (3)
Mean size (mm)	5.1 (±3.7)
Median size (mm)	4 (±3.7)
Number of aneurysms treated	
1	37 (78.7)
2	7 (14.9)
3	2 (4.3)
>3	1 (2.1)

Regarding the location of the UIAs, 12 patients (25.5%) had aneurysms located on the left side, 15 patients with UIAs on the right side (31.9%) and 20 cases with aneurysms on both sides (43.6%). Most common location was MCA (31.1%), followed by AcomA (14.6%). **(Figure 15)**

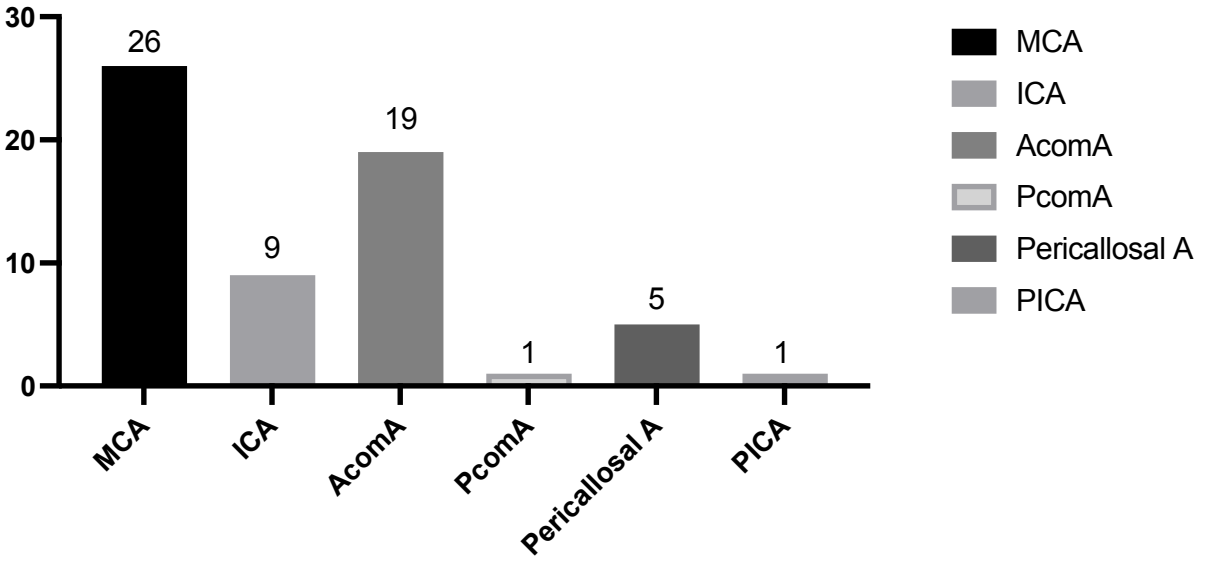

Figure 15: Locations of Aneurysms clipped. MCA – Middle cerebral artery; ICA – Internal carotid artery; AcomA – Anterior communicating artery; PcomA – Posterior communicating artery; Pericallosal A – Pericallosal artery; PICA – Posterior inferior cerebellar artery.

Median PHASES Score was 5 (±2.5) (range 0-12). A PHASES score of 4, was obtained in 20.8 %, as well as a PHASES score of 5. 12.5% of the patients had PHASES score ≤ 2, translating to a 5-year risk of aneurysm rupture of 0.4%. Extremely high PHASES scores ≥ 10 were rarely seen (4.2%). **(Figure 16)**

Median 5-year risk of aneurysm rupture for the included cohort was 1.3% (0.8-2.4).

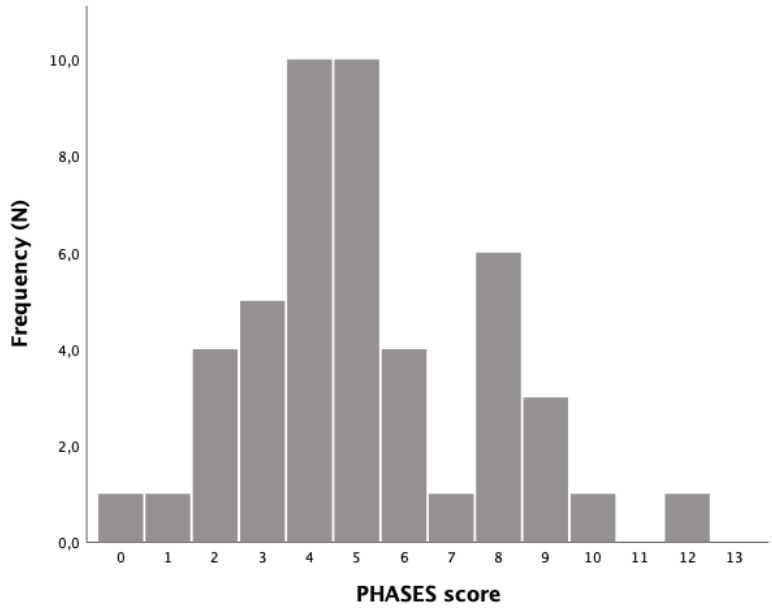

Figure 16: Overview and frequency of PHASES scores of included patients.

3.3. Preoperative clinical data

Primary symptoms were very heterogeneous and ranged from headache (14.9%), vertigo (6.4%), previous SAH (31.9%) to various other neurological symptoms, while 29.8% did not have any symptoms. In preoperative clinical examination, 7 patients (14.9%) presented with a motor deficit, 1 patient (2.1%) had a sensory deficit, 2 (4.3%) had a cranial nerve deficit and, 2 (4.3%) patients showed neuropsychological deficits. **(Table 7)**

Table 7: Preoperative clinical data of the patient cohort.

Demographics	**All patients (n=47) N (%) or median (±SD)**
Primary Symptoms	
No symptoms	14 (29.8)
Headache	7 (14.9)
Vertigo	3 (6.4)
Other symptoms	23 (48.9)
Preoperative neurological status	
Motor deficit	7 (14.9)
Sensory deficit	1 (2.1)
Cranial nerve deficit	2 (4.3)
Neuropsychological deficit	2 (4.3)

Moreover, median GCS was 15 (±0.15), and median ASA PS Classification 2 (IQR 1-3). With a median of 100 % and a mean of 93.6% (±12.2), the preoperative KPSS of the majority of the included patients was between 90 and 100%.

3.4. IOM

IOM was technically successful in all 47 cases.

3.4.1. Decline of amplitude and postoperative deficit

Stable parameters of IOM (tcMEPs, SSEPs, AEPs, facial nerve EMG) during surgery were seen in 87,2% (41 patients). In 6 cases (12,8%), there was a temporary decline of amplitude in IOM signals. **(Figure 17)** All the declines were decreases of amplitude in tcMEP. There were no declines seen in SSEP, AEP and facial EMG.

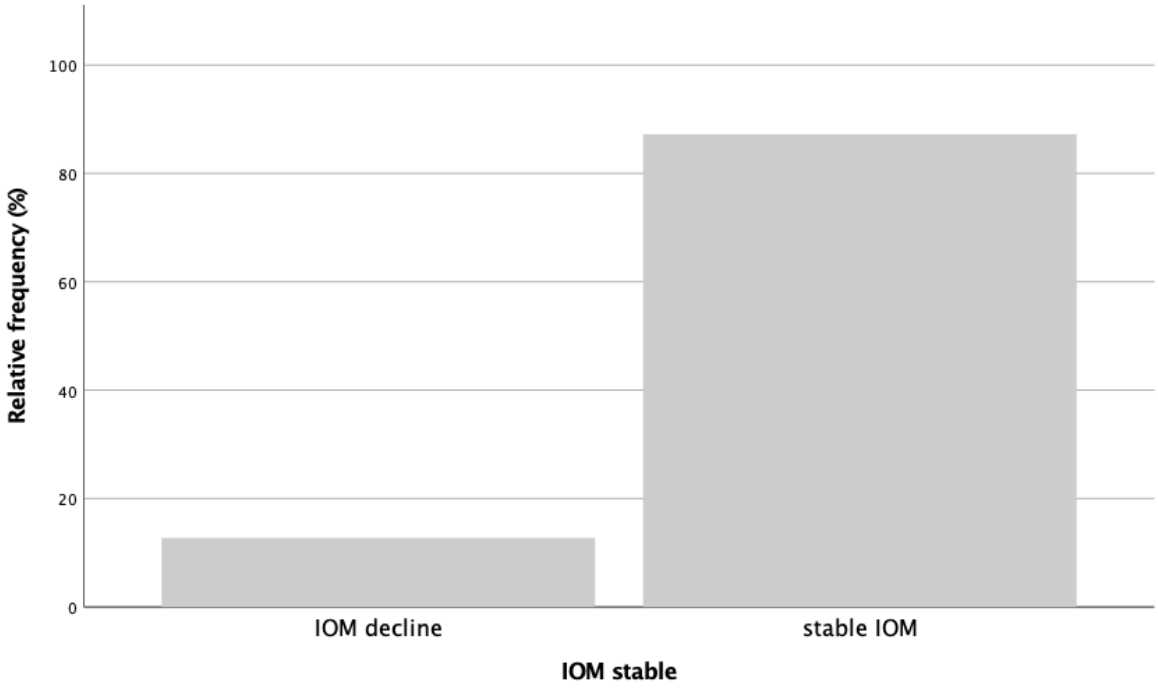

Figure 17: Stability of IOM. Relative frequency of cases with decline in IOM and stable IOM.

Looking at the patients who had a decline in tcMEP signals during microsurgical clipping, none of the patients showed an irreversible decrease. In the 6 patients with temporary tcMEP decline, 5 patients had a single decline and 1 patient had 2 declines during surgery.

All patients returned to baseline level at the end of the surgery when the skin suture was completed. The recovery time for the 6 patients ranged from 0.5 to 40 minutes. (mean: 13.8 ±18.5 minutes). In 2 of the 6 cases with a decline in tcMEP, surgery was interrupted immediately, and the operating surgeons irrigated with a solution of nimodipine in saline..

Patients with a transient decline in EPs could be divided into three subgroups according to the reasons that caused the transient decline: Circulatory deficits, temporary clipping and aneurysm/vessel rupture. Characteristics of the patients with a transient decline in tcMEP are presented in Table 8. **(Table 8)**

Table 8: Patients with a transient tcMEP decline and their postoperative neurological status. Patient and aneurysm characteristics are presented. Additionally, intraoperative data, including the modality of IOM that showed a decline in evoked potentials, the duration until recovery (min), the performance of temporary clipping and the number of declines in IOM. Postoperative focal neurological deficits are depicted.
f=female, m=male, MCA=A. cerebri media, AcomA=A. communicans anterior

Transient decline in IOM										
Patient			**Aneurysm**				**Surgery**			**PostOP**
ID	**Sex**	**Age**	**PHASES**	**Location**	**Size (mm)**	**IOM decline: modality**	**Duration until recovery (min)**	**Temporary clipping (duration in min)**	**Number of declines (IOM)**	**New neurol. deficit postop**
7	f	59	10	MCA	22	tcMEP	35	yes (18)	1	no
12	f	59	4	AcomA	6	tcMEP	40	yes (6)	1	no
37	f	57	5	MCA	3	tcMEP	0.5	yes (2)	2	no
39	f	70	9	Pericallosal A.	7	tcMEP	3	no	1	no
40	f	76	8	MCA	9	tcMEP	2	yes (3,5)	1	no
41	m	60	5	AcomA	5	tcMEP	2	yes (8)	1	no

Disruptive variables could be located as the cause of the intraoperative decline in evoked potentials in 5 out of 6 patients. We differentiated the disruptive factors into three subgroups:

- Circulatory deficits: including changes in blood pressure
- Aneurysm/vessel rupture
- Temporary clipping.

In one case (patient 39), a temporary hypotension of the blood pressure was the reason for a decline of tcMEP signals.
The blood pressure decreased to 90/45 mmHG, equivalent to a mean arterial pressure (MAP) of 60 mmHg. After pharmacological elevation of blood pressure with an increased dose of noradrenaline, the amplitude of evoked potentials recovered completely and returned to baseline after three minutes.

In two cases (patients 7 and 12), the aneurysm ruptured during surgical clipping, resulting in a decline in amplitude of tcMEP signals. After successful clipping of the ruptured aneurysm, the amplitude went back to baseline. The duration until recovery was 35 minutes in case 7 and 40 minutes in patient 12.

In two other cases (patients 37 and 41), the drop in tcMEP signals was caused by TC of the parent artery, since there was a chronological sequence between the TC and the commencement of amplitude decline. After the temporary clip was removed, the evoked potentials recovered entirely. The duration until the amplitude returned to baseline were 0.5 minutes in case 37, and 2 minutes in case 41.

In one case (patient 40), there was no explanation found for the decline in amplitude of tcMEP signals.

When comparing the two groups (IOM decline vs. IOM stable) in terms of postoperative focal neurological deficits, there were no postoperative focal neurological deficits in the group with reversible tcMEP depletion. In the group with stable IOM, one patient a PICA aneurysm developed a new focal neurological deficit (facial nerve palsy) in the PACU. In this case, facial nerve EMG, which is unable to monitor brainstem or cortical lesions, was conducted during surgery. **(Figure 18)**

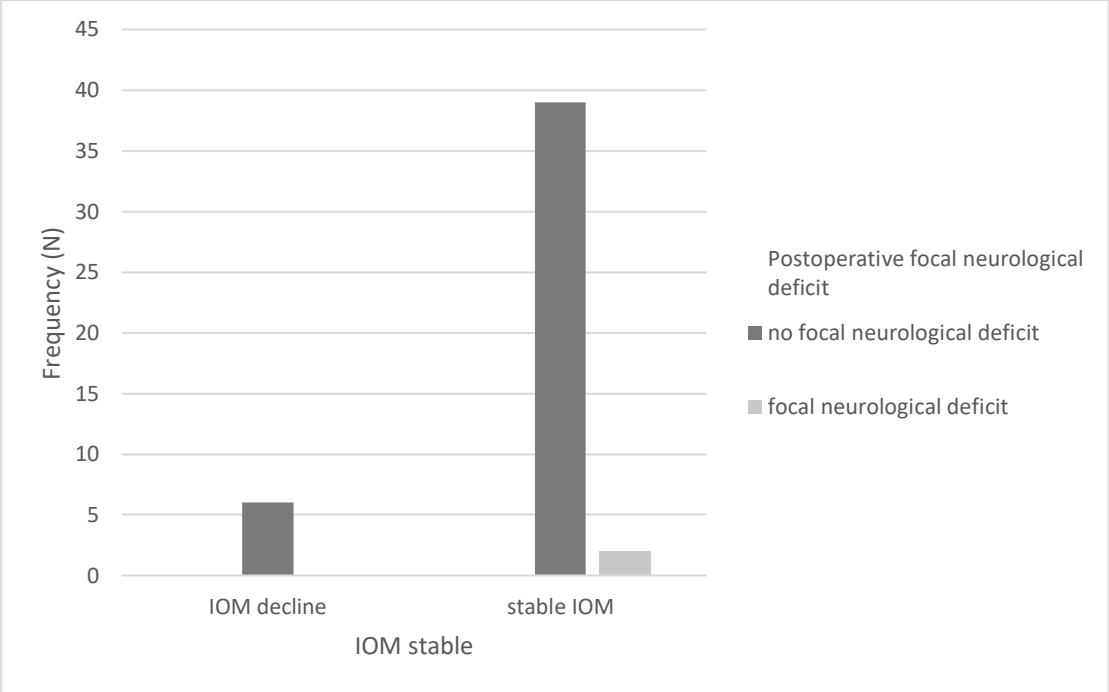

Figure 18: Postoperative deficit of patients with stable IOM (tcMEP, SSEP, AEP, facial nerve EMG) and patients with decline in amplitude.

The patients' functional outcome, postoperative clinical course, and mRS and GCS at the day of discharge (DOD) as well as the length of hospital stay were examined to determine the effects of a decline in IOM. When comparing the length of hospital stays for the two groups

(IOM decline vs. IOM stable), the Mann-Whitney-U-Test revealed a significant difference (p=0.044) between the length of stays for the "IOM stable" group and the "IOM decline" group. **(Figure 19)**

Median duration of stay in the “IOM stable” group was 7 days (mean: 9 ± 7 days) compared to 13.5 days (mean: 24 ± 21 days) in the “IOM decline” group. Two patients in the “IOM decline” group needed a second surgery due to complications (intracranial abscess evacuation, external ventricle drainage due to impaired circulation of cerebrospinal fluid) during their hospitalization. The duration of stay was therefore longer in these cases (61, 42 days).

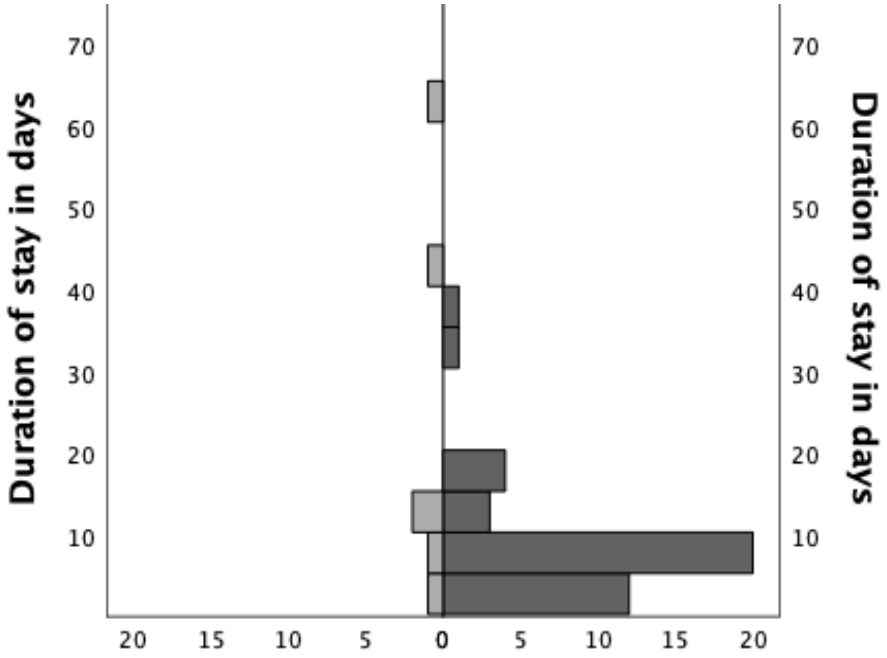

Figure 19: Independent-Samples Mann-Whitney-U Test: Comparison of the duration of stay (days) in the hospital between the "IOM stable" and the "IOM decline" group.

With regard to the functional outcome, the focus was on the survey of the mRS at DOD.

Mann-Whitney-U-Test showed no significant difference between the mRS at DOD in the “IOM stable” group and the “IOM decline” group. **(Figure 20)**

Therefore, no significant difference can be stated between the functional outcome, quantified as mRS, between the patients with a transient decline in IOM and the patients with stable IOM. On the assumption that the amplitude of the evoked potentials was back to baseline at the end of surgery, functional outcome was not significantly different.

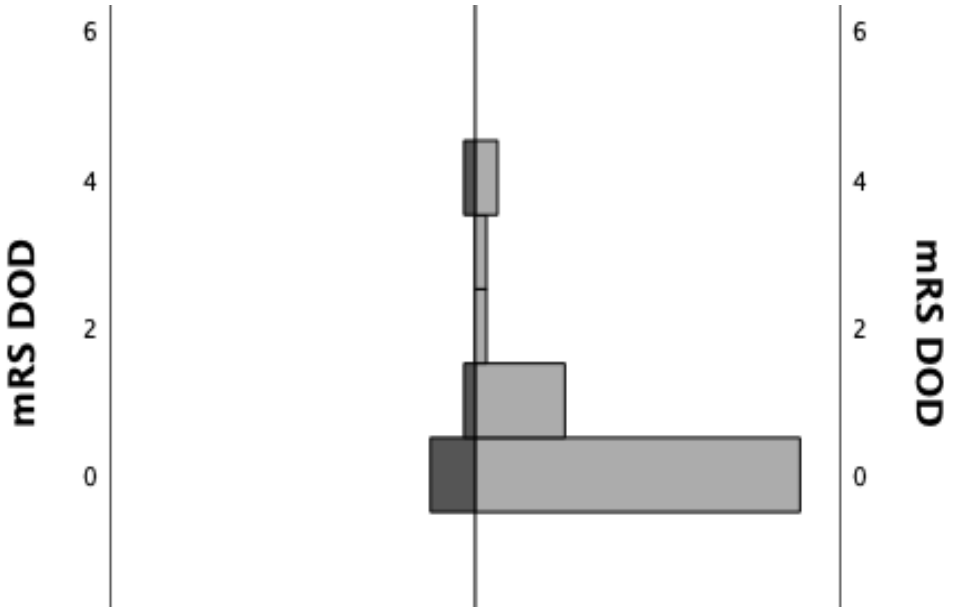

Figure 20: Independent-Samples Mann-Whitney-U Test: Comparison of the mRS at DOD between the "IOM stable" and the "IOM decline" group.

3.4.2. tcMEP

When only analyzing tcMEP, statistical analysis demonstrates that 6 patients (12.8%) suffered a transient decline in amplitude of tcMEP, 41 patients (87.2%) had stable tcMEP during surgery. In terms of postoperative motor impairments, none of the patients with stable tcMEP developed new postoperative motor deficits. Furthermore, none of the patients who experienced a transient decline in amplitude of tcMEP presented a new motor deficiency after surgery. **(Table 9)**

Thus, a stable IOM of tcMEP or only a transient decline of tcMEP is associated with a good neurological outcome regarding the motor function of the patient. This finding clearly indicates that IOM is able to prevent major neurological deficits.

Table 9: Intraoperative Monitoring Data of the tcMEP, regarding declines in tcMEP and associated postoperative motor function.

tcMEP	**All patients (n=47) N (%) or median (±SD)**
Stable tcMEP	41 (87.2)
Reversible decline in tcMEP	6 (12.8))
Irreversible decline in tcMEP	0 (0)
postOP motor function	
No postoperative motor deficit	41 (87.2)
Transient motor deficit*	0 (0)
Permanent motor deficit*	0 (0)

*A transient motor deficit is defined as a neurological deficit, that was regredient until day of discharge. A permanent focal neurological deficit was still present at the day of discharge.

3.4.3. Validity of IOM in clipping of UIA

A diagnostic analysis was conducted using a 2x2 summary table to determine the validity of IOM based on the findings of this investigation. **(Table 10)**

All occurrences of evoked potential amplitude drop correspond to a temporary decline only, as no permanent declines were identified. As mentioned above, all declines were declines in amplitude of tcMEP. There were no declines in SSEP, AEP or facial nerve EMG.

Postoperative focal neurological deficits were either motor deficit, sensory deficit, or a cranial nerve deficit in form of a facial nerve palsy.

Table 10: 2x2 summary table calculating Specificity (SPE), Sensitivity (SEN), positive predictive value (PPV) and negative predictive value (NPV) of IOM in the surgical clipping of UIA. Postoperative deficits included permanent focal and transient focal neurological deficits.

	New postoperative neurological deficit	No new postoperative neurological deficit	
IOM decline (transient)	True positive	False positive	**PPV**
IOM stable	False negative	True negative	**NPV**
	Sen	**Spe**	

For IOM (encompassing tcMEP, SSEP, AEP, and facial nerve EMG) in the clipping of UIA, a negative predictive value (NPV) of 97.6% was calculated.

As a result, in case of a stable IOM during surgery, there is a high probability that there won't be any new postoperative focal neurological deficit.

The specificity of IOM in the included patient cohort was 87%. The sensitivity and positive predictive value (PPV) are reported as 0 because there are no patients with new postoperative focal neurological deficits after a transient decrease in IOM during surgery.

Since there weren't any new postoperative neurological deficits after transient decrease of IOM during surgery, PPV and sensitivity are 0. As a result, the statistical value of NPV and specificity is very limited.

3.5. Temporary Clipping

3.5.1. Duration and Quantity of Temporary Clipping

TC was performed in 12 cases (25.5%). The duration of TC ranged from 2 minutes to 18 minutes. Median duration of TC was 6 min (±4.1), mean duration was 7 min (±4.1). **(Table 11)**

Table 11: Temporary clipping data, including decline of IOM and duration of temporary clipping.

Temporary Clipping N (%)	
Temporary Clipping	12/47 (25.5)
No Temporary Clipping	35/47 (74.5)
Decline of IOM during temporary Clipping	4/12 (33.3)
Duration of Temporary Clipping min (±SD)	
Mean duration	7 (±4.1)
Median duration	6 (±4.1)

In 4 of the 12 cases (33.3%), there was a decline in amplitude (tcMEPs) during the TC procedure. **(Figure 21)**

All the declines were transient declines in amplitude of tcMEP, and at the end of surgery, when the suture of the skin was finished, the amplitude has always returned to baseline level. Postoperative focal neurological outcome was uneventful in all cases.

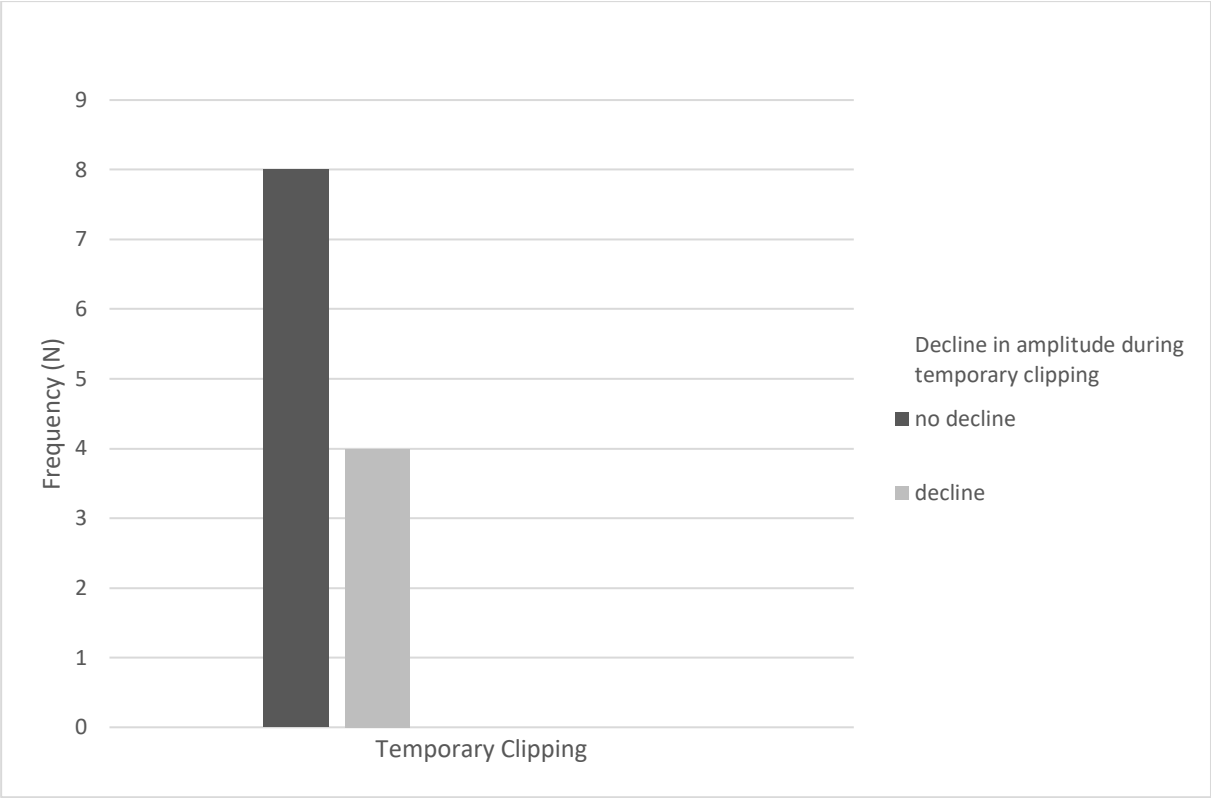

Figure 21: Decline in amplitude during temporary clipping. 8 of 12 patients had a stable IOM, in 4 cases there was a reversible decline in amplitude.

Looking more closely at the patients who experienced a reversible decrease in amplitude during TC, these patients can be divided into two groups.

On the one hand, there are the patients who experienced a decrease in evoked potential amplitude as a result of the TC procedure. On the other hand, there is a group in which the aneurysm ruptured, resulting in a subsequent decrease in the amplitude of the evoked potentials.

Group 1: Decline due to TC

Group 2: Decline due rupture of the aneurysm.

In 2 of the 4 cases (50%) with a decline in amplitude during TC, the decline was due to the TC. In the other 50 % of the cases, it was a subsequent drop after rupture of the aneurysm. In both groups, the decline in amplitude was reversible. **(Table 12)**

Table 12: Data of patients with a decline in amplitude of IOM during TC. Duration and quantity of declines, reason for the decline and the intervention of the surgeon against the decline in amplitude are displayed. Postoperative neurological deficits are described.

Transient decline in IOM during Temporary Clipping									
Patient	**Aneurysm**	**Surgery**							**Post OP**
ID	**Location**	**IOM decline modality**	**Duration of TC (min)**	**Number of declines**	**Reason for the decline**	**Complete recovery of tcMEP**	**Duration until recovery**	**Intervention against decline**	**New neurol. Deficit postop**
7	MCA	tcMEP	18	1	Aneurysm rupture	yes	35	Permanent clip on the ruptured aneurysm	no
12	AcomA	tcMEP	6	1	Aneurysm rupture	yes	4	Permanent clip on the ruptured aneurysm	no
37	MCA	tcMEP	2	2	TC	yes	0.5	TC removal	no
41	AcomA	tcMEP	8	1	TC	yes	2	TC removal	no

Group 1: Intervention against the decline in amplitude

In the first group (decline due to TC), after removal of the temporary clip, the amplitude returned to baseline level.

Group 2: Intervention against the decline in amplitude

In the second group (rupture of the aneurysm), the ruptured aneurysm was treated, by application of a permanent clip.

3.5.2. Impact of temporary clipping on neurological outcome

Further analysis was performed using Mann-Whitney-U Test for comparison of differences in dependent variables for the two independent subgroups (TC vs. no TC). Functional outcome of the patients was analyzed using mRS at DOD as a dependent variable. The duration of stay in the hospital was also compared between the two groups.

No significance was found between minutes to recovery of amplitude to baseline and postoperative clinical outcome, quantified as mRS at DOD. Patients who had a TC during surgery did not have a longer hospital stay (mean rank 23.4 vs. 25.75 for no TC vs. TC) or a worse functional outcome (mean rank 23,54 vs 25,33 for no TC vs. TC) as shown by Mann-Whitney-U-Tests. Consequently, TC is no risk factor for a longer hospitalization or a worse functional outcome of the patient. **(Figure 22)**

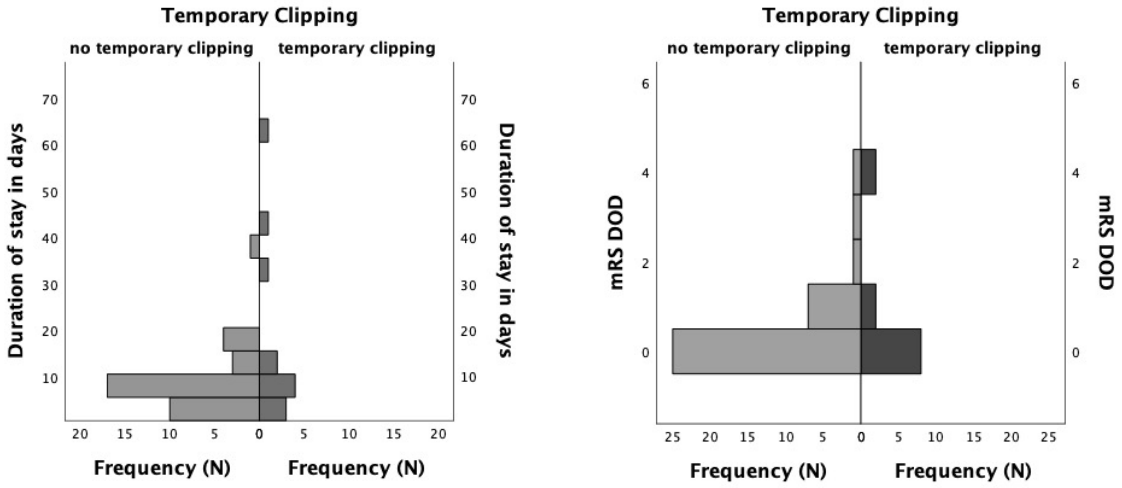

Figure 22: Mann-Whitney-U Tests regarding the duration of stay and the mRS at day of discharge compared in two independent subgroups (temporary clipping/ no temporary clipping during surgery).

When only analyzing the patients with a decline in amplitude, the time until recovery of IOM showed no significance regarding the duration of stay at the hospital. Patients with a longer time of decline in amplitude did not have a significantly longer stay at the hospital compared to patients with a shorter decline in amplitude.

3.6. Evaluation of the surgeon questionnaire

Intraoperative circumstances and their impact on postoperative outcomes were documented from the surgeon's perspective.

In particular, the evaluation of the IOM was the focus of the questionnaire. In order to achieve a favorable outcome, the surgeon's subjective feeling of safety cannot be ignored. For this reason, the question of whether the IOM leads to an increased subjective feeling of safety was of crucial importance in the analysis of the surgeon's questionnaire. In addition, the impact of the IOM on the surgical outcome was analyzed in terms of several aspects.

On the one hand, there is the result of microsurgical aneurysm clipping in terms of complete obliteration of the IA, no residual flow into the aneurysm and the assured perfusion of brain areas perfused by vessel branches from the aneurysm. On the other hand, there is the neurological outcome of the patient, as a part of surgical outcome. The neurological outcome

of the patient is quantified by mRS in the postoperative course., Besides, a neurological examination by an experienced neurosurgeon can provide information about a new focal neurological deficit that has developed postoperatively.
This is critical to provide reliable information on the correlation of postoperative focal neurological deficits with intraoperative adverse events or evoked potential amplitude reductions.

In terms of subjective sense of security, using IOM granted the surgeon a higher sense of security in 30 of 47 cases (63.8%) compared to not using IOM during surgery. The surgeon reported the impact of IOM on the sense of security as neutral in 17 of 47 cases (36.2%). There were no occasions in which the IOM had a negative impact on surgeon's sense of security. **(Table 13)**

Table 13: Evaluation of the questionnaire for the surgeon, including subjective sense of security and the impact of IOM on the surgical outcome.

Subjective sense of security, using IOM N (%)	
lower	0/47 (0)
neutral	17/47 (36.2)
higher	30/47 (63.8)
Impact of IOM on the surgical outcome	
negative	0/47 (0)
neutral	38/47 (80.9)
positive	9/47 (19.1)

Thirty-five aneurysms were clipped in the 30 cases where IOM was rated as improving the subjective sense of security. Regarding the location of the treated aneurysm, particularly during clipping of MCA aneurysms, the surgeon described a higher subjective feeling of security. **(Figure 23)**

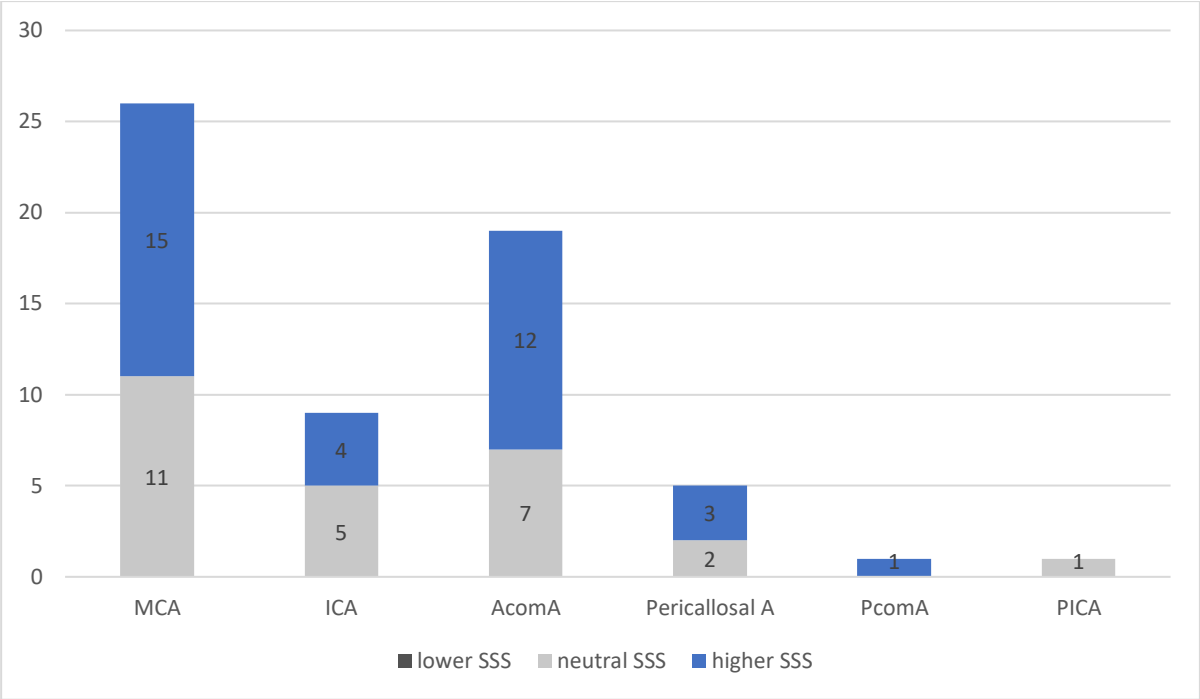

Figure 23: Locations of aneurysms and the surgeons' subjective sense of security (SSS) using IOM compared to the imagination of not having used IOM during microsurgical aneurysm clipping at this location. Higher SSS = IOM provided the surgeon with a higher subjective sense of security during surgery compared to the hypothetical case of not having used IOM.

In terms of surgical outcomes, the surgeons evaluated the influence of IOM as neutral in the majority of microsurgical clippings (80,9%). IOM was found to have a beneficial impact on surgical outcome in 9 of 47 cases (19.1%). Regarding the aneurysms' locations, IOM was proven to have a positive impact on the surgical outcome, particularly after the clipping of MCA (46.2% of all MCA aneurysms clipped) and AcomA aneurysms (30.8%).

3.7. False negative results

We reported one case of a patient with a PICA aneurysm, who developed a facial nerve palsy (House and Brackmann grade III) in the PACU, that was still present at DOD. There was no decline in amplitude of IOM during surgery. **(Table 14)**

IOM modalitiy used in this case during surgery was facial nerve EMG. Facial nerve EMG cannot monitor the brainstem or the cortex of the brain and therefore, it is not able to detect brainstem or cortical lesions.

Table 14: False negative case in IOM characterized as an uneventful IOM course resulting in a postoperative focal neurological deficit.

False negative case									
Patient			**Aneurysm**			**Surgery**			**PostOP**
Patient ID	**Sex**	**Age**	**PHASES**	**Location**	**Size (mm)**	**Number of decreases**	**Duration until recovery**	**Temporary clipping**	**Neurological deficit**
19	female	75	9	PICA	7	0	/	no	Facial nerve palsy

The postoperative DSA was uneventful in this case. Therefore, the new neurologic deficit was not caused by vascular occlusion of a supplying artery that perfuses the nuclei of the facial nerve.

False negative cases must be divided into true false negative cases and putative false negative cases. In a true false negative case, there is intraoperative diminished perfusion of an eloquent area that is monitored by IOM. Consequently, there should be a decrease in amplitude of the affiliated IOM modality. However, if this is not the case and a new postoperative focal neurological deficit occurs, it represents a true false negative case. On the other hand, secondary events can cause a postoperative focal neurological deficit, that could have not been predicted by IOM, as IOM measures the function of eloquent brain areas during surgery. Secondary events for example are described as postoperative hemorrhage or edema.

In our case (patient 19), further analysis revealed that the new neurologic deficit was caused by a subacute ischemia after surgery. The facial nerve palsy was thus the consequence of a subsequent postoperative event. As IOM can only monitor the function of eloquent areas during surgery, a deficit due to a secondary event after surgery must be rated as a putative false negative case. Therefore, our study did not report any true false-negative cases.

3.8. Postoperative evaluation

A complication-free postoperative clinical course was documented in 36 out of 47 cases (76.6%), without the development of new focal neurological impairments or other adverse events (AE) linked to a deterioration of the patient's preoperative state. AEs, including postoperative delirium, disorientation, reduced vigilance, and new focal neurological deficits, occurred in 11 of 47 cases (23.4%). Two of the eleven patients who experienced an unanticipated AE following surgery had a new focal neurological deficit. **(Table 15)**

Table 15: Evaluation of the postoperative clinical course, including unexpected adverse events and FNDs.

Postoperative AE	**N (%) or median (±SD)**
Adverse Event	11/47 (23.4)
Recovery during Stay	10/11 (90.9)
Timing of AE	
PACU	5/11 (45.5)
POD 1	4/11 (36.4)
POD 5	2/11 (18.2)
New postoperative focal neurological deficit	
New postop focal neurological deficit	2/47 (4.3)
Recovery during Stay	1/2 (50)

During their stay at the hospital, 10 of the 11 patients (90.9%) recovered completely. At the DOD, the clinical deterioration was completely reversed. The clinical status of the patient was the same or even better after hospitalization compared to the patients' preoperative status.
There was one case, of a patient who developed a facial nerve palsy (House and Brackmann °III) in the PACU, that was still present at day of discharge. This case was explained in more detail in the previous chapter (3.7).
In terms of timing of unexpected AEs, the great majority of them occurred either in the PACU (45.5%) or on POD 1 (36.4%). After POD 1 unanticipated AEs were comparatively unlikely (18.2%).

4. DISCUSSION

4.1. Objectives

This thesis presents a case series with a remarkably low rate of postoperative focal neurological deficits. The findings of the study demonstrate, that for elective microsurgical clipping of UIAs, IOM is capable of preventing postoperative neurological deficits by granting the surgeon real-time information about to integrity of motor eloquent brain areas. IOM is a trustworthy indicator of neurological function since, as evidenced by our results, a new postoperative neurological deficit is extremely unlikely in cases where there was no amplitude decline of IOM during surgery.

Furthermore, the study shows that TC lasting up to 18 minutes is feasible without resulting in neurological deficits after surgery. However, only the use of IONM can inform the surgeon on the tolerability of TC in each case. Yet, neuropsychological factors, including postoperative delirium have not been included in this research.

4.2. IOM

4.2.1. IOM application

Acquisition of evoked potentials, including tcMEPs, SSEPs, AEPs and facial nerve EMG was successful in all cases (100%), proving IOM to be an extremely practical and secure intraoperative technique. During surgery, the approach was demonstrated to be exceptionally simple to apply and free of technical difficulties. These findings are in accordance with previous literature. [1,8,12,19,53]

4.2.2. Temporary Clipping

The present study proved TC, to be a potential reason for a reversible decline in amplitude of EPs. A causal link between the TC and the drop in amplitude of EPs can be averred in half of the cases with an amplitude decline during TC.

This finding of a causal relationship between TC and decline in. amplitude of EPs is in accordance with recent studies, showing that patients with a temporary occlusion of a vessel, have a significantly higher risk of ischemic lesions in the vascular territory of the parent artery. [54,55]. According to Park et al, TC was also associated with postoperative ischemic complications [54].

Our research demonstrates that TC up to 18 minutes in duration is possible without leading to postoperative neurological deficits. According to Lavine et al., patients can only tolerate a TC duration of 10 minutes [56] Ogilvy et al. reports that patients with TC < 20 minutes have a

significantly lower risk for brain ischemia compared to patients who undergo TC for more than 20 minutes[57].

As previously mentioned, in all the declines in amplitude of IOM there was a complete recovery of EPs until the end of surgery, because due to the real time feedback of IOM, the surgeon was able to react promptly during the reversible period of structural brain injury. Therefore, particularly during TC, which is, besides its advantages, linked to a higher risk of ischemic brain injury, the IOM is able to prevent lasting neurologic impairments, since it can be used to detect the eventual shift in nerve conduction caused by decreased blood flow and structural injury in the reversible phase. [1,9,12,53] This depiction of IOM's crucial role in TC, which highlights both its necessity and its predictive value as determined by our clinical observations, has not yet been described in the previous literature. Taking a closer look at the locations of UIAs clipped, our study shows that particularly during TC of MCA and AcomA aneurysms IOM is hugely advantageous.

4.2.3. False negative cases

In our clinical observation, there was one patient with an intracranial aneurysm of the PICA, who developed a facial nerve palsy (House and Brackmann °III) after surgery in the PACU. The facial nerve palsy did not recover until the discharge of the patient. There was no decrease in amplitude of IOM during surgery.

Subsequently, the question why IOM was not able to sense the impending loss of function, must be asked. When asking this question, it is important, to keep in mind, that IOM is only able to monitor the function of eloquent brain areas during surgery. If there is a subsequent ischemia, hemorrhage or edema after surgery, it is not possible to provide evidence on the patient's neurological status by data obtained from IOM during surgery. IOM can only monitor a neurological function where it is also actually measured. The intracranial localization responsible for the new postoperative focal neurological deficit must therefore be precisely determined. If the new deficit occurs in a nonmonitored muscle group for example, it must be classified as putative false negative, not truly false negative.

It is crucial to examine all ostensibly false negative cases in detail, in order to differ exactly between a real false negative case and a putative false negative case.

Prior literature reported and confirmed false negative cases in their reports. Greve et al. 2019 described five false negative cases in a study with a total cohort of 274 patients.

In a patient population of 1514 patients that was retrospectively gathered, Chung et al. 2019 reported eight cases of false negative IOM. In their investigations, no mechanistic explanation for the false negative IOM result was found. [13,58]

Neuloh et al. 2007 also described a case, which is comparable to the case in the present investigation. In his research a patient developed a new postoperative focal neurological

deficit, presenting with a transient facial nerve palsy. Analysis revealed that this case was not a real false negative case. In the described case only arm MEPs were recorded. Therefore, the paresis occurred in a muscle group, not monitored by IOM during surgery. [59]
In our case, further examination revealed that the facial nerve palsy resulted from subacute ischemic complications after surgery. This postsurgical effect could have not been detected by IOM, as it can only monitor the nerve function during surgery. Therefore, this case in our study must be rated as ostensibly false negative case. No true false negative cases were reported in this study.
Similar cases, with postoperative effects, leading to a new paresis, were described by Kombos et al[60].

With respect to the incidence of postoperative AEs, the importance of PACU observation is clearly evident, as 45.5% of the study's AEs were observed within the PACU.
In a recent clinical study regarding IOM with MEP in Glioma surgery, our clinical research group (Krieg et al. 2012) discussed the critical question of false negative cases. The study aimed to analyze supposedly false negative cases of IOM further, in order to reveal structural explanations for these cases. We reported five patients who presented with a new and permanently deteriorated motor function after surgery, even though the MEPs were stable during surgical glioma resection. These ostensibly false-negative cases were examined in more detail. Postoperative MRI scans revealed all these cases to be non-genuine ones, as secondary edema and ischemic lesions were the reason for the new postoperative motor deficit. Thus, after analysis of the data, no true false negative cases were observed in our investigation. For this reason, we have pointed out the decisive influence of secondary events on the postoperative neurological outcome.
As mentioned above, secondary edema and hemorrhage cannot be picked up by IOM. As a result, according to our recent research, differentiating between authentic false negative cases and non-genuine cases is even more invaluable in order to not to jeopardize the surgeon's trust in the monitoring. [19]
Regarding the impact of false negative cases on the surgeons' trust in IOM, Gläsker et al. 2006 also discussed the problem of (ostensibly) false negative cases, as they have a deleterious impact on the surgeon's trust in IOM. Especially the false negative results, compared to false positive cases, are even worse, as they come along with new postoperative neurological deficit, without intraoperative warning by IOM. Thus, false positive cases should also not occur too often, as they significantly reduce the credibility in IOM. [20]
This also underlines the importance of distinguishing true and putative false negative cases properly.

4.2.4. Predictive value of IOM

Our study showed that IOM has a high NPV in terms of postoperative neurological outcome since there was only one ostensibly false negative case with a permanent neurological deficit and all the other postoperative courses were uneventful, when the amplitude of IOM recovered and returned to baseline level at the end of surgery. In essence, this study revealed IOM to provide reliable real-time information about the integrity of eloquent brain areas. There is a high correlation between monitored intraoperative events and postoperative neurological functional status.

Consequently, it can be assumed that in cases where IOM remains stable or decreases only transiently, the occurrence of a postoperative motor deficit is highly unlikely. This predictive value has often been a controversially discussed variable in the few studies to date, not least because of contradictory results. Also, the conducted studies were mainly retrospective studies. [16–19].

In our study, NPV (97.6%) and specificity (87%) were high for the included patient cohort, demonstrating a high probability for no postoperative focal neurological deficit in cases of stable IOM (including tcMEP, AEP, facial nerve EMG). Our PPV and sensitivity were null, as there were no postoperative neurological deficits recorded after transient IOM decline. Therefore, the statistical value of the NPV and the specificity is very limited in our study. Compared to other studies, recent investigations have shown a high specificity and NPV for IOM, while the sensitivity and PPV were low, respectively. [13,54,58]

4.3. Surgeons' perspective

In our study, the application and feedback from the IOM granted the surgeon a higher sense of security (63.8%) compared to the imagination of not having used IOM during the microsurgical clipping. There were no occasions in which IOM had a negative impact on the subjective sense of security.

Gläsker et al. 2006 already emphasized the importance of surgeon's secure feeling while performing surgical procedures. A higher secure feeling due to IOM can encourage the surgeon during surgery and provide him/her with more confidence. [20] This is also reflected in the TC constraint imposed by tcMEPs. For this reason, the subjective feeling of security of the surgeon must not be neglected in order to achieve a favorable result.

As a result, in accordance with the literature, our study demonstrated that IOM does not only evaluate the functional integrity of the observed system in real-time during surgical procedures, but also provides the surgeon with more confidence concerning the postoperative outcome of the patient. [19,20]

Naturally, this notion assumes some experience with IOM, especially since intraoperative signal changes can be complex to interpret. The modality does present a learning curve, when

the surgeon encounters unexpected changes in IOM by demonstrating to the surgeon which manipulation steps result in deterioration of neurological function. Thus, the learning curve of this modality often requires a form of trial and error for the more inconclusive findings.

4.4. Limitations and future perspectives

Limitation of the present research is the number of patients included in this study. We included 47 patients prospectively in a period from February 2019 to February 2021. As statistical power is higher with a higher case number, a larger patient cohort is needed in order to increase the statistical power. Therefore, a prospective multicenter study might be necessary to provide the real impact of IOM on neurological outcome.

In a larger cohort, with a higher number of cases, there would be a better distribution regarding the patients with stable IOM, transient decline in IOM and permanent decline in IOM. This would be a huge advantage for calculating NPV, PPV, sensitivity and specificity. For determining the maximum time frame of TC, a larger cohort would be of great value.

Since the objective of this research was to determine the predictive value of IOM in UIA elective microsurgical clippings, it is important to note that a randomized controlled study design would be even more advantageous to determine the impact of IOM on the neurological outcome. Thus, from an ethical perspective, the conduction of a randomized controlled trial would be unjustifiable for this question because there is already far too much positive evidence on IOM in previous uncontrolled studies. It would be disadvantageous to the study's control group if IOM was not used.

Furthermore, a limitation of this study is that neuropsychological aspects, including postoperative delirium, were not included in the present research.

4.5. Conclusion

IOM is invaluable during elective microsurgical clipping of UIAs, especially during TC of MCA and AcomA aneurysms. It provides accurate, real-time information on the functionality of motor eloquent brain areas. There is an extremely high correlation between IOM and the patient's postoperative neurological functional status, regarding the intraoperative development of new neurological deficits. In cases where no decline in amplitude of EPs is observed, a new postoperative neurological deficit is highly unlikely, as our results have shown.

Especially during TC, IOM offers a crucial benefit, as it senses impending ischemic injury of eloquent brain areas and alerts the surgeon in the reversible phase, which permits the surgeon to react immediately to prevent neurological impairment and also maximizes the time frame for TC.

Since the cerebral supply regions of the arteries differ, it is critical to tailor the electrophysiological examination area to the arterial supply in order to acquire a reliable result.

Furthermore, IOM has highly increased surgeons' subjective feeling of security and beneficially impacts the surgical procedure. IOM does not only evaluate the functional integrity of the observed system but also provides the surgeon with more confidence while confirming the functional integrity of eloquent structures during surgery.

In conclusion, the study shows that IOM is of significant benefit to both the patient and the surgeon.

5. SUMMARY

5.1. English

Objective:

Ischemic complications after aneurysm clipping are a source of immense postoperative neurological morbidity. Intraoperative neuromonitoring (IOM) of motor and somatosensory evoked potentials is a well-established approach for reducing morbidity. The aim of this study was to determine the predictive validity of IOM for postoperative functional outcome and its perceived added value for intraoperative real-time feedback of functional impairment in the surgical treatment of unruptured intracranial aneurysms (UIAs).

Methods:

This study prospectively included patients scheduled for elective microsurgical clipping of UIAs between 02/2019 – 02/2021. Transcranial motor evoked potentials (tcMEP) were used in all cases, a significant decline was defined as a loss of at least 50% in amplitude strength or a 50% increase in latency. Clinical data were analyzed and correlated to postoperative deficits. A surgeon's questionnaire, assessing the subjective perceived value while using IOM during clipping and the impact of IOM on the surgical outcome, was conceived.

Results:

47 patients were included, median age at surgery 57 years (range 26 – 76). IOM was successful in all cases. In 87.2%, IOM modalities were stable throughout surgery, although 1 patient (2.4%) of these demonstrated a permanent postoperative neurological deficit. All patients with an intraoperatively reversible decline of tcMEPs (12.7%) showed no surgery-related deficit, regardless of the duration of the decline, ranging from 0.5 – 40.0 minutes (mean: 13.8 min). Temporary clipping (TC) was performed in 12 cases (25.5%). A decline in amplitude was seen in 4 of these patients (8.5%). After removal of the clip, all amplitudes returned to baseline. IOM provided the surgeon with a higher sense of subjective security for the clipping procedure in 30 of 47 cases (63.8 %).

Conclusions:

IOM is invaluable during elective microsurgical clipping, particularly during TC of MCA and AcomA aneurysms. It alerts the surgeon of impending ischemic injury and offers a way of maximizing the time frame for TC. Furthermore, it has highly increased surgeons' subjective feeling of security during the procedure.

5.2. Deutsch

Zielsetzung:

Ischämische Komplikationen nach dem mikrochirugischen Clipping von intrakraniellen Aneurysmen sind eine immense Quelle für postoperative neurologische Morbidität. Das intraoperative Neuromonitoring von motorisch und somatosensorisch evozierten Potenzialen ist ein bewährtes Verfahren, um diese Morbidität zu reduzieren. Ziel dieser Dissertation war es, die prädiktive Validität des intraoperativen Neuromonitorings für das postoperative funktionelle Ergebnis des Patienten und seinen wahrgenommenen Mehrwert für die intraoperative Echtzeit-Rückmeldung funktioneller Beeinträchtigungen bei der chirurgischen Behandlung unrupturierter intrakranieller Aneurysmen zu ermitteln.

Methoden:

In diese Studie wurden prospektiv Patienten eingeschlossen, bei denen zwischen 02/2019 und 02/2021 ein elektives mikrochirurgisches Clipping eines nicht rupturieren intrakraniellen Aneurysmas geplant war. In allen eingeschlossenen Fällen wurden transkranielle motorisch evozierte Potenziale verwendet, wobei ein signifikanter Abfall als Verlust von mindestens 50% der Amplitudenstärke oder eine 50%ige Zunahme der Latenzzeit definiert wurde. Die klinischen Daten wurden analysiert und mit den postoperativen Defiziten korreliert. Es wurde zudem ein Fragebogen für Chirurgen konzipiert, der den subjektiv empfundenen Wert des intraoperativen Neuromonitorings während des Aneurysma-Clippings und die Auswirkungen des intraoperativen Neuromonitorings auf das Operationsergebnis bewertete.

Ergebnisse:

Es wurden 47 Patienten in die Studie eingeschlossen, das Durchschnittsalter bei der Operation betrug 57 Jahre (Spanne 26 - 76). Das intraoperative Neuromonitoring war in allen Fällen erfolgreich. Bei 87,2 % waren die intraoperativen Monitoring-Modalitäten während der gesamten Operation stabil, wobei 1 Patient davon (2,4 %) ein dauerhaftes postoperatives neurologisches Defizit aufwies, in Form einer Fazialisparese. Alle Patienten mit einem intraoperativ reversiblen Abfall der transkraniellen motorisch evozierten Potentiale (12,7 %) zeigten keine operationsbedingten neurologischen Defizite, unabhängig von der Dauer des Abfalls, der zwischen 0,5 und 40,0 Minuten lag (Mittelwert: 13,8 Minuten). Ein temporäres Clipping wurde in 12 Fällen (25,5 %) durchgeführt. Bei 4 dieser Patienten (8,5 %) wurde ein Abfall der Amplitude beobachtet. Nach Entfernung des temporären Clips kehrten alle Amplituden wieder zum Ausgangswert zurück. Das intraoperative Neuromonitoring vermittelte dem Chirurgen in 30 von 47 Fällen (63,8 %) ein höheres Gefühl der subjektiven Sicherheit für das mikrochirugischen Aneurysma-Clipping.

Schlussfolgerungen:

Intraoperatives Neuromonitoring ist bei elektiven mikrochirurgischen Aneurysma-Clippings von unschätzbarem Wert, insbesondere beim temporären Clipping von MCA- und AcomA-Aneurysmen. Das intraoperative Neuromonitoring warnt den Chirurgen vor einer drohenden ischämischen Schädigung und bietet eine Möglichkeit, den Zeitrahmen für das temporäre Clipping zu maximieren. Darüber hinaus hat es das subjektive Sicherheitsgefühl der Chirurgen während des Eingriffs stark erhöht.

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Parts of this dissertation have recently been published in the journal "Brain and Spine":

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7. ABBREVIATIONS

A.	Arteria
ACA	Anterior cerebral Artery
AcomA	Anterior communicating Artery
AE	Adverse Event
AEP	Acustic Evoked Potentials
aSAH	Acute subarachnoid hemorrhage
BA	Basilar artery
cCT	Cranial computer tomography
DOD	Day of discharge
DSA	Digital Subtraction Angiography
EP	Evoked Potentials
GCS	Glasgow Coma Scale
IA	Intracranial Aneurysm
ICA	Internal carotid Artery
ICG-Angiography	Indcyanid Green Angiography
IOM	Intraoperative Neuromonitoring
KPSS	Karnofsky Performance Status Scale
MCA	Middle cerebral Artery
MEP	Motor evoked potential
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NPV	Negative Predictive Value
PACU	Postoperative Anesthesia Care Unit
PCA	Posterior cerebral Artery
PcomA	Posterior communicating Artery
PICA	Posterior inferior cerebellar Artery

POD	Postoperative Day
PPV	Positive Predictive Value
Sen	Sensitivity
Spe	Specificity
SSEP	Somatosensory evoked potential
TC	Temporary Clipping
tcMEP	Transcranial Motor evoked potentials
TES	Transcranial evoked stimulation
UIA	Unruptured intracranial aneurysm
VA	Vertebral Artery

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8. LIST OF FIGURES

9. LIST OF TABLES

11. PUBLICATIONS

Original papers

Anetsberger A, Jungwirth B, Blobner M, Ringel F, Bernlochner I, Heim M, Wostrack M, Schneider G, Meyer B, **Baumgart L**, Gempt J
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