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Efficiency of transcranial motor evoked potential monitoring in the clipping of unruptured intracranial aneurysms

vorgelegt von
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TABLE OF CONTENTS

Background: Ischemic complications during aneurysm surgery constitute a prevalent cause of postoperative neurological deficits**.** As a standard technique, transcranial motor-evoked potentials (tcMEP) are used in order to minimize the risk of such deficits. According to our own observations as well as references, there seemed to be a number of biasing and disruptive factors interfering with the validity of tcMEP monitoring in aneurysm clipping. We posed the question whether these disruptive factors inhibit the evaluation of tcMEP monitoring in an extent to which its usage in aneurysm clipping is of no further advantage to the surgical team. Summarizing, the aim of this study was to characterize the efficiency of tcMEP monitoring regarding its impact on the motor morbidity in the clipping of unruptured intracranial aneurysms.

Methods: We performed a retrospective analysis of 163 consecutive cases of surgical clippings of incidental intracerebral aneurysms between 2010 and 2016. The monitoring data were reviewed and related to new postoperative motor deficits and postoperative imaging.

Results: TcMEP monitoring was successful in all cases. In 90.8% of surgical interventions, stable tcMEP monitoring signals were observed. In 9.2% of cases, a transient change in tcMEP signals occurred during surgery. No cases of permanent decline in tcMEP monitoring became apparent in our patient cohort.

We found a significant increase of the relative risk of a transient and permanent loss of motor function in the cases of intraoperative tcMEP decline. The risk of postoperative restricted motor function was 6.68 (95%-confidence interval: 1.19-36.32) times higher in a patient with a transient decline than in a patient with stable tcMEP signals. Furthermore, we reviewed the observed disruptive factors of intraoperative tcMEP monitoring and defined three major classes: positional influences, mechanical effects, and, most frequently, circulatory deficits.

Conclusion: An association between intraoperative tcMEP status and postoperative motor function can be assumed according to our data. A positive impact of the surgical action on the postoperative motor outcome can be expected by a correct identification and treatment of a symptomatic tcMEP decline. We therefore concluded, that tcMEP monitoring is a valuable device in the prevention of ischemic complications and focal neurologic deficits in aneurysm clipping.

1. LIST OF ABBREVIATIONS

Abbreviation	Meaning
95%-CI	95%- Confidence interval
A.	Arteria
aSAH	Acute subarachnoid hemorrhage
cCT	Cranial computer tomography
CMAP	Compound muscle action potential
DSA	Digital Subtraction Angiography
EEG	Electroencephalography
EMG	Electromyography
ICG-Angiography	Indocyanid Green- Angiography
IONM	Intraoperative neuromonitoring
MRI	Magnetic resonance imaging
NNT	Number needed to treat
NPV	Negative predictive value
PPV	Positive predictive value
RR	Relative Risk
SSEP	Somatosensory evoked potential
tcMEP	Transcranial motor evoked potential
TIVA	Total intravenous anesthesia

2. INTRODUCTION

Intraoperative Neuromonitoring (IONM) has become increasingly common in present Neurosurgery. It covers a large variety of technical systems and electrophysiological modalities, which consequently results in a wide range of possible application fields. It is used to give a real-time status quo of the patient`s motor and sensitive functions as well as in the identification of neuronal structures in tumor and epilepsy surgery or anatomically complex regions (LeRoux et al. 1991; Simon 2013; Kodama et al. 2014; Shkarubo et al. 2017). The main significance of IONM lies in the continuous surveillance of the narcotized patient and aims – by giving a persistent feedback to the surgeon – to detect a neuronal damage as early as possible. Hereby, the resulting dysfunction may still be reversible and, by taking sufficient means, a loss of function may be prevented. Therefore, it is supposed to have a positive impact on the postoperative outcome and the patient`s health related quality of life. Being recently added to the possibilities of surgery, IONM is widely used and valued, not only in neurosurgery but also in thoracic interventions and thyroidectomy (So and Poon 2016; Baek et al. 2017). Its' possible utilization is still expanding, as for example for the autonomic nervous system in urological surgeries. This possible expansion assures it is not only a device of present but of future surgical interventions (Skinner 2014). Applied to the specific tracing of motor function, it is achieved by the usage of transcranial motor evoked potential (tcMEP) monitoring (MacDonald 2006; Macdonald et al. 2013).

2.1. Historic background of tcMEP monitoring

The theoretical basis of tcMEP monitoring goes back to the beginning of the 19th century when Marie-Jean-Pierre Flourens published his results on the function of pigeons' brains (Yildirim and Sarikcioglu 2007). By resecting different parts of the birds' brain, he was able to show that specific physiologic functions were controlled by specific parts of the brain and characterized these parts as cerebral cortex, cerebellum and medulla oblongata. In 1870, Fritsch and Hitzig extended their experimental research on mammals (Fritsch and Hitzig 2009). After craniotomy, they used ten galvanic cells to apply an electric current to the brain of dogs and were able to show that the brain is divided into a motor part and a non-motor part. Around the turn of the

century, there were a couple of outstanding achievements affecting the mapping of the human brain: Sir Victor Horsley, as a pioneer of neurosurgical experiments, studied the brain of monkeys (Ellis 2016) and Korbinian Brodmann published his work on the cytoarchitectural organization of neurons using the Nissl-Method and defining the Brodmann areas, which are in use to this day (Kawamura 2017). Innovative for IONM were Penfield and Boldrey's observations in 1937 (Penfield and Boldrey 1937). In order to treat epilepsy, they stimulated the cortex of conscious patients intraoperatively and described the contralateral arrangement of the somatosensory homunculus. By using this electrical stimulation, they were able to precisely target the areas of the brain responsible and optimize their patients' outcome.

The basis of tcMEP monitoring was provided in 1954 by Pattson and Amassian. They described the effect of a single electrical pulse applied to the motor cortex of a monkey (Patton and Amassian 1954). In 1980, Merton and Morton developed a transcranial electrical stimulation which enabled them to record muscle evoked potentials in conscious humans (Merton and Morton 1980). In 1991, LeRoux et al. were the first to describe the usage of tcMEP monitoring in neurosurgery. They used cortical and subcortical stimulation mapping techniques in the resection of intrinsic glial tumors (LeRoux et al. 1991). Today, tcMEP is routinely used in various neurosurgical treatments, such as intramedullary spinal cord tumor surgery, spinal deformity surgery, posterior fossa tumor surgery, peri-rolandic brain surgery, and aneurysm surgery (Nuwer et al. 1995; Dong et al. 2005; Kothbauer 2017).

2.2. Intracranial aneurysms

Aneurysm is the medical term for a permanent, circumscribed vascular dilatation. These progressive changes are not congenital but acquired due to multifactorial disorders. The origin, as well as influencing factors, are not clear. Mainly, three factors have been identified in recent studies: firstly, common vascular risk factors such as hypertonia, arteriosclerosis, nicotine, and alcohol abuse may result in a loss of vascular stability and its oxygen supply, and therefore not only favor the existence of intracranial aneurysms, but also their progress and the probability of rupture (Backes et al. 2016; Brinjikji et al. 2016; Etminan and Rinkel 2016). For example, smoking increases the chance of developing an intracranial aneurysm by 3.0 to 5.61 times in different studies (Etminan and Rinkel 2016).

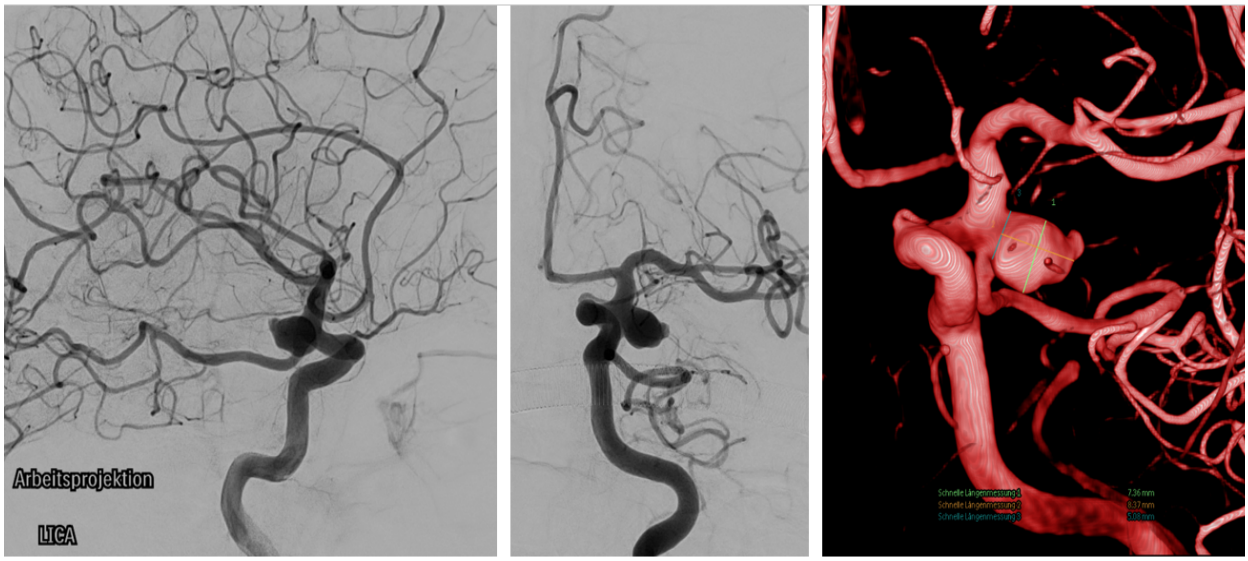

Figure 1: Unruptured intracranial aneurysm of the arteria communicans posterior depicted by digital subtraction angiography (DSA) and 3D- angiography.

Secondly, hemodynamic stress was identified as a contributing factor in the pathogenesis of aneurysms. Based on mathematic simulations, higher wall shear stress causes significant changes of the vessel wall favoring the existence of intracranial aneurysms (Cebral et al. 2011; Cebral et al. 2015; Suzuki et al. 2019). Thirdly, certain genetic factors were shown to elevate the incidence of intracranial aneurysms. Hereditary weakness of the collagenous connective tissue, for example in patients suffering from Marfan's syndrome, is considered to be positively correlated to the existence of intracranial aneurysms (Lejeune 1997). Furthermore, autosomal polycystic kidney disease and a positive family anamnesis have been described to have an increased probability of developing vascular anomalies (Lejeune 1997; Vlak et al. 2011).

2.2.1. Clinical aspects of intracranial aneurysms

Mostly, unruptured intracranial aneurysms are asymptomatic and therefore an incidental finding on magnetic resonance imaging (MRI) (Bos et al. 2016). In the cases of growth of the aneurysm, cranial nerve loss by mass effects may occur, most commonly affecting the third or sixth cranial nerve (Kasner et al. 1997; Durner et al. 2018). However contrary to the benign clinical course as long as unruptured, the consequence of a rupture is a life-threatening condition: an acute subarachnoid

hemorrhage (aSAH). An aSAH is characterized by free blood in the subarachnoid space between the two layers of the soft cranial meninx, arachnoid membrane and pia mater. Patients describe a characteristic “thunderclap headache”. Depending on the severity, symptoms vary from a slight headache, vomiting, and dizziness to seizures and coma (Petridis et al. 2017). An aSAH is associated to a mortality of more than 30% (Petridis et al. 2017). Especially, the 24-hour mortality is high with ten to 25 percent of all patients. It moreover has a profound impact on long-term morbidity: Although clinical outcome has improved over the last years due to an optimized quality of medical care, approximately one third of the patients suffering an aSAH remain permanently disabled (Kundra et al. 2014; D'Souza 2015).

There are three different classification scales, characterizing an aSAH either according to clinical features or radiologic findings: The Hunt and Hess scale, the modified Fisher Scale and the modified world federation of neurosurgical societies subarachnoid hemorrhage grading system (Hunt et al. 1966; Hunt and Hess 1968; Frontera et al. 2006; Sano et al. 2015). Most commonly used in clinical settings is the Hunt and Hess classification system, dividing an aSAH into five categories. It has two main functions: Firstly, the Hunt and Hess classification system grades patients in acute situation according to their symptoms. Based on their clinical appearance, it moreover provides a prognostic reference of the probable outcome (Hunt and Hess 1968).

2.2.2. Therapeutic options of unruptured intracranial aneurysms

The population-based Rotterdam Scan Study found a prevalence of 2.3% (95%-Confidence interval: 2.0% to 2.7%) for unruptured, incidental cerebral aneurysms in MRI scans of the brain (Bos et al. 2016). Referring to the high short- as well as long-term mortality and morbidity of an aSAH depicted in chapter 2.2.1., an incidental finding of an unruptured intracranial aneurysm implies the question of a possible advantage by a rupture preventive therapy compared to its natural course. As discussed above, the decision of therapeutic action is a highly individual one as the risk of rupture depends on a variety of factors (Wiebers et al. 2003). For clinical decision making, several scores have been introduced. Frequently used in clinical practice is the PHASES Score. It represents a meta-analysis of six prospective cohort studies with individual data of 8382 patients and 29166 patient years follow-up. It combines age, hypertension, history of subarachnoid hemorrhage, population (the Finnish and Japanese Population were found to have 2-8 times increased risk of rupture), size and

site of the aneurysm treated. The hereby calculated score correlates to a certain 5-year risk of rupture, providing valid assistance in the decision of further therapeutic strategies (Fig. 2) (Greving et al. 2014). However, there are certain limitations of the PHASES score, as it bases on incomplete data on risk factors, for example exclusion of smoking, an age distribution with less than 5% of patients included being less than 40 years old, and the lack of a long-term prognosis (Neyazi et al. 2019; Pagiola et al. 2019).

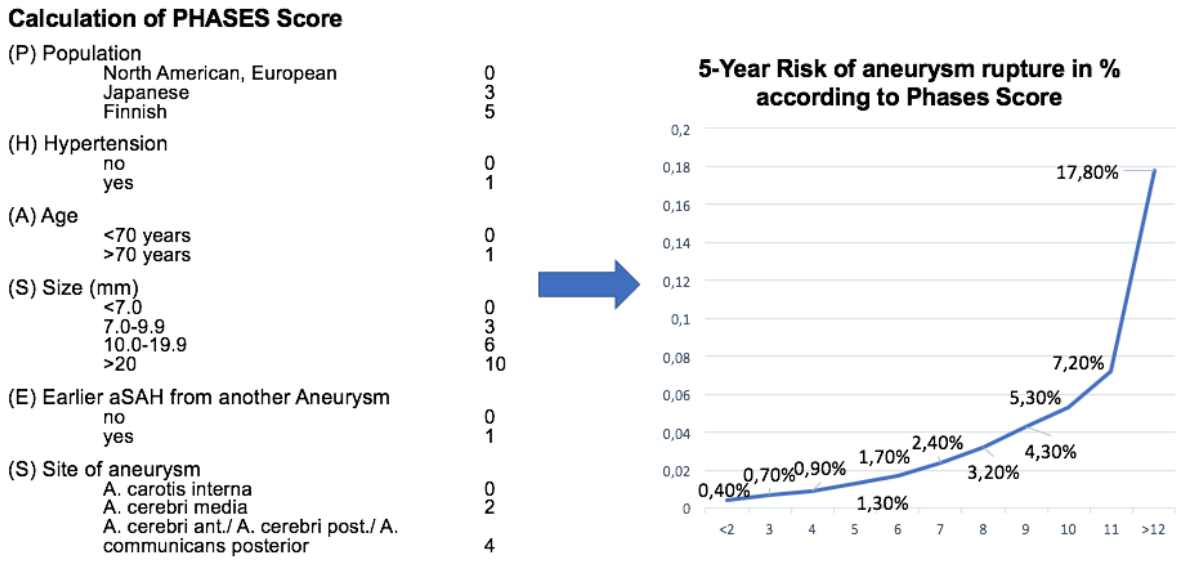

Figure 2: PHASES Score and the hereby calculated five-year risk of aneurysm rupture. It combines the factors population, hypertension, age, size, earlier aSAH, and site indicating a certain probability of rupture within five years. This probability of rupture increases exponentially according to the number of points calculated (Greving et al. 2014).

Regarding the life-long risk of rupture, a score by Juvela et al. was published in 2019 with a median follow-up of 21.0 years of 142 patients diagnosed with incidental unruptured intracranial aneurysm from 1956 to 1978 (Juvela 2018; Juvela 2019). Another score of clinical importance is the unruptured intracranial aneurysm treatment score (UIATS), which represents an experts' opinion on the decision of treatment (Etminan et al. 2015). Additionally, a topic of current interest is whether a gadolinium enhancement of the aneurysm wall might be associated to an increased risk of rupture: the absence of aneurysm wall enhancement might therefore be an imaging aspect of aneurysm stability (Texakalidis et al. 2018; Vergouwen et al. 2019).

If the decision is made in favor of treatment, two methods have to be considered: endovascular coiling and surgical clipping. For completeness, it has to be mentioned

that there are currently several case studies on endovascular flow diverter applications as well as surgical bypass options reserved for complicated intracranial aneurysm lacking the possibility of conventional coiling or clipping (Briganti et al. 2015; Tayebi et al. 2017; Lawton and Lang 2019). Due to these highly selected applications, these methods will not be discussed in the following.

2.2.2.1. Interventional treatment: Coiling

Coiling is an endovascular intervention, which aims on a complete embolization of the aneurysm treated with platinum coils. Using image intensification, these coils are directly placed into the aneurysm by a micro catheter via an arterial access, most commonly the arteria (A.) femoralis or A. radialis (Guglielmi et al. 1991; Guglielmi and Vinuela 1994; Raymond et al. 1997). Specific complications described in interventional coiling are aneurysmal rupture or perforation, catheter-related emboli, either peripheral at puncture site or central, as well as coil migration (Raymond and Roy 1997; Ajiboye et al. 2015).

2.2.2.2. Surgical treatment: Clipping

Clipping is an open microsurgical operation. By setting a titanium clip, the aneurysm is completely disconnected from blood flow. This procedure is performed under general anesthesia. The location of the aneurysm is decisive for positioning the head of the patient with a three-pin skull fixation device and the manner of craniotomy chosen; In most cases a pterional craniotomy is performed (Chaddad-Neto et al. 2012). After dissection and detachment of the temporalis muscle, craniotomy is realized starting from three points of trepanation. The dura is opened, laid back and the access to the aneurysm is prepared according to anatomic structures. The clip is placed under optimum protection of the nearby vessels. Assisted by technical devices, such as Indocyanid Green- Angiography (ICG- Angiography), a Microvascular Doppler system, and further IONM devices the surgeon inspects the position of the clip closely in order to ensure optimum setting (Neuloh and Schramm 2004; Gruber et al. 2011). General complications related to surgical intervention include infection, anaphylactic reaction to anesthetic medication, wound healing disorder, or an elevated probability of thrombosis. Moreover, there are several specific complications of aneurysm clipping,

such as short-term memory problems, seizures, epilepsies, or postoperative motor restriction (Ajiboye et al. 2015).

2.2.2.3. Comparison of the two methods of treatment

To evaluate a superiority of one method several studies have been introduced. The international subarachnoid aneurysm trial (ISAT) compared endovascular coiling and surgical clipping in patients with ruptured intracranial aneurysms in which both methods of treatment could be accomplished. They found a significantly lower mortality and morbidity in aneurysm coiling in short-term follow-up (one year). In long-term follow-up, both methods seemed to be equal. Especially concerning aneurysm re-bleedings, no significant difference could be detected (Molyneux et al. 2002). Similarly, Gonda et al. described a significant higher perioperative (30-day) mortality in the clipping of unruptured aneurysms. This imbalance adjusted in long-term follow up and they argued that it might be due to a significantly higher risk of seizures and epilepsy associated to clipping (Hoh et al. 2011).

The barrow ruptured aneurysm trial (BRAT) compared treatment of wide neck aneurysms, which were characterized by a maximum neck width of at least 4 mm or a ratio between the dome of the aneurysm to the neck of over two. They found a significantly higher number of wide neck aneurysm in surgical aneurysm clipping. This difference became even more emphasized in patients with a therapeutical switch from coiling to clipping. Concerning the clinical outcome, an imbalance between the two methods did not become apparent at any time. However, the aneurysm obliteration rate was significantly lower and the retreatment rate higher in the coiling group (Mascitelli et al. 2018).

A further problem in both clipping and coiling are vasospasms. Vasospasms can lead to minor perfusion or even ischemia and cause multiple transient or permanent symptoms (Dumont et al. 2010; Tsyben et al. 2016; Malinova et al. 2017). Comparing the two methods, de Oliviera et al. found no significant difference in the incidence of vasospasms (de Oliveira et al. 2007).

Summarizing, a shift of paradigm in favor of endovascular coiling in the treatment of unruptured intracranial aneurysms became apparent in the last years, especially due to the ISAT trial.

2.3. Physiological basis and technical performance of tcMEP monitoring

The risks of surgical clipping described above demand for profound methods of intraoperative surveillance. To monitor the motor pathway, tcMEP monitoring was introduced into aneurysm surgery (MacDonald 2006; Macdonald et al. 2013). A wrongly adjusted clip deprives the blood flow and hereby the oxygen supply of the cortex, consequently causing brain ischemia. If the motor cortex is affected, this results in a decrease of tcMEP and consequently directs the surgeon's attention to a potential threat to the motor integrity of the patient. TcMEP monitoring bases on the neuroanatomy and the physiologic function of the motor cortex and the pyramidal path. According to Brodmann, the primary sensorimotor cortex lies in the gyrus precentralis and is considered the origin of arbitrary motor skills (Chouinard and Paus 2006; Kawamura 2017). As depicted in Figure 3, its corticonuclear and corticospinal efferences, functionally combined as the pyramidal tract, descend through the capsula interna. 70 to 80 percent of the nerve fiber cross in the medulla oblongata to the contralateral site finally ending in the front horn of the spinal cord in a synapsis with the alpha motor-neurons. These alpha moto-neurons provide the spinal nerves, which, through its chemical synapsis at the neuromuscular junction, innervate the skeletal muscles and thereby cause contraction (Porter 1985). Specific motor areas can be addressed individually because of the somatotopic outline of the gyrus precentralis in the so-called homunculus (Metman et al. 1993).

By applying an electric current to the scalp, this pathway can be activated externally: the membrane potential of the nearby neurons depolarizes and is brought up to threshold triggering an action potential. Following the anatomic pathway described above, it eventually causes a contraction of the stimulated muscles, which can be derived by electromyography (EMG) (Fig. 3).

In tcMEP monitoring, this knowledge is being brought to clinical use. After anesthesia is induced, electrodes are placed to the scalp of the patient according to the international 10-20 system central sides overlaying the motor cortex, as depicted in Figure 3 and 4 (o.V. 1958).

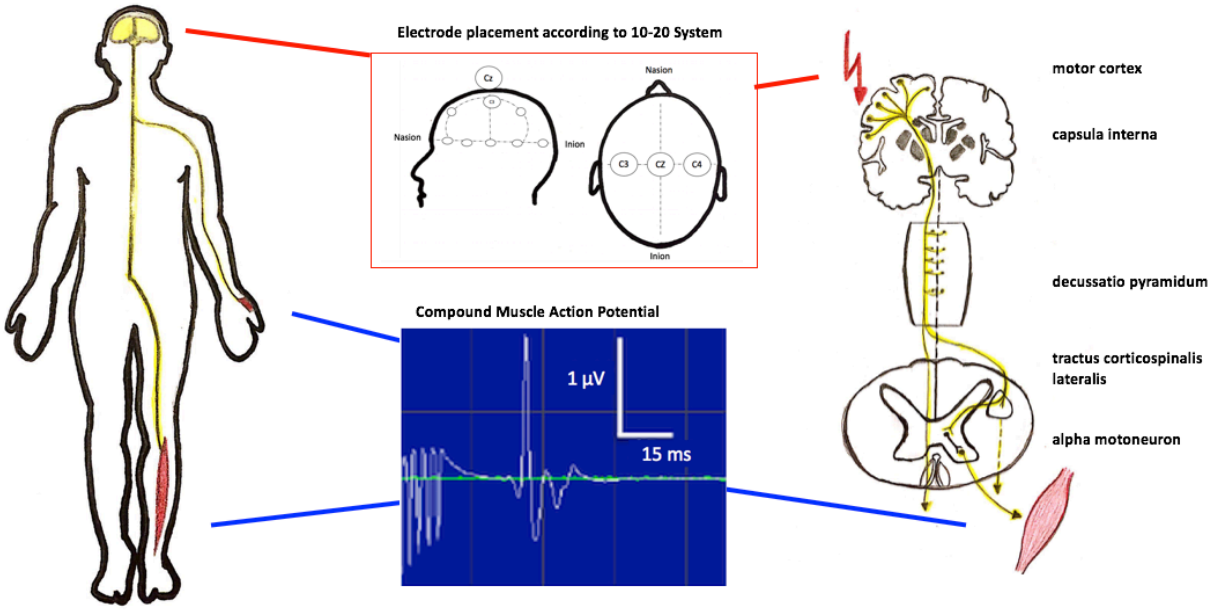

Figure 3: Anatomic and physiologic basis of tcMEP monitoring. By applying an electric current to the scalp (arrow) the motor pathway can be activated externally. The pyramidal path descending through the capsula interna, crossing in the decussatio pyramidum with a synaptic transmission to the alpha moto neuron finally results in a muscle contraction visualized by EMG as a compound muscle action potential (CMAP) (MacDonald 2006).

The EMG recording needles are placed at the contralateral M. abductor pollicis brevis, M. biceps brachii, or M. extensor digiti communis. The muscle potential is generated through a constant voltage stimulation either through a fast or slow delivery method (characterized by duration and current). Trains of three to nine rectangular pulses with a one to five millisecond pulse interval are being applied to the scalp. It has to be noted that these parameters differ individually and mainly depend on anesthetic depth, stimulus intensity, and targeted muscle (Macdonald et al. 2013). In order to selectively address the area of interest, the anode has to be placed precisely over the targeted site; Cathodic stimulation requires higher threshold stimulation resulting in a lack of meaningfulness regarding superficial subcortical structures and is therefore neglected in tcMEP monitoring.

Concluding, by surveilling the neurophysiological function of the motor cortex and pyramidal path, tcMEP offers the ability to monitor the narcotized patient`s motor function throughout neurosurgical maneuvers.

2.4. Objectives of this thesis

Ischemic complications during aneurysm clipping constitute a prevalent cause of postoperative neurological deficits (Irie et al. 2010; Bacigaluppi et al. 2012; Chung et al. 2018). As a standard technique, tcMEP are used in order to intraoperatively screen patients at risk of an unintended deprive of the blood supply to the motor cortex. Based on this real-time feedback to the surgical team, it aims on minimizing postoperative ischemic motor deficits by fast therapeutic action (Bacigaluppi et al. 2012). Reviewing references, it became apparent that despite its suggested benefits, there seemed to be several problems of tcMEP monitoring in aneurysm clipping. Inter alia, a number of biasing and disruptive factors were described interfering with the validity of tcMEP monitoring in aneurysm clipping resulting in non-specific intraoperative declines (Szelenyi et al. 2006; Irie et al. 2010; Holdefer et al. 2016; Greve et al. 2019). This was in accordance to our own observations. Secondary, there seemed to be a number of cases of false negative results, in which patients suffered a postoperative hemiparesis although tcMEP remained stable throughout the surgery (Irie et al. 2010; Chung et al. 2018). And thirdly, the site of the aneurysm treated seemed to have an influence on the performance of tcMEP (Horiuchi et al. 2005; Sasaki et al. 2007; Kodama et al. 2014; Yue et al. 2014). Based on these observations, we evaluated our patient cohort in retrospective approach: Was there an association between intraoperative tcMEP monitoring status and the postoperative motor outcome? Which disruptive factors interfered with intraoperative tcMEP monitoring? Do the disruptive factors observed inhibit the evaluation of tcMEP monitoring in an extent to which its usage in aneurysm clipping is of no further advantage to the surgical team? Summarizing, the aim of this study was to characterize the efficiency of tcMEP monitoring regarding its impact on the postoperative motor function in the clipping of unruptured intracranial aneurysms.

This thesis is structured as follows.
Chapter three "Material and Methods" presents an overview of our patient cohort as well as medical and technical details of tcMEP monitoring applied. It furtherly gives an introduction to the statistical tests performed in the analysis.
Chapter four shows the results of this thesis. It is divided into two parts: In the descriptive evaluation, detailed information is given about the cases of false negatives in tcMEP monitoring and patients with a transient intraoperative tcMEP monitoring decline observed in our patient cohort. It furtherly depicts the pathomechanism

responsible for the intraoperative tcMEP decline differentiating between disruptive factors and symptomatic tcMEP decline. The analytic evaluation focusses on the statistical analysis of the impact of the intraoperative tcMEP status on the postoperative motor outcome, the validity of tcMEP monitoring in aneurysm clipping, and the impact of the site of the aneurysm treated on the occurrence of disruptive factors and the postoperative motor outcome observed.

In Chapter five, the descriptive as well as analytic results are discussed. We compare our findings to literature, further intraoperative monitoring devices, and critically review the quality of our study. As mentioned in chapter four, we furtherly characterize a transient intraoperative tcMEP decline according to the underlying cause into symptomatic tcMEP declines and disruptive factors and intend on giving an overview of the disruptive factors most frequently observed.

Finally, Chapter six presents the summary and outlook of this thesis. Based on the analytic as well as descriptive evaluation we surprisingly found results differentiating to our initial assumptions, which will be of importance for future application and evaluation of intraoperative tcMEP monitoring decline.

3. MATERIALS AND METHODS

In the chapter "Material and Methods" we firstly present the patient cohort, exclusion criteria, and patient characteristics included into statistical analysis. Secondly, the medical and technical details of tcMEP applied will be outlined and explained in detail. Lastly, this chapter gives an introduction into the statistical test performed in the analytic evaluation of tcMEP monitoring in aneurysm clipping.

3.1. Ethic votum

This work on anonymous patient data was approved by the ethic committee of the Technical University of Munich (TUM). The refering project number is 2826/10.

3.2. Patient cohort

We performed a retrospective analysis of 171 consecutive cases of surgical clipping of incidental intracerebral aneurysms. Between January 2010 and April 2016, 149 Patients underwent surgery at the neurosurgical department of Klinikum rechts der Isar. Due to multiple aneurysm, incomplete clippings, or intraoperative complications 22 patients had to undergo a second surgical approach. The complete table of all patients observed is included in the Appendix. Mean age was 54.9 years with a range of 18 to 77. 107 of the patients included were women, 42 were male. Median PHASES score was four depicting a probability of rupture within five years of 0.9%; PHASES score ranged from one to 14.
TcMEP monitoring was successful in all cases.

3.2.1. Exclusion criteria

In total, we excluded eight patients from the patient cohort from statistical analysis for three main reasons: pre-existent health issues, general risks of surgery, and specific risks of aneurysm clipping (Fig. 4).
Excluded from statistical analysis were four patients with preoperative motor limitations (case 28, 50, 77 and 110) as no definite statement regarding the reliability of tcMEP monitoring could be deduced by their pre-existent health restrictions.

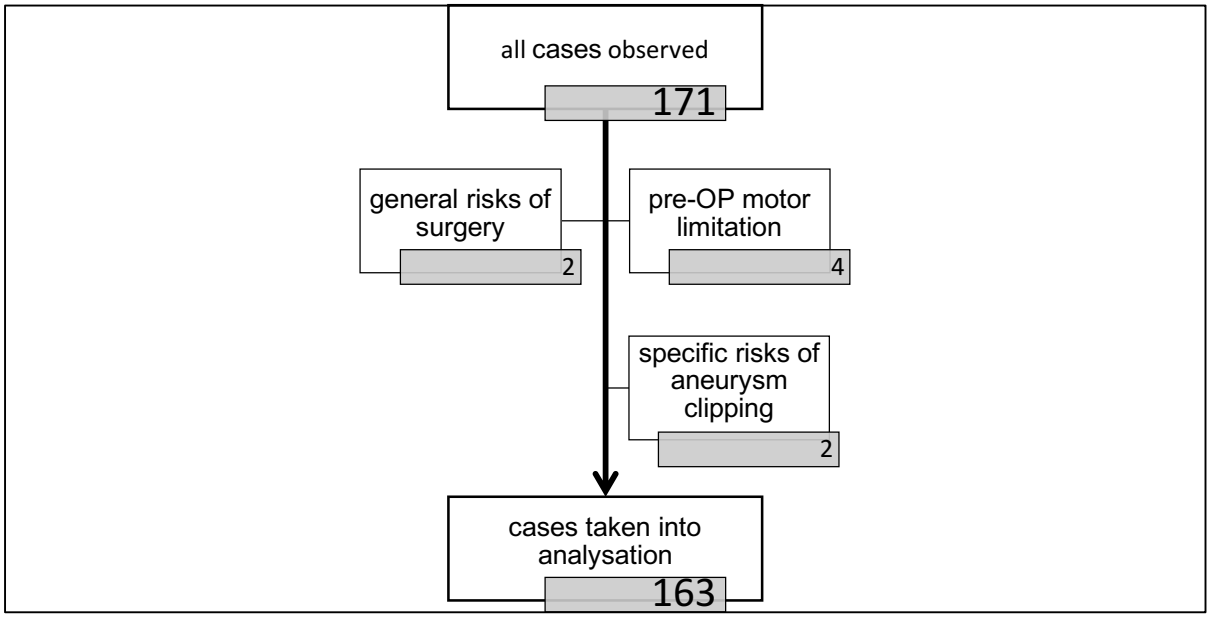

Figure 4: Exclusion criteria including general risks of surgery, specific risk of aneurysm clipping lacking the possibility of tcMEP monitoring surveillance, and pre-existent motor restrictions. 163 patients were taken into statistical analysis

Two cases were excluded because of early postoperative re-bleedings (case 78, 124). For once, these events lack the possibility of being examined by intraoperative monitoring. Secondly, they may occur in all forms of (neuro-)surgical intervention and constitute a general risk of surgery possibly adding postoperative motor events unrelated to intraoperative course.

As described above, tcMEP monitoring was introduced into aneurysm clipping aiming to minimalize specific risks. However, there are certain specific risks of aneurysm clipping, which have to be excluded from statistical analysis as they cannot be monitored by tcMEP. For this reason, intraoperative as well as postoperative seizures were excluded from further examination because of their interferences with either monitoring itself or postoperative recovery. We observed one case in each period (case 61, 73) (Hoh et al. 2011; Conte et al. 2015).
Consequently, 163 cases were taken into analysis.

3.2.2. Patient characteristics included into statistical analysis

Table 1 gives an overview of the patients' characteristics included into statistical analysis.

Patient Characteristics				
		Total	**Stable tcMEP**	**Transient decline**
Patient	Number	163	148	15
	Age			
	Median	55.0	55.1	51.0
	Min	22	22	38
	Max	77	77	77
	Gender			
	Female	102 / 72.3%	90 /70.8%	12 / 80.0%
	Male	40 / 28.4%	37 / 29.1%	3 / 20.0
	Hypertonus	70 / 49.6%	64 / 50.4%	6 / 40.0%
	Earlier aSAH	48/ 34.0%	45 / 35.4%	3 / 20.0%
Aneurysm	PHASES Score			
	Median	4	4	5
	Min	1	1	1
	Max	14	14	10
	Site			
	Anterior	79	70	9
	Media	109	104	5
	Posterior	10	9	1
PostOP	Motor outcome		145	
	Uneventful	158	3	13
	Eventful	5		2

Table 1: Patient characteristics included into statistical analysis. The patient cohort is divided into two subgroups: stable tcMEP monitoring and transient intraoperative decline. Patient characteristic, aneurysmal factors, and postoperative status are depicted.

It focusses on personal as well as aneurysm factors of importance for the calculation of the PHASES score and differentiates between patients with stable tcMEP monitoring matched to patients with an intraoperative tcMEP decline. Median age included into statistical analysis - after exclusion of the eight patients described above - was 55.0 years ranging from 22 to 77 years. 72.3% of patients included were female. 49.6% of patients included suffered from arterial hypertension regarded as one of the most important risk factors of aneurysm growth and rupture (Brinjikji et al. 2016; Neyazi et al. 2019). PHASES score ranged from one to 14 with a median of four. Comparing the group of stable tcMEP and a transient intraoperative decline, we noted a difference in gender distribution: Compared to 70.8% female patients in the group with stable intraoperative tcMEP monitoring, there were 80.0% females in the group of a transient

tcMEP decline. Less pronounced, there seemed to be less early aSAH in patients with a transient decline. We argued, that these differences were due to the restricted sample size included into statistical analysis. Regarding age, arterial hypertension, and PHASES Score there seemed to be no significant difference. The influence of aneurysm site and tcMEP status on postoperative motor outcome will be discussed in chapter 4.2.

3.3. Application of tcMEP monitoring

3.3.1. Anesthesia

Anesthetic effects on tcMEP monitoring have been described by various studies (Kano and Shimoji 1974; Kalkman et al. 1992; Glassman et al. 1993; Sloan 2002; Hemmer et al. 2014; Sloan et al. 2015) and need to be considered in all forms of IONM. A significant decrease of tcMEP amplitude can be observed in volatile anesthetics, as they reduce the excitability of alpha motor neurons. A total intravenous anesthesia (TIVA) induced by opioids, benzodiazepines, and propofol is therefore state of the art in neurophysiological monitoring. The effects of opioids and benzodiazepines have been described as minimal and seem to have no effect on sufficient tcMEP monitoring (Sloan et al. 2015). Most importantly, the usage of muscle relaxants has to be restricted due to their interference with the peripheral transmission at the end organ of the muscle monitored (Xie et al. 2018). The physiologic mechanism of muscle relaxants bases on a competitive antagonism at the n-cholino-receptor of the muscle end organ and hereby inhibits a depolarization, initializing a muscle contraction. Hence, if a muscle is completely antagonized, no tcMEP monitoring signal can be derived (Xie et al. 2018). In our cases, a TIVA was induced by the application of 0.03 mg/kg midazolam, 4-6ug/mL propofol and remifentanil. Due to the previously described influence on tcMEP signaling, vecuronium was given as a muscle relaxants for tracheal intubation only. As an intermediate-duration, non-depolarizing neuromuscular blocking agent vecuronium offers the advantage of relaxation during intubation and craniotomy without interfering in later tcMEP monitoring. Propofol was used for maintaining anesthesia as well as remifentanil for analgesia.

Additionally, a continuous monitoring of blood pressure, temperature, heart rate, and blood-oxygen concentration was performed.

3.3.2. Stimulation of tcMEP monitoring: 10-20 system of electrode placement

After positioning the patient, the electrodes were placed subcutaneously according to the international 10-20 system of electrodes placement. The 10-20 system is based on 19 reference electrodes, which have to be placed according to relative distances: The distance between two points is measured and the electrodes are distributed at distances of 10-20% total measured distance, which results in an assigned topographic position of each electrode. The position bases on two directions: sagittal - nasion to inion- and transverse - preauricular both sides. This placement ensures that inter-individual differences in head size and -form are equalized (Fig. 5). The 10-20 system bases on the description by Jasper et al. in 1957 (o.V. 1958).

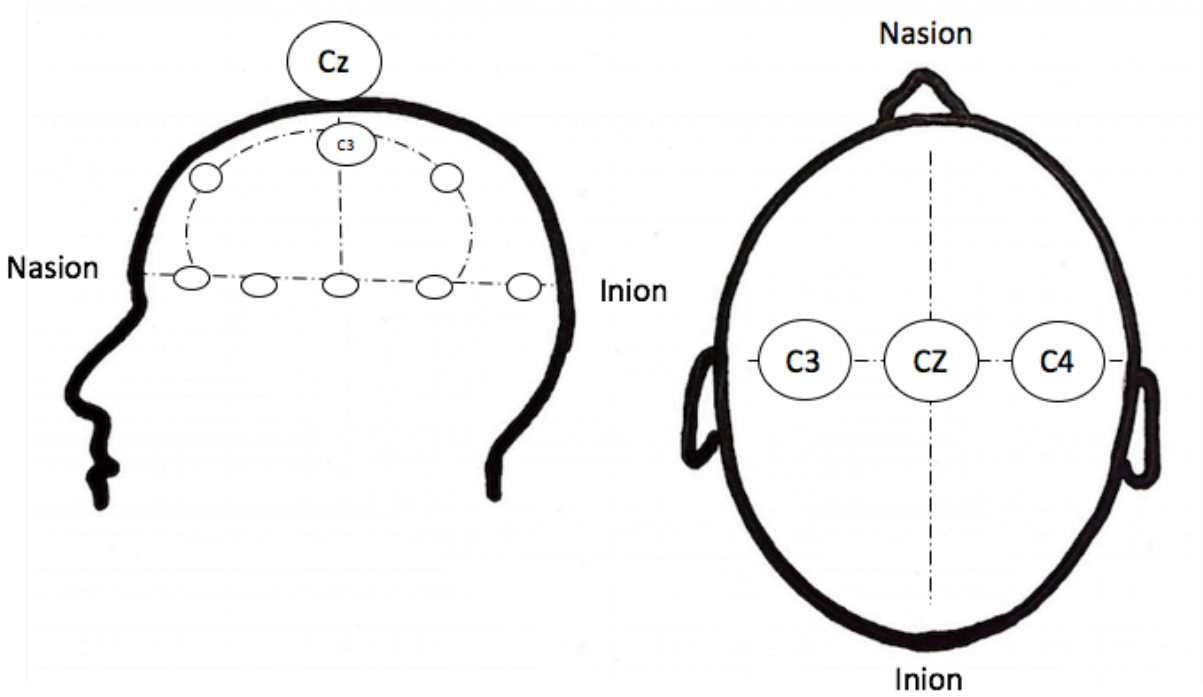

Figure 5: Electrode placement according to 10-20 system with emphasis on the reference electrodes of importance for tcMEP monitoring C3 and C4. Position of electrodes bases on sagittal (nasion to inion) and transverse (preauricular both sides) direction depicted by the dashed line (o.V. 1958).

In tcMEP monitoring, the anode position for optimum stimulation varied according to the side of interest: for right hemispheric stimulation, the anode was placed at the C4 position with the cathode being situated at C3. A left hemispheric stimulation was vice versa achieved by a C4-anode and C3-cathode arrangement (Taniguchi et al. 1993; MacDonald 2006; Macdonald et al. 2013).

The “train of five” stimulation technique characterized by a train of five square-wave anodal pulses of 300 microseconds duration generated the motor evoked potential

(Taniguchi et al. 1993). The initiated muscle response (compare 2.2.3.) was detected by needle electrodes (27-gauge disposable subdermal needle electrodes by Inomed needle electrode, Inomed, Germany or AD-Tech needle electrode, AD-Tech) distributed bipolarly on the thenar and hypothenar muscles on both hands. Transformation of the data obtained was achieved by the "Axon EpocheXPe neuromonitoring system" (Axon Systems, Hauppage, NY) or the "Inomed ISIS IOM system" (Inomed Medizintechnik, Germany).

3.3.3. Recording of tcMEP: Compound muscle action potential

For TcMEP monitoring, a compound muscle action potential (CMAP) in peripheral muscle groups of the thenar, most commonly the M. adductor pollicis, as well as hypothenar muscles on the side of interest, is recorded. The CMAP is defined as the temporal and spatial summated action potentials of a group of several motor units activated by external activation either peripheral or central (Lateva et al. 1996). The signal derived is a biphasic potential with an initial upward deflection from baseline. The amplitude is calculated as the baseline to peak distance in microvolt. Furtherly, latency and duration can be measured in milliseconds. Latency is characterized as the time period from initial stimulation to first deflection from baseline (Lateva et al. 1996). These characteristics of CMAP are graphically depicted in Figure 6.

The recorded CMAP were closely monitored for sudden changes in amplitude or latency of the muscle response and recorded frequently with emphasis on critical surgical maneuvers. The surgeon was informed about every alteration of signal. A loss of amplitude of more than 50% of baseline level was considered significant and consequently represented a warning criterion (Macdonald et al. 2013; Yue et al. 2014).

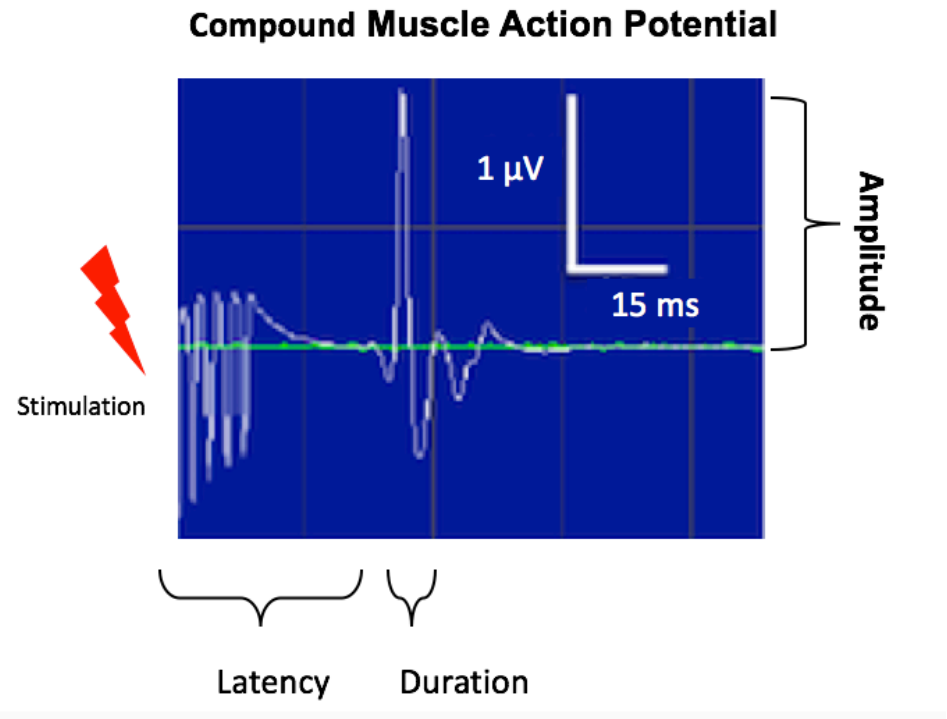

Figure 6: Illustration of a CMAP: Latency, duration, and amplitude (Lateva, McGill et al. 1996). In tcMEP monitoring the measurement of amplitude is of highest significance. A loss of 50% of baseline level is characterized as a significant loss of tcMEP monitoring (Yue et al. 2014) .

3.4. Outcome evaluation: Intraoperative tcMEP status, primary endpoints

Intraoperative status was retrospectively assessed by dividing the patient population in three subtypes:

- 0: a consistent tcMEP signal,
- 1: a transient change of tcMEP amplitude,
- 2: a permanent loss.

As depicted in chapter 3.3, a transient change of tcMEP amplitude was considered significant and therefore included into statistical analysis in the cases of a loss of amplitude of CMAP of more than 50% of baseline level. Furtherly, we defined a transient decline as every decline, in which tcMEP monitoring signals leveled back to baseline level throughout the surgical maneuver; we did not set a certain time limit to furtherly differentiate between these declines.

In the cases of a transient intraoperative decline in tcMEP monitoring, an exact evaluation of each case was made in order to comprehend the pathomechanism responsible for the intraoperative change. Therefore, we also compared intraoperative

tcMEP status to postoperative imaging including cranial computer tomography (cCT) and MRI in order to detect ischemic complications.

The postoperative status at discharge was evaluated according to the concluding doctor's letter and we defined three primary endpoints:

- an unchanged motor status,
- a transient loss of motor function, which was reversible until date of discharge,
- a permanent hemiplegia or -paresis.

Additionally, we defined a combined outcome for any motor restriction at discharge including transient as well as permanent postoperative motor deficits. Because of the described reduction to motor status only, a postoperative focal neurologic deficit may still have been present at discharge. Furtherly, in the cases of a permanent or transient postoperative paresis, an analysis of onset and attendant symptoms was striven for in order to reliably exclude postoperative confounding factors and postoperative complications from statistical analysis. Especially vasospasms and a Todd paresis due to postoperative seizures were excluded from statistical analysis; this is discussed in chapter 3.2.1.

3.5. Statistical Analysis

Statistical analysis was performed according to a multi-stage random experiment. We reviewed monitoring data and related them to new postoperative motor restriction at discharge and postoperative imaging. Our main interest lay in the comparison of the postoperative motor function between the group of patients with and without transient changes in tcMEP monitoring. We suggested the null hypothesis that disruptive factors in tcMEP monitoring inhibit the evaluation to an extent in which its usage is of no further benefit to the surgical team. The alternative hypothesis would consequently imply a positive impact of tcMEP monitoring on the postoperative motor outcome. In order to determine a possible association between intraoperative tcMEP status and postoperative motor outcome and calculate the corresponding p-value, an exact Fisher`s-Test for categorical data with a small sample size was performed.

The p-value is a number between 0 and 1 characterized as the probability that, if the null hypothesis was true, the result observed is similar or even more extreme than the actual result (Tenny and Abdelgawad 2019). The smaller the p-value, the stronger the evidence to reject the null hypothesis.

A categorical variable is characterized as a variable, which can be divided into two or more categories without intrinsic ordering (Whitehead 1993). The segmentation of our data into categoral data is depicted in chapter 3.4.

The exact Fisher's Test is a statistical significance test used in the analysis of 2x2 contingency tables. Hereby, data can be tested for a significant association by comparing the expected frequency of a certain event if the null hypotheses was true to the observed frequency in the analysis. As the deviation from the tested null hypothesis can be calculated exactly, it is valid for all sample sizes and frequently used in small sample sizes (Agresti 1992; Jung 2014).

Alpha level or type I error is conventionally set to 5% (Banerjee et al. 2009). This error constitutes the probability of a rejection of a true null hypothesis and can therefore also be described as a false positive result (Tenny and Abdelgawad 2019). Concluding, the null hypothesis could be rejected, if the calculated p-value was below 0.05. As multiple comparisons are taken into statistical analysis in our cases, multiple testing correction, with for example Bonferroni correction, has to be applied adjusting the p-value (Pocock et al. 1987).

Furthermore, the risk ratio (RR), or relative risk, was determined for the primary endpoints including the combined endpoint subjected to the intraoperative tcMEP status and evaluated according to 95%-confidence intervals (95%-CI). The RR is a statistical analysis derived from epidemiology. It compares the probability of a disease, according to the exposure, to the risk factor of interest (Mantel and Haenszel 1959; Zhang and Yu 1998). Applied to our analysis, it refers to the probability of a postoperative motor deficit (disease) subjected to an intraoperative tcMEP monitoring decline (risk factor) and is therefore calculated as follows.

$$RR = \frac{P\,(\,postoperative\ motor\ deficit/\ intraoperative\ tcMEP\ decline)}{P\,(postoperative\ motor\ deficit/\ stable\ tcMEP)}$$

Representing a quotient of probabilities, the RR can assume values from 0 to infinite. An RR of 1 constitutes that the exposure to the risk factor observed does not affect the probability of disease or, applied to our data, an intraoperative tcMEP decline does not favor the postoperative occurrence of a hemiparesis. If the RR assumes values >1 the risk of disease is increased by the exposure to the risk factor. Applied to our data, this constitutes that an intraoperative tcMEP decline results in a higher probability of a postoperative loss of motor function. As depicted above, in this calculation, the

statistical significance was evaluated from CI. Confidence level was set to 95 %. CI represent an interval or range with an upper and lower variable to estimate the precision of a parameter of interest (Greenland et al. 2016; O'Brien and Yi 2016). Mathematically, a CI is an interval, which, if calculated frequently, contains the true parameter with the probability of the defined confidence level - in our case 95%.

Furtherly, we wanted to analyze the impact of the site of the aneurysm treated on the occurrence of disruptive factors. This was evaluated according to the Fisher's exact test described above (Jung 2014). We set the null hypothesis that there is no statistically significant association between the site of the aneurysm treated and the occurrence of disruptive factors. The alternative hypothesis was vice versa that there is a significant association between the occurrence of disruptive factors and the site of the aneurysm treated.

To determine the accuracy of tcMEP monitoring in the clipping of unruptured intracranial aneurysms, we calculated predictive values, sensitivity and specificity according to a fourfold table (Tetrault 1991; Agresti 1992; Altman and Bland 1994). These values are characterized as statistical quality criteria of diagnostic tests. As no permanent loss of tcMEP signals occurred, the analysis referred to a temporary decline only. The sensitivity represents the ratio between the number of patients with an intraoperative tcMEP decline and postoperative motor function number to all patients included with a postoperative loss of motor function. The specificity accordingly gives the ratio between the number of patients with stable intraoperative tcMEP monitoring and no postoperative motor limitation to all patients without postoperative motor limitation; It can also be described as correctly negative results. The positive predictive value (PPV) is characterized as the probability of postoperative motor deficit, if tcMEP monitoring signals declined throughout surgical clipping. The negative predictive value (NPV) vice versa represented the probability of no postoperative motor deficit if tcMEP monitoring remained stable. The underlying calculations are depicted in Table 2.

		postoperative motor limitation		
		yes	no	
tcMEP Monitoring	decline	a	b	**PPV = a/a+b**
	stable	c	d	**NPV= d/c+d**
		Sen= a/a+c	**Spe= d/b+d**	n

Table 2: Validity of tcMEP monitoring according to a fourfold table.

Sen = Sensitivity, Spe= Specificity, PPV = positive predictive value, NPV = negative predictive value (Tetrault 1991).

4. RESULTS

In the following chapter, the results of this thesis are depicted. The chapter is divided into two parts: The descriptive evaluation depicts the case reports of patients with no intraoperative tcMEP abnormality but postoperative loss of motor function as well as patients with a transient intraoperative tcMEP monitoring decline. We furtherly differentiated the cause of the transient intraoperative decline into symptomatic tcMEP decline and disruptive factors. The analytic evaluation focusses on the statistical analysis of the impact of the intraoperative tcMEP decline on the postoperative outcome, the validity of tcMEP monitoring in aneurysm clipping, and the influence of the site of the aneurysm treated on the occurrence of disruptive factors.

4.1. Descriptive evaluation of tcMEP monitoring in the clipping of unruptured aneurysms

To understand the pathomechanism responsible for an intraoperative change or the absence of an intraoperative change of tcMEP monitoring, case reports of false negatives in tcMEP monitoring as well as patients with a transient tcMEP decline will be given in the following.

4.1.1. False negatives in tcMEP monitoring

In four patients, characterized by stable intraoperative tcMEP monitoring conditions, a postoperative motor deficit occurred (case 6, 8, 89, 127). According to Irie et al., we characterized these as false negatives (Irie et al. 2010). While three patients suffered a transient loss of motor function, one case developed a permanent hemiparesis. These false negatives will be depicted in the following table (Tab. 3) describing patient and aneurysm factors, as well as intraoperative and postoperative status. Regarding the intraoperative status, a correlation to ICG-Angiography is depicted. The postoperative status gives an overview of the motor deficit overserved, its onset, and further complications observed. These may include neurologic, for example meningitis, as well as non-neurologic complications, such as thrombosis.

False negatives

Patient			Aneurysm			IntraOP	PostOP	
no.	gender	age	size (mm)	PHASES	site	ICG	motor deficit	com.
6	m	40	CC	3	MCA	-	left hemiparesis on the 4rd postOP day	+
8	m	67	4, Std. nasc.	6	ACI, A.comA	+	transient brachial hemiparesis left	+
89	m	72	5	2	MCA	-	brachiofacial hemiparesis left, dysarthria, dysphagia, neglect left	+
127	f	73	7	4	MCA	-	transient hemiparesis right	-

Table 3: False negatives in tcMEP monitoring characterized as an uneventful intraoperative tcMEP course resulting in a transient or permanent postoperative hemiparesis.

no.= number, m=male, f=female, CC=Coil compaction, Std. nasc= Stadium nascendi, MCA= A. cerebri media, ACI= A. cerebri interna, A. ComA= A. communicans anterior, IntraOP= intraoperative, ICG: "+" = detected anomaly by ICG-Angiography, "-" = uneventful course, postOP= postoperative, com.= complications, "+"= postoperative complications present, "-"= absent.

4.1.1.1. False negatives due to postoperative vasospasms

Case 6 constitutes an important postoperative disruptive factor. After a traumatic aSAH in 2007, case 6 was incidentally diagnosed with three aneurysms. After coiling in 2007, a compaction of coiling material in the A. cerebri media aneurysm became apparent in a follow-up MRI scan, demanding for surgical treatment. TcMEP signals remained stable and ICG-Angiography did not detect a vascular stenosis of main or perforating arteries. On the 4th day after surgery, the patient became clinically apparent with a hemiparesis of the left side. A cranial computer tomography (cCT) revealed an infarction of the right basal ganglia and capsula interna. In accordance to cCT findings, DSA revealed vasospasms resulting in a reduction of blood flow of the right A. cerebri media. A triple-therapy (hypertonia, haemodilution, hypervolemia) and medical application of nimodipine was induced and the hemiparesis was quickly regressive, leaving the patient symptom-free at hospital discharge (Sen et al. 2003; Etminan and Macdonald 2017).

Vasospasms are a phenomenon frequently observed after aneurysm clipping as well as interventional coiling (de Oliveira et al. 2007; Dumont et al. 2010; Tsyben et al. 2016). A determination of physiological correlate is insufficient to the day and an

assumed correlation to temporary clipping could not be determined (Malinova et al. 2017). Consequently, all patients need to be carefully monitored by blood flow velocity by Doppler sonography of intracranial arteries and, if amplified, need to be treated accordingly (Sen et al. 2003; Etminan and Macdonald 2017). As the ischemic damage by vasospasm can include loss of motor function and can hereby intervene with the retrospective evaluation of our study, we aimed on a detailed interpretation of cases with postoperative loss of motor function in order to eradicate this diagnose bias. A prolonged onset of focal-neurologic deficits was seen as a red flag indicating possible vasospasms.

As postoperative complications lie beyond the possibilities of intraoperative detection, this case will be characterized as uneventful in further statistical analysis.

4.1.1.2. False negatives: Case reports

Case 8 suffered an aSAH 5 months prior to the surgical clipping of interest and was hereby diagnosed with two aneurysms of the anterior circulation. TcMEP signals remained stable throughout the surgery. ICG-Angiography detected a reduced blood supply of perforating arteries, which was interpreted as arteriosclerotic sludge. Immediately after surgery, the patient presented a transient hemiparesis of the left arm. The etiology remained unknown. A postoperative cCT did not detect an ischemic lesion explaining the clinical status. As motor status recovered until dismissal, a complementary MRI was not performed. Therefore, it is possible that an ischemic mechanism by the arteriosclerotic sludge detected by ICG-Angiography could have caused the postoperative deficit, which tcMEP monitoring failed to detect.

In Case 127, a transient hemiparesis of the right side became apparent after clipping of a left side A. cerebri media aneurysm. The 73-year old patient was incidentally diagnosed with two aneurysms of the A. cerebri media as part of an evaluation regarding an increasing forgetfulness. TcMEP monitoring remained uneventful throughout the procedure. The hemiparesis became apparent instantly after surgery; a thereupon performed CT-Angiography showed a perfusion deficit left frontal in accordance to a severe clip stenosis of the M2 segment. As motor status impaired quickly, no need for re-surgery was surmised and no focal neurological deficit was reproducible at discharge.

One patient with stable tcMEP monitoring conditions developed a permanent decrease of postoperative motor skills: Case 89, a 72-year old man, was diagnosed with a right-

side A. cerebri media aneurysm during medical clarification of a severe headache. A surgical approach was determined and no intraoperative complications occurred. TcMEP monitoring was assessable only via phase reversal, which will be taken as equivalent. It remained stable and no ICG-Angiographic anomalies became noticeable. Immediately after surgery, the patient presented a brachiofacial hemiparesis on the corresponding left side, dysarthria, dysphagia and a neglect of the left side. The postoperative cCT and MRI revealed an infarction of the basal ganglia on the right side. Hemi- and facial palsy of the left side remained persistently until discharge. In retrospective consideration, neither the reason for the ischemia, nor the uneventful intraoperative tcMEP status could be determined.

Summarizing, in these three cases a permanent or transient loss of motor function occurred despite stable tcMEP monitoring conditions. For all aneurysms, a pterional approach had been chosen. PHASES score ranged from 2 to 6, depicting a 5-year risk of rupture of 0.1-1.5% and 1.1-2.7% respectively (Fig. 2). In two of these three cases, further postoperative complications, including meningitis and late re-bleedings, delayed the patients' recovery. However, the motor deficits became apparent immediately after clipping and the complications described cannot be taken as a sufficient explanation for their presence.

4.1.2. Patients with transient tcMEP decline

In total, we observed 15 patients with transient changes in tcMEP monitoring during surgical clipping of unruptured intracranial aneurysms. Patient, aneurysm, and intra- as well as postoperative motor status are compiled in Table 5. In 13 patients, the intraoperative tcMEP decrease resulted in no postoperative motor deficit; transient tcMEP changes resulted in a transient impair of postoperative motor status in one case (case 109) and a permanent loss of function in another case (case 2) (Tab. 4).

According to the source of the intraoperative change, patients with a transient intraoperative tcMEP decline in aneurysm clipping could be furtherly divided into three subgroups: changes due to disruptive factors, symptomatic tcMEP declines, and unknown intraoperative changes. The case reports of these three categories will be given in detail in the following.

Transient decline in tcMEP signals

Patient			Aneurysm			IntraOP		PostOP
no.	gender	age	size (mm)	PHASES	site	ICG	consequences	motor deficit
2	f	48	n.a.	3	MCA	+	+	+
24	f	56	2; 5	5	A.ComA, ACI	-	-	-
29	f	41	6.5	2	MCA	-	+	-
34	f	47	8; 1	5	2xACI/ P.com	-	+	-
44	f	69	10	4	P.com le	-	-	-
58	f	51	7	1	ACI	-	-	-
66	m	57	8.1	7	A.ComA	-	+	-
95	m	52	CC	5	A. choroidea ant.	n.a.	-	-
97	f	61	13	7	ACI ri	n.a.	-	-
109	f	69	12	10	ACI ri/ P.Com, A. pericallosa le	-	-	+
125	f	49	13	9	MCA le	+	+	-
138	f	43	5	4	A.ComA	-	+	-
147	m	48	CC	2	Carotis-T	-	-	-
150	f	38	8	4	ACI/ A. ophtalmica ri	-	+	-
171	f	77	15	9	MCA ri	-	-	-

Table 4: Patients with a transient decline in tcMEP signals and their postoperative motor outcome. Patient and aneurysm factors are depicted. Furtherly, intraoperative ICG-Angiography and intraoperative consequences due to the decline are depicted. Postoperative motor function is assessed not differentiating between a transient or permanent paresis.

f=female, m=male, n.a.= not available, CC= Coil compaction, MCA= A. cerebri media, A, ComA= A. communicans anterior, ACI= A. cerebri interna, P.Com= A. communicans posterior, ri= right, le=left, ICG Angiography: "+"= intraoperative anomaly, "-"= uneventful course, Intraoperative consequences: +=present, -=absent, Motor deficit: += present, -=absent.

4.1.2.1. Disruptive factors in tcMEP monitoring

In eight cases, disruptive factors could be identified as the source of an intraoperative tcMEP decline. We characterized disruptive factors as either unspecific or intended external influences on tcMEP manipulating the intraoperative status and hereby adding intraoperative events unrelated to the postoperative motor outcome. Consequently, these factors do not require specific management or treatment and should theoretically have no impact on the motor function at discharge. We furtherly differentiated the disruptive factors observed into three categories.

In six cases and therefore most frequently, intended circulatory deficits caused a transient intraoperative tcMEP decline (Fig. 7). Firstly, in one case (case 97), a loss of tcMEP signals was induced by therapeutic hypotension and quickly regressive after rise of blood pressure; After definite disconnection of the aneurysm from the blood supply and elevation of blood pressure, tcMEP signals regenerated. The patient did not develop a motor deficit in postoperative course. Secondly, a therapeutic cardiac arrest by administration of adenosine was needed and resulted in a transient decline of tcMEP monitoring (case 58). According to the case described above, tcMEP signals leveled back to initial level after re-strengthening the circulatory system. Postoperative course was uneventful and motor outcome satisfactory after surgery. Thirdly and most frequently, temporary clipping of the parent artery was identified as the source of a transient intraoperative decline of tcMEP signals (case 44, 109, 147, 171). In all of these cases, there is a chronological sequence between temporary clipping and onset as well as conclusion of tcMEP decline. Postoperative outcome was uneventful in three cases. In one case (case 109), a transient, postoperative, left-sided hemiparesis became apparent. An ischemic lesion or re-bleeding could be ruled out by cCT and MRI. Motor deficit was quickly regressive after surgery. Therefore, the understanding of etiology remained incomplete. A transient ischemic attack by temporary clipping could be considered.

We defined the second disruptive observed as a positional influence on tcMEP monitoring: In one case (case 29), the intraoperative changes were regarded to be brainshift-associated. After re-positioning of the patient, tcMEP signals leveled back to initial level and no postoperative motor deficit became apparent at any time during hospital stay. Brainshift describes a regular change of the brain in position and shape during neurosurgical interventions (Gerard et al. 2017).

And lastly, in one case (case 138), a loss of tcMEP signals was associated to the removal of a spatula during preparation of an A. communicans anterior aneurysm. As no correlation to either intra- nor postoperative imaging could be made and no loss of motor function became clinically apparent, we claimed this to be a mechanical disruptive factor.

4.1.2.2. Symptomatic tcMEP decline

We characterized a symptomatic tcMEP decline as a decline, in which a deprive of blood supply to the motor cortex and hereby an ischemic mechanism caused the intraoperative change. Contrary to the disruptive factors described above, if not solved sufficiently, postoperative motor function of the patient is affected by a symptomatic tcMEP decline.

In two cases (case 150, 125), the impairment of tcMEP monitoring signals could intraoperatively, by further imaging devices, be associated to an unintended clip stenosis (Tab. 5, Fig. 7). In both cases, by resetting the clip, tcMEP signals leveled back within a short time and no new postoperative motor deficit arose.

In one case (case 66), neither a vessel correlate nor a disruptive factor could be defined intraoperatively as an explanation for the loss of tcMEP signals and therefore an immediate postoperative digital subtraction angiography (DSA) was enforced. This detected a high-grade clip stenosis of the A. cerebri anterior. An immediate re-craniotomy was striven for in order to reset the clip. Hereby a loss of motor function could be prevented by the surgical team.

In case 2, a loss of tcMEP signals was associated to an intraoperative kinking and vasospasms of small vessels. By administration of nimodipine and after elevation of blood pressure, tcMEP signaling equaled initial value. However, a brachiofacial hemiparesis and aphasia occurred immediately after surgical intervention and, with a delay of 12 hours, a reduction of vigilance imposed need for intubation. Although medical treatment was immediately administered, the described hemiparesis persisted until dismissal. Case 2 may be seen as a symptomatic tcMEP decline due to intraoperative vasospasms. Although sufficient intraoperative means were taken, a lasting solution of the situation could not be achieved.

Summarizing, three cases of a definite deprivation of intracerebral blood supply by a clip stenosis could be detected (case 66, 125, 150). Additionally, one case (case 2) can be considered as a symptomatic decline due to intraoperative vasospasm (Fig. 7).

4.1.2.3. Unknown tcMEP decline

Regarding the remaining three cases (case 24, 34, 95) with intraoperative tcMEP decline, a profound explanation of the tcMEP change was hard to determine in retrospective approach (Fig. 7).

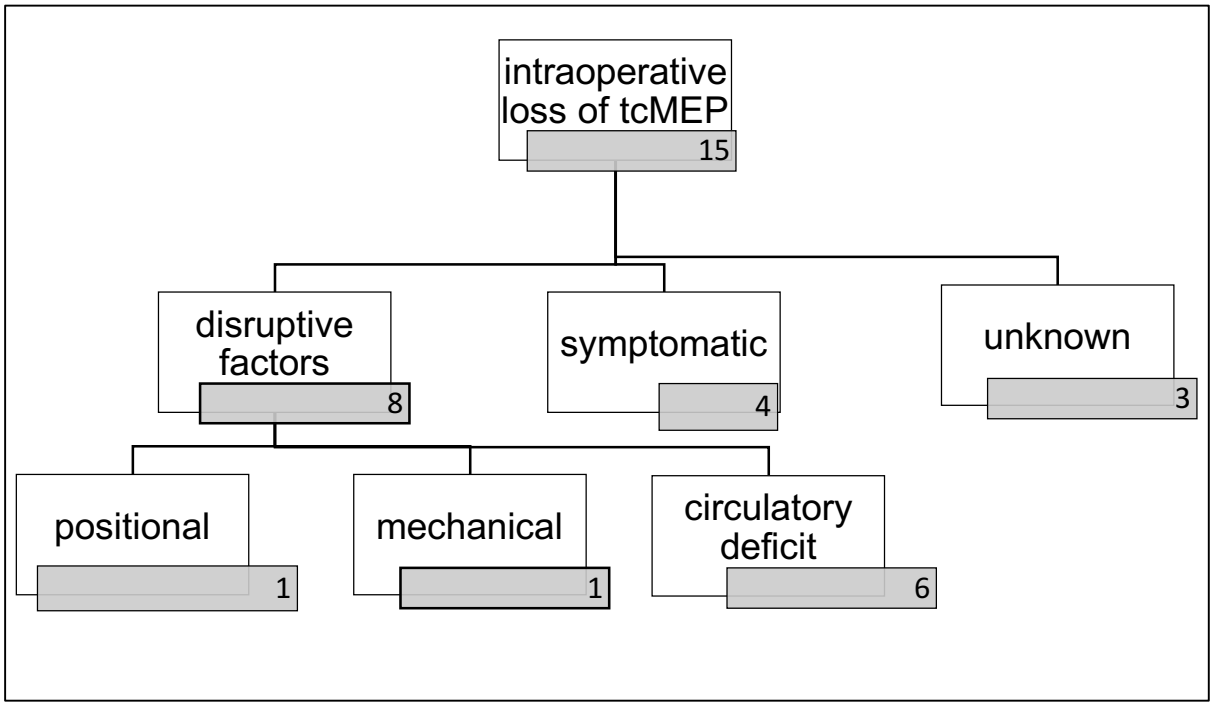

Figure 7: Intraoperative loss of tcMEP monitoring according to the etiology observed: disruptive factors, symptomatic tcMEP decline, and unknown intraoperative changes.

One case (case 34) seemed worth noting in retrospective evaluation. After a transient tcMEP decline, a large residuum of the A. communicans posterior aneurysm was shown by immediate postoperative DSA. Doubtlessly, an early detection of this residuum was beneficial to the patient. Nevertheless, the transient loss of tcMEP signals cannot be satisfyingly explained by its presence: A permanent mass effect on the supplying artery by the residuum or the clip would have caused a permanent loss of intraoperative monitoring, an ischemia and a postoperative clinical detoriation. Further, in the whole patient cohort, we observed five more incomplete aneurysm clippings, which were detected by regular postoperative imaging. Summarizing, a superposition of tcMEP and residuum of unknown cause seemed likely.

4.1.3. Patients with a complete loss of tcMEP

No cases of permanent tcMEP decline were observed in our patient cohort.

4.2. Analytic evaluation of tcMEP monitoring in the clipping of unruptured aneurysms

The analytic evaluation in the following chapter focusses on the statistical analysis of three main topics: the impact of the intraoperative tcMEP status on the postoperative outcome, the validity of tcMEP monitoring in aneurysm clipping, and the impact of the site of the aneurysm treated on the occurrence of disruptive factors.

4.2.1. Influence of intraoperative tcMEP status on postoperative motor outcome

Firstly, we wanted to study the influence of the intraoperative tcMEP status on the postoperative motor outcome. The results are shown in Table 5, which shows the probabilities of our primary endpoints: An unchanged motor function, a transient postoperative hemiparesis, and a permanent postoperative loss of motor function. Furtherly, the probability of the combined endpoint regarding any change of motor function including transient as well as permanent postoperative hemiparesis is given. These probabilities were calculated for all patients included (general), patients with stable intraoperative tcMEP and patients with a transient decline of tcMEP monitoring. In order to evaluate a significant association, the p-value was calculated according to the exact Fisher`s test and its power was determined. Lastly, we defined the RR with 95%-CIs.

In 90.8% of surgical interventions, stable tcMEP monitoring signals were observed. In 9.2% of cases observed, a transient change in tcMEP signals occurred throughout clipping. No cases of permanent decline of tcMEP became apparent in our patient cohort.

In all cases, regardless their intraoperative tcMEP status, we observed five cases of postoperative motor deficit. In two cases, a permanent loss of motor function in postoperative course occurred defining a probability $P(2_{po})$ of 1.2% (case 2, 89). In three cases, setting a probability $P(1_{po})$ of 1.8%, a transient limitation in muscle strength became clinically apparent during hospital stay (case 8, 109, 127) (Tab. 5).

In the cases of stable tcMEP monitoring, we observed three cases of postoperative transient or permanent motor restriction. According to literature, these were defined as

false negatives (Tab. 3). Nevertheless, this defined a chance of an unchanged motor status P(0_{po}) at discharge of 98.0% (Tab. 5, Fig. 8).

Intraoperative tcMEP monitoring and postoperative motor outcome

	$\mathbf{P(0_{po})}$	$\mathbf{P(1_{po})}$	$\mathbf{P(2_{po})}$	$\mathbf{P(1 \cup 2_{po})}$
General	97.0%	1.8%	1.2%	1.9%
Stable tcMEP	98.0%	1.3%	0.7%	2.0%
Decline	86.7%	6.7%	6.7%	13.3%
P-value		0.24	0.17	0.069
Power p-value		0.2	0.27	0.49
RR		5.25	10.43	6.58
Lower 95%-CI		0.51	0.69	1.19
Upper 95%-CI		54.34	157.85	36.32

Table 5: Intraoperative tcMEP monitoring and postoperative motor outcome. We calculated the probability of the primary endpoints, unchanged postoperative motor status, transient postoperative motor decline and permanent postoperative loss of function as well as the combined endpoint referring to any change of postoperative motor function according to the intraoperative tcMEP status. P-value was calculated according to the exact Fisher`s test. Furtherly, the RR with 95-CIs were calculated.

P(0po) = Probability of an unchanged motor status postoperatively, P(1po)= Probability of a transient loss of motor function postoperatively, P(2po)= Probability of a permanent paresis, P(1u2po)= Probability of a transient or permanent postoperative motor restriction.

Regarding the cases of a transient decline in tcMEP signaling, we found a difference in the prognostic outcome. If tcMEP signals declined throughout the surgical maneuver, it resulted in an unchanged patients' physical status P(0_{po}) in only 86.6%. Furthermore, we registered a permanent and a transient loss of motor function (P(1_{po}), P(2_{po})) in each 6.7% and a combined outcome (P($1u2_{po}$)) of 13.3%, if tcMEP declined throughout the surgical procedure. This difference is graphically depicted in Figure 8. We calculated an exact Fisher's Test for categoral data with a small sample size in order to determine a significant difference between the two groups. Alpha error was set to 5%. However closely, no significant difference in the postoperative outcome could be detected in our patient cohort (Tab. 5). Due to the small patient cohort and restricted sample size, the power of the exact Fisher's test was poor (Tab. 5).

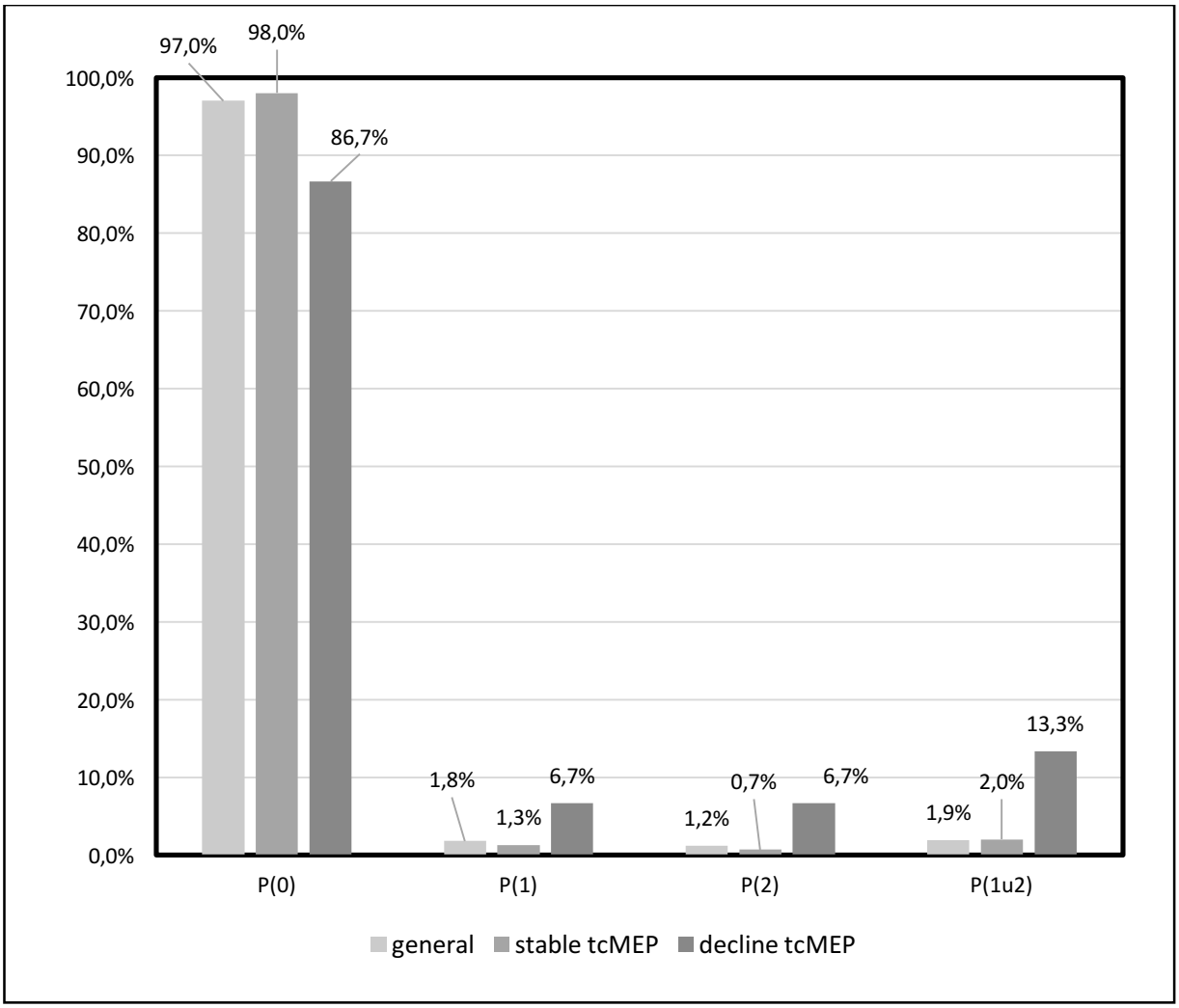

Figure 8: Graphic depiction of probabilities of the endpoints regarding the postoperative motor outcome according to the intraoperative tcMEP status

P(0po)= Probability of an unchanged motor status postoperatively, P(1)= Probability of a transient loss of motor function postoperatively, P(2)= Probability of a permanent paresis, P(1u2)= transient or permanent postoperative motor deficit.

Furthermore, we calculated the RR for a postoperative motor deficit subjected to the intraoperative motor status; It represents the specific risk increase for a transient, permanent or combined transient and permanent motor deficit if tcMEP signals declined during aneurysm clipping. In this calculation, we could show a significant difference regarding the postoperative motor outcome: The relative risk of a postoperative loss of motor function was 6.68 (95%-CI 1.19-36.32) times higher in a patient with a transient intraoperative tcMEP decline than in a patient with stable intraoperative monitoring.

4.2.2. Influence of aneurysm site on the postoperative motor outcome

In total, 198 intracranial aneurysms have been treated from January 2010 to April 2016. Into statistical analysis, we included 109 aneurysms of the media and ten of the posterior circulation. 79 aneurysms of the anterior circulation have been clipped, including nine A. communicans posterior aneurysms and 23 A. communicans anterior aneurysms (Tab. 1, Tab. 6).

Regardless the intraoperative status, we observed five cases of postoperative motor deficits (Tab. 6). Two occurred in the treatment of anterior circulation aneurysms and three in the treatment of A. cerebri media aneurysms. This small sample size left no possibility of statistical analysis. Hence, a definite difference regarding the postoperative motor outcome according to the aneurysm site did not become obvious in our patient cohort.

Regarding patients with an uneventful intraoperative tcMEP status but a postoperative transient or permanent hemiparesis characterized according to literature as "false negatives", no analytic evaluation could be made due to the restricted number of cases found (Tab. 3).

We furtherly had a closer look at the cases with a transient decline of tcMEP monitoring (Tab. 6). After subtracting the cases of symptomatic tcMEP decline (Fig. 7, Tab. 4), we stated that the false positive findings in tcMEP monitoring equaled the cases, in which disruptive factors inhibited the intraoperative recording. It has to be critically mentioned that we added the cases of unknown intraoperative decline even though the pathomechanism could not be determined in retrospective evaluation. We compared these cases of disruptive factors to the number of aneurysms treated on each site. To evaluate a statistical significant difference, the p-value was calculated according to Fisher's exact test for categoral data with a small sample size and alpha error was set at 5%. In the treatment of anterior aneurysms, we observed a transient decline in tcMEP in 11.4% and a transient decline due to a disruptive factor in 8.9%. Regarding A. cerebri media aneurysms, we noted a transient decline in 4.6% of clippings observed and a transient decline caused by a disruptive factor in 2.8%. (Tab. 6). In the clipping of posterior aneurysm, ratio of disruptive factors nearly equaled anterior circulation aneurysm clipping; however, statistical analysis was limited due to the restricted number of posterior circulation aneurysms clipped (Tab. 4, Tab. 6). Comparing anterior and media circulation aneurysms and the number of disruptive

factors observed, a statistically significant difference did not become apparent in our patient cohort.

Impact of aneurysm site on the occurrence of disruptive factors

	anterior	media	posterior
total no. treated	79	109	10
no. of motor deficits	2	3	0
transient decline	9	5	1
symptomatic tcMEP decline	2	2	0
disruptive factors	7	3	1
ratio transient decline/no treated	11.4%	4.6%	10.0%
ratio disruptive factor/total number treated	8.9%	2.8%	10.0%
p-value		0.0978	1

Table 6: Impact of aneurysm site on occurrence of postoperative motor deficits and disruptive factors. We compared anterior, media, and posterior aneurysm. We calculated the ratio between transient decline to the number of aneurysms treated on each site as well as the ratio of disruptive factors to the total number treated on each site. P-value was calculated according to the exact Fishers test.

4.2.3. Validity of tcMEP monitoring in aneurysm clipping

A diagnostic analysis was performed according to a 2x2 summary table determining the validity of intraoperative tcMEP monitoring according to our observations (Tab. 2, Tab. 7). These values are characterized as statistical quality criteria of diagnostic medical tests. As stated above, all cases of tcMEP monitoring decline refer to a transient decline only.

Applied to our data, a Sensitivity of 40.0% and a Specificity of 91.7% could be calculated for tcMEP monitoring in the clipping of unruptured intracranial aneurysms.

NPV was set at 97.9%, indicating a good chance of no new motor deficit, if stable tcMEP monitoring conditions were recorded. The PPV depicted the risk of a permanent or transient loss of motor function, if a reversible decline of tcMEP monitoring

developed during surgery. It may be described as the reversible risk and was calculated with 13.3% in our patient cohort (Tab. 7).

		postoperative motor deficit		
		yes	no	
tcMEP monitoring	decline	2	13	**PPV 13.3%**
	stable	3	145	**NPV 97.9%**
		Sen 40%	**Spe 91.7%**	**163**

Table 7: 2x2 summary table calculating Sensitivity, Specificity, PPV and NPV of tcMEP monitoring in the clipping of unruptured intracranial aneurysms according to the influence on postoperative motor deficits. Postoperative deficit included permanent and transient restrictions.

Sen= Sensitivity, Spe= Specificity, PPV= positive predictive value, NPV= negative predictive value

5. DISCUSSION

In Chapter five, the descriptive as well as analytic results are combined and interpreted in order to determine their clinical importance. We compared our findings to literature, further intraoperative monitoring devices, and critically reviewed the quality of our study. We furtherly divided a transient intraoperative tcMEP decline according to the underlying etiology into symptomatic tcMEP declines and disruptive factors, which will be described according to the frequency observed.

5.1. Comparison to literature

In order to comprehend and correctly interpret our data, we first compared it to further literature on tcMEP monitoring in the clipping of unruptured intracranial aneurysms.

5.1.1. False negatives in tcMEP monitoring

Irie et al. were the first to state the problem of false negatives in tcMEP monitoring (Irie et al. 2010). In their retrospective study including 111 patients treated from 2003-2009, they observed six patients without intraoperative tcMEP changes but postoperative motor restriction and defined these as false negatives. On the one hand, the authors stated that these false negatives of tcMEP monitoring might be caused by an intraoperative tcMEP overstimulation: Activation below an injured cortex area could feign intact motor function. On the other hand, this phenomenon mainly occurred in the treatment of A. cerebri media aneurysms (five out of six) and the study by Irie et al. doubted the usefulness of tcMEP on this site (Irie et al. 2010). Further studies confirmed these false negative findings, for example a retrospective analysis by Chung et al. in 2018 found eight cases of false negatives in their patient cohort of 1514 patients, or a retrospective study by Greve et al. in 2019 described five false negatives in 274 patients included (Chung et al. 2018; Greve et al. 2019). An explanation for their presence could not be given in these studies.

Compared to our own clinical observation, we could not show a significant subjection of the incidence of false negatives according to aneurysm site. The missing explanatory power was mostly due to the restricted number of false negative: We observed three cases of false negatives. 66.6% of these occurred in the clipping of A.

cerebri media aneurysms; A statement regarding Irie et. al's findings was hard to determine. The reason for the preserved intraoperative monitoring signals could neither be identified in retrospective analysis in any case. Postoperative imaging devices detected ischemic lesions or perfusion deficits in all of the cases observed. Similar to Irie et al's consideration, stimulation of lower cortex areas has to be considered as an explanation for the lack of tcMEP monitoring correlate. How to furtherly avoid this problem remains unclear.

5.1.2. Influence of aneurysm site on tcMEP monitoring

Similar to the issue of false negatives, several studies tried to examine an influence of aneurysm site on the performance of tcMEP monitoring. However, a general statement regarding the influence of the aneurysm site was hard to evaluate from recent studies. A positive trend may be claimed for the treatment of A. choroidea aneurysms, as sufficient results have been shown in various clinical studies (Aleman-Rivera and Camacho-Gomez 2001; Suzuki et al. 2003; Sasaki et al. 2007; Irie et al. 2010; Lin et al. 2011). A plausible correlation can be deduced by its neuroanatomic basis, as the A. choroidea provides the arterial blood supply of the anterior capsula interna and consequently causes a contralateral hemiparesis if harmed (Helgason et al. 1986).

In the surgical treatment of the posterior circulation and brainstem lesions both a superiority to somatosensory evoked potentials (SSEP), a high sensitivity, and NPV referring to the postoperative neurological status were shown (Quinones-Hinojosa et al. 2004). However, especially in the treatment of brainstem tumors, several confounding factors were described by Kodama et al., which posed the need for careful intraoperative interpretation (Kodama et al. 2014).

Regarding aneurysms of the A. cerebri media, opinions differed about the validity of tcMEP monitoring in aneurysm clipping. The problem of false negatives is already discussed above (Irie et al. 2010). Horiuchi et al. described a sufficient outcome in A. cerebri media aneurysms, especially, if A. lenticulustriatae were concerned (Horiuchi et al. 2005). Slézeny et al. published a case report demonstrating a patient with an intraoperative decline of tcMEP monitoring and stable SSEP, who presented a correlating postoperative hemiparesis with intact sensation (Szelenyi et al. 2003). A study by Yue et al., emphasized the meaning of tcMEP monitoring in A. cerebri media aneurysms. Firstly, they introduced a two-stage warning criterion by dividing intraoperative changes into a decline above and below 50% baseline level. Secondly,

they did a prospective study on the outcome of tcMEP monitoring patients compared to a control group. They found an improved motor status in the latest follow-up at 31.9 months and therefore regarded tcMEP monitoring as an independent prognostic factor of the motor outcome in long-term results. A short-term benefit could not be proven (Yue et al. 2014). Sasaki et al. combined the two arterial supply areas of anterior and media circulation and stated a reliable performance of tcMEP monitoring concerning A. choroidea and Ae. Lenticulostriate (Sasaki et al. 2007).

In our analysis, there seemed to be an indistinct difference in the occurrence of disruptive factors in favor of anterior and posterior circulation, which was not statistically significant (Tab. 6). However, regarding posterior aneurysms, statistical analysis was limited due to the restricted number of cases included. For anterior aneurysms, a possible explanation could be deduced by its neuroanatomic basis. In our cases, tcMEP monitoring signals were derived by electrodes of the thenar muscles. A decline in these potentials in anterior circulation monitoring can only be expected if A. choroidea interna branches were affected harming the capsula interna. This is in accordance to the studies discussed above. However, the anterior circulation mostly supplies the parasagittal cortical zone. This area, according to Brodmann's depiction of functional brain areas, represents the lower limb (Helgason et al. 1986; Suzuki et al. 2003). Consequently, monitoring of the lower limb could be favorable or, at least, a possible further diagnostic device in sufficient tcMEP monitoring in the clipping of anterior circulation intracranial aneurysms.

However, it seems important to state a shortcoming of our statistical analysis in this matter. In case of a simultaneous treatment of aneurysms of different circulation and sites, a superposition of influences cannot be excluded in retrospective differentiation and a cause-effect cannot be determined.

Concluding and in regard of the limited number of observations, a metaanalysis might be useful in order to fully estimate the impact of the aneurysm site on tcMEP monitoring in the clipping of unruptured intracranial aneurysms.

5.1.3. Validity of tcMEP monitoring

As depicted above, we deduced a sensitivity of 40.0%, a specificity of 91.7%, a PPV of 13.3%, and a NPV 97.9% of tcMEP monitoring in our patient cohort (Tab. 7). As no cases of permanent loss of motor function became apparent in our patient cohort, calculation refers to transient tcMEP decline only. A comparison of the specific risk

between reversible and irreversible changes may consequently not be deduced by this study.

The values calculated are characterized as statistical quality criteria of diagnostic medical tests. As calculated by transient intraoperative declines only, the sensitivity and PPV are subjected to the positive impact of tcMEP monitoring on the postoperative motor outcome. By taking sufficient means in the surgical prevention of an ischemic complication, a transient intraoperative decline shall not result in a postoperative loss of motor function. Therefore, the smaller the value, the better the postoperative motor outcome and the higher the influence of tcMEP monitoring on the prevention of a loss of motor function. With a PPV of 13.3%, the chance of an unchanged postoperative motor status, if tcMEP transiently declined throughout surgery, was good.

In comparison to literature, the specificity and NPV are approximately in accordance to other studies on the performance of intraoperative tcMEP monitoring (Szelenyi et al. 2003; Szelenyi et al. 2006; Yeon et al. 2010; Sahaya et al. 2014; Yue et al. 2014; Holdefer et al. 2016; Chung et al. 2018; Greve et al. 2019; Lee et al. 2019). The absence of cases with a permanent loss of tcMEP monitoring explains a difference in calculation to some studies, such as a meta-analysis done by Holdefer et. al, in which they described a specificity of 100%. According to their findings of permanent tcMEP declines in a larger patients' cohort, they excluded transient loss of signals from this parameter (Holdefer et al. 2016). Similarly, Tanaka et al. calculated a higher sensitivity in tcMEP monitoring in aneurysm surgery (Tanaka et al. 2011). Nevertheless, an uneventful intraoperative tcMEP status was highly associated to a favorable postoperative motor outcome in our patient cohort.

5.2. The problem of a missing cause-effect-relationship

Though tcMEP monitoring is a highly valued and useful device in IONM, it cannot provide complete monitoring possibilities for two main reasons. On the one hand, it is restricted to motor function only. On the other hand, it is unable to detect the cause of its intraoperative decline. Further IONM devices are needed in order to provide intraoperative diagnostic methods ensuring reliable and fast clarification of tcMEP changes. Only if this is achieved, a positive impact can be expected by the use of tcMEP monitoring. Both reasons result in the need for a correlation to further IONM and intraoperative imaging devices.

5.2.1. Possible advantages by ICG-Angiography

ICG-Angiography is a regularly used device in intraoperative monitoring of the intracranial vessels and an aid to real-life depiction of the intraoperative arterial blood flow. Its basis lies in the intravenous application of a fluorescent agent, which can be made detectable by near- infrared light of a wavelength of 800 nm. Raabe et al. described its technical usage in aneurysm surgery in 2005, especially in the documentation of a complete occlusion of the aneurysm treated and its perforating vessels (Raabe et al. 2003; Raabe et al. 2005). Further studies confirmed its diagnostic value in providing fast and safe information about the obliteration of aneurysm and vessel patency, especially of small vessels and perforating branches (de Oliveira et al. 2007; Dashti et al. 2009; Ozgiray et al. 2013). Roessler et al. found a significant intraoperative clip modification rate due to ICG-Angiographic detected stenosis of the parent vessel or occlusion of the perforators. Consequently, they stated that ICG-Angiography had a positive influence on the patients' outcome (Roessler et al. 2014).
TcMEP monitoring itself cannot provide a cause-effect-relationship. A correlation to further intraoperative devices is needed in order to differentiate between a disruptive factor and a symptomatic tcMEP decline. Therefore, in our patient cohort, ICG-Angiography was performed regularly in all clippings included. Regarding the subgroup characterized by a transient tcMEP decline, an abnormality of ICG-Angiography became apparent in two cases. In case 2, ICG-Angiography detected a kinking and vasospasms of the supplying vessels. In case 125, a suspected clip stenosis could be confirmed by ICG-Angiography. In these cases, ICG-Angiography posed an additional benefit to the determination of the primary cause of the tcMEP decline. In two cases (66, 150), in which a clip stenosis had been identified as the source of the intraoperative decline in tcMEP signaling, ICG-Angiography did not present a device of advanced diagnostic information: In case 66, a small remaining blood flow may have deceived its expressiveness. In case 150, ICG- Angiography could not identify the unintended clip stenosis. In retrospective approach, this failure could not be explained. Summarizing, two cases of intraoperative tcMEP decline profited directly by the usage of ICG-Angiography. However indirectly, by a reliable and short-time confirmation of an appropriate artery flow, we claimed that every patient, regardless the intraoperative tcMEP status, benefited by its practice. We concluded that ICG-Angiography posed a vital tool to integral intraoperative monitoring and intraoperative diagnostic imaging.

5.2.2. Interaction of different monitoring methods as a gold standard for intraoperative patient surveillance

There are several studies evaluating the different subtypes of intraoperative surveillance, either neurophysiological, using evoked potentials, or medical imaging based, as, for example, ICG- Angiography depicted above or intraoperative ultrasonography (Aleman-Rivera and Camacho-Gomez 2001; Neuloh and Schramm 2004; Gruber et al. 2011).

Intraoperative microvascular Doppler-ultrasonography uses ultrasound and the so-called Doppler effect, which describes a change of frequency of the ultrasound wave subjected to local changes of the blood flow: Using this effect, intraoperative microvascular Doppler-ultrasonography is able to make vascular flow characteristics visible and audible (Stendel et al. 2000; Siasios et al. 2012). This non-invasive technique is highly sensitive in the detection of a clip stenosis and is therefore routinely used in aneurysm surgery (Stendel et al. 2000).

Concluding, each technique provides its distinct advantages and shortcomings, resulting in the need for a precise preoperative evaluation of each patient`s needs (Aleman-Rivera and Camacho-Gomez 2001; Neuloh and Schramm 2004; Gruber et al. 2011). The ideal control was shown to be based on an individualized application of interacting and supporting systems. Therefore, we ought to aspire an optimum interaction of different monitoring methods regarding each patient individually. This concerns general intraoperative surveillance as well as handling of IONM changes during surgical approach.

5.3. Influence of surgical experience on the patients' outcome

As aneurysm clipping is regarded as one of the most precise and technically sophisticated procedures in neurosurgery, the assessment of an intraoperative decline in tcMEP relays upon a qualified evaluation of the surgical situation. There are several studies stating that the surgical experience of the team had a positive correlation to the postoperative outcome, especially, if a rupture of the treated aneurysm occurred (van Lindert et al. 2001; Lawton and Du 2005; Hsu et al. 2016). It was found that efficiency, confidence, and the insight in the management of an unexpected intraoperative event increased over time, improving the surgical performance and, hereby, the postoperative outcome. One could easily imagine, that a decline in tcMEP signaling

resembles such an event and a competent know-how on the handling of this decline is in favor of a satisfactory outcome.

5.4. Safety aspects of tcMEP monitoring

In order to give a comprehensible overview of the possible advantages of tcMEP monitoring, certain safety aspects have to be considered. MacDonald et al. did a comparative analysis, matching tcMEP monitoring to further brain stimulation methods in more than 15000 cases and described the following adverse effects of tcMEP monitoring. For once, triggering of an intraoperative seizure by tcMEP was described. However, it has to be noted that this may have been secondary as seizures are categorized as a general risk of neurosurgical procedures (Conte et al. 2015). Furthermore, tcMEP monitoring provoked lip as well as tongue injuries, which was opposed to by the use of bite blocks. A mandibular fracture was described in one case. Minor scalp burns were rare. A point of importance seemed to be the initiation of cardiac arrhythmia, which was observed in five times.

Summarizing these events, MacDonald et al. defined relative contraindications for tcMEP monitoring including, inter alia, epilepsy, cardiac diseases, pace makers, and convexity skull defects. Maintaining these contraindications, the authors stated that tcMEP monitoring is a secure surgical device in evaluating the patients' intraoperative motor status (MacDonald 2002). We did not observe any events suspicious of adverse reaction to tcMEP monitoring in our patient cohort.

5.5. Decline in tcMEP monitoring: symptomatic vs. disruptive factors

The aim of this retrospective study was the definition of the possible disruptive factors in the clipping of unruptured intracranial aneurysms. In total, we observed 15 patients with an intraoperative tcMEP decline. In eight cases, disruptive factors could be identified as the source of the intraoperative decline.

5.5.1. Observed disruptive factors

We characterized disruptive factors as either unspecific or intended external influences on tcMEP manipulating the intraoperative status and hereby adding intraoperative

events unrelated to the postoperative motor outcome. Consequently, these factors did not require specific management or treatment and should theoretically have no impact on the motor function at discharge.

5.5.1.1. Positional influences on tcMEP monitoring

One case (case 29) of intraoperative tcMEP decline was associated to an intraoperative brain-shift (Tab. 4, Fig. 7). This phenomenon has been described in different neurosurgical procedures, especially in the treatment of brain tumors, and is characterized by a change of position and shape of the brain throughout the surgical maneuver (Gerard et al. 2017). As a specific area of the brain needs to be stimulated in order to generate a sufficing external activation in tcMEP monitoring, this case sets a perfect example of positional influences on tcMEP monitoring, which need to be considered in aneurysm clipping as a possible disruptive factor.
A further aspect of positional influences lies in the avoidance of mechanical stress on plexus and peripheral nerves by a correct positioning of extremities. This is seen as a principle of good surgical practice and its impact on tcMEP monitoring is additional specification - it is listed here for completeness.

5.5.1.2. Mechanical effects during surgery

In case 138, a decline of tcMEP monitoring was attributed to the removal of a spatula during surgical preparation (Tab. 4, Fig. 7). The removal most likely caused a dislodging of, or interference with stimulation electrodes. It emphasizes a possible influence of mechanical disruptive factors on tcMEP monitoring.

5.5.1.3. Circulatory deficits

Six cases, characterized by a transient decline in tcMEP signaling, were ascribed to various circulatory deficits: therapeutic cardiac arrest, hypotension, and temporary artery clipping. These deficits constitute the most frequent cause of disruptive factors observed in the surgical clipping of unruptured intracranial aneurysms (Fig. 7).
Medically induced hypotension is a procedure commonly described in vascular neurosurgery and aims on reducing the blood load in the subarachnoid space in case of an intraoperative rupture, consequently preventing a resulting increase of the

intracranial pressure as well as postoperative complications such as vasospasms (Sloan 2002). This was needed in one case (case 97). Similar to this case's reasoning, a cardiac arrest was medically administered in one case and resulted in a transient decline of tcMEP signals in temporal connection to the beginning and end of the circulatory deficit (Wright et al. 2014). Both of the cases had an uneventful postoperative motor outcome.

Temporary clipping was identified as the source of the intraoperative tcMEP decline in four cases (Fig. 7). Temporary clipping in aneurysm surgery has been described as the source of an intraoperative loss of evoked potential monitoring in literature before (Schramm et al. 1990). Indication for temporary clipping is mainly set in two scenarios. Firstly, in order to optimize clipping conditions, it can be administered in the treatment of giant aneurysms or in aneurysms with a thin-walled fundus, especially in cases, in which it is adherent to perforating vessels (Jabre and Symon 1987). Secondly, it may be of benefit in intraoperatively ruptured aneurysms; Batjer et al. described a significantly reduced morbidity and mortality, if temporary clipping is administered in these cases (Batjer and Samson 1986). As temporary clipping was found to be attributed to an elevated incidence of postoperative strokes, a reasonable application of this surgical intervention is necessary. This includes consideration of aneurysm factors, such as the regional anatomy, aneurysm size, and aneurysm consistency, as well as patient related influencing factors, especially age (Batjer and Samson 1986; Jabre and Symon 1987; Taylor et al. 1996). An important influencing factor on the postoperative outcome is the duration of temporary clipping. Several studies have been introduced in order to determine an optimum time span (Ha et al. 2009). A final conclusion could not be resolved thus far and a minimum application is recommended (Aleman-Rivera and Camacho-Gomez 2001; Griessenauer et al. 2014; Tanabe et al. 2017). In the cases of intraoperative tcMEP decline, we observed two cases of elective temporary clipping as well as two cases of intraoperative rupture. Three cases were characterized by an uneventful postoperative course. One case (109) developed a prolonged contralateral hemiparesis immediately after surgery. In this case, the pathomechanism responsible for the postoperative deficit could not be determined in retrospective approach. On the one hand, the intraoperative rupture may have caused a damage resulting in a decreased motor function. On the other hand, the temporary clipping may have caused a stroke as described above (Ha et al. 2009). This could

however not be proven by postoperative imaging, which did not detect an ischemic lesion.

Considering duration of temporary clipping time, in all cases a minimum application time was striven for. Therefore, as far as reproducible from retrospective data and infrequent documentation of temporary clipping application and times, these cases did not significantly vary from the cases observed without transient intraoperative decline. A prospective work on application, duration time, IONM changes, and postoperative outcome might be of interest regarding optimum application time of temporary clipping balancing surgical benefits and risk of postoperative strokes in unruptured intracranial aneurysms. Furtherly, it could be investigated, whether a decline in tcMEP monitoring during temporary clipping constitutes a warning criterion for postoperative motor restriction.

5.5.1.4. Unknown intraoperative tcMEP changes

Regarding the other three cases, a profound explanation of the intraoperative tcMEP change was hard to determine in retrospective approach. As none of these patients developed a corresponding motor deficit or imaging explanation, we argued that these cases most likely constitute disruptive factors lacking the possibility of retrospective definition (Fig. 7).

5.5.2. Further intraoperative disruptive factors

There are several further physiologic, medical, and technical effects altering tcMEP monitoring, which we have not observed in our patient population. However, such effects have been described in literature and need to be considered in intraoperative reasoning, which is done in the following.

5.5.2.1. Physiological effects intervening with tcMEP monitoring

Firstly, ventilation is described to have an influence on tcMEP signals. On the one hand, a deprived oxygen delivery may result in a downregulation of cellular metabolism and hereby decrease the amplitude of IONM. Furthermore, a change of the partial pressure of oxygen and carbon dioxide has a profound effect on the intracerebral blood flow. Especially carbon dioxide is a sensitive control variable in the autoregulation of

intracranial pressure and blood supply. As these parameters can accurately be influenced by volume controlled or pressure-cycled ventilation, a correct adjustment has to be striven for (Clowes et al. 1953; Kitahata et al. 1969; Grundy et al. 1982; Nakagawa et al. 1984; Haghighi et al. 1993).

Another factor to be considered in peripheral tcMEP derivation is temperature. A decrease of temperature is known to induce a deceleration of nerve velocity (Letz and Gerr 1994; Maetzler et al. 2012). This effect may dissemble a prolonged latency in CMAP and has to be considered in core body temperature as well as regional hypothermia (Oro and Haghighi 1992; Seyal and Mull 2002). A spatial arrangement of tcMEP monitoring on the one extremity and infusion on the other could, for example, easily elate a possible interference.

Further, anemia was found to influence neuromonitoring by two mechanisms: firstly, the oxygen capacity is reduced, resulting in a suppressed metabolism. Secondly, the cerebral blood flow is altered, possibly depriving the cortex of oxygen supply (Nagao et al. 1978). Although it has to be noted that in vascular neurosurgical procedures a relevant hemorrhage and acute anemia is unlikely.

Accordingly, but nevertheless important, each patient has to be considered individually. The following factors may not be associated to a sudden loss of tcMEP monitoring, however, a connection has to be considered: Diabetes mellitus, smoking, age, height, and alcohol consumption have inter alia been found to have an influence on the conduction of peripheral nerves, affecting latency as well as amplitude of CMAP, and can therefore bias the effect of tcMEP monitoring (Letz and Gerr 1994).

5.5.2.2. Medical effects

As mentioned before, medical effects need to be considered in tcMEP monitoring.

Firstly, anesthetic effects on tcMEP monitoring have been described by various studies (Kalkman et al. 1992; Glassman et al. 1993; Sloan 2002; Hemmer et al. 2014; Sloan et al. 2015). Summarizing, a significant decrease of tcMEP amplitude may be observed in volatile anesthetics, resulting in a preference of intravenous anesthesia. These effects are caused by a depression in synaptic activity and tcMEP responses are affected by minimum concentrations. Therefore, a TIVA is state of the art in tcMEP monitoring. Propofol has been described to have a slight effect on SSEP as well as tcMEP in high doses. At therapeutic dose, no intervention has been found in previous studies (Sloan et al. 2015). Although it is widely used, one disadvantage of propofol

has to be considered: In comparison to volatile anesthetics, a slower wake-up has to be accepted. Such delays the postoperative neurologic examination and an early time slot of possible reversibility of the postoperative focal neurologic deficit could be missed.

Most importantly, the usage of muscle relaxants needs to be restricted due to their interference with the peripheral transmission at the end organ of the muscle monitored (Xie et al. 2018). Muscle relaxants base on a competitive antagonism on the n-cholino-receptor of the muscle end organ and hereby inhibit a depolarization, initializing a muscle contraction. If a muscle is completely antagonized, no tcMEP monitoring signal can be derived. Therefore, short- to intermedium acting no depolarizing neuromuscular blocking agents ought to be used for endotracheal intubation and craniotomy only (Xie et al. 2018).

The effects of opioids and benzodiazepines have been described as minimal and seem to have no effect on a sufficient tcMEP signal (Sloan 2002).

5.5.2.3. Technical effects

Finally, technical interferences due to stimulation or recording electrodes malfunction, dislodging, and change of location due to edema could interfere with stable tcMEP signaling.

5.5.3. Symptomatic tcMEP decline

Contrary to the cases of disruptive factors, we characterized a symptomatic tcMEP decline as a decline, in which an unintended deprive of blood supply to the motor cortex and hereby an ischemic mechanism caused the intraoperative change. As depicted above, a wrongly adjusted clip deprives the blood flow and therefore the oxygen supply to the cortex. If the motor cortex is affected, this results in a decline of tcMEP monitoring signals and hereby directs the surgeon`s attention to a potential threat to the motor integrity of the patient. By resetting the clip, the damage to this highly eloquent area may still be reversible and a postoperative paresis can be prevented. In a total of four cases, a symptomatic tcMEP decline became apparent in our patient cohort:

In three cases, the impairment of tcMEP monitoring signals could be associated to an unintended clip stenosis. By resetting the clip, in all of these cases, a transient or

permanent postoperative hemiparesis could be prevented. These cases represented the ideal intraoperative work flow and we stated that these patients highly profited by the use of tcMEP monitoring.

In one case, the loss of tcMEP signals was associated to an intraoperative kinking and vasospasms of small vessels. Although immediate application of nimodipine was administered, a permanent postoperative paresis could not be prevented. The pathomechanism underlying intraoperative vasospasms in neurovascular surgery could not be identified thus far; a correlation to mechanical influences as well as neuroinflammatory processes due to an aSAH are discussed (Miller et al. 2014; Tsyben et al. 2016; Huang et al. 2017). An association to temporary clipping could not be resolved up-to-date (Malinova et al. 2018) and there seemed to be no significant difference in the occurrence of vasospasms comparing interventional coiling and surgical clipping (Dumont et al. 2010). Regarding subarachnoid hemorrhage, the influence of ultra-early vasospasm on the presence on symptomatic vasospasms with consecutive infarction and an unfavorable outcome has been described in various studies (Al-Mufti et al. 2017; Phan et al. 2017). Whether this can similarly be applied to intraoperatively ruptured intracranial aneurysms has not been resolved so far, but might be considered. In this case, the presence of intraoperative vasospasm and kinking of small vessel negatively influenced the clinical outcome.

To conclude, in case of an intraoperative tcMEP decline, a fast and reliable screening for a symptomatic tcMEP decline has to be striven for. As depicted above, this can be achieved by a relation to further intraoperative imaging devices, such as ICG-Angiography, microvascular Doppler- ultrasonography or DSA if necessary, in order to exclude a symptomatic, unintended clip stenosis, which is depicted in Figure 9. Only if this is achieved, a positive impact of the surgical action on the postoperative motor outcome can be expected.

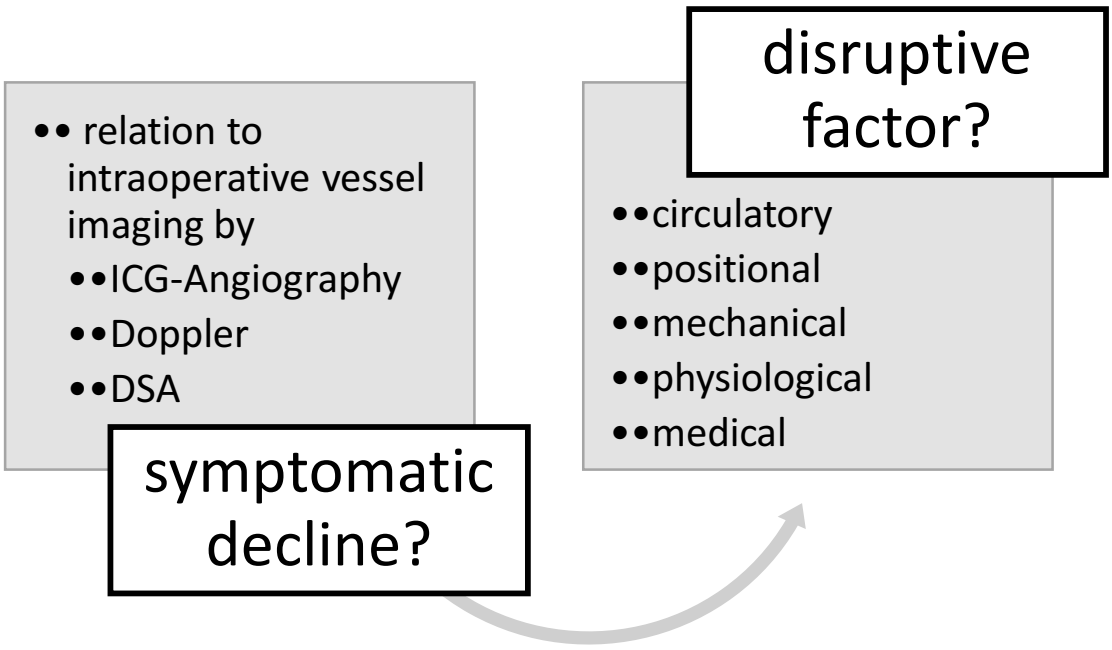

Figure 9: Workflow in case of an intraoperative tcMEP decline. Detection of a symptomatic tcMEP decline as the key factor to reasonable tcMEP monitoring in aneurysm clipping.

5.6. Limitations of this study

Our analysis of tcMEP monitoring in the clipping of unruptured intracranial aneurysms, performed from 2010-2016 at the neurosurgical department of the Klinikum rechts der Isar, has certain limitations:

Firstly, the retrospective character raises two main concerns. For once, the analysis was based on surgical letters and discharge documents, making it hard in every particular case to fully comprehend the intraoperative procedures and making one dependent on the diagnostic statements regarding the postoperative outcome. Characterized as an information bias, a differential misclassification due to incomplete medical records, recorded errors and misinterpretation cannot be fully eliminated. The postoperative recovery of a patient after an intracranial surgery is complex and interference factors needed to be correctly identified in each case. A careful interpretation of the data collected was necessary in order to avoid a resulting diagnose bias. Secondly, a cause-effect relation between intraoperative tcMEP monitoring and postoperative outcome of motor status cannot be claimed by this retrospective study.

This study rather aimed on being precedent-setting for future use of tcMEP monitoring in aneurysm clippings.

A further problem lay in the restricted number of patients included. With 171 cases observed in a period of five years, ranging a rate of 18-38 per year, the incidence of aneurysm clippings performed was infrequent and leaved only restricted possibilities of statistical analysis. The significance of the statistical test performed was limited to a small sample size, hereby limiting the explanatory power of this study, and resulting in a predominant depiction of tendencies.

Another limitation of this study lay in the short-term observation time. The focal neurologic status was assessed according to the surgical letter at discharge. However, Yue et al. showed a significant difference in their prospective study regarding the impact of tcMEP monitoring in middle artery surgery only in the latest follow-up at a median of 31.9 months. Therefore, the surveillance period may have been chosen too short (Yue et al. 2014).

Using a retrospective analysis, however had certain advantages, for which this format had been chosen. For once, a fast and near-term statement can be deduced by the retrospective approach. Hereby, a direct advantage for future neurosurgical tcMEP monitoring in aneurysm clippings could be achieved.

5.7. Is a prospective study ethically justifiable?

In order to eliminate the shortcomings of our retrospective study depicted above and determine a specific number needed to treat (NNT) and an absolute risk reduction associated to intraoperative tcMEP monitoring in aneurysm clippings, a randomized, prospective study would have to be induced. However, the ethical question arose, whether this is truly necessary. In our opinion, there are several reasons against an initiation of a prospective study. Firstly, the safe application of tcMEP monitoring favors its further utilization. Secondly, the infrequent number of surgical clipping results in a long-term observation time. And thirdly and most importantly, we found, that at least 1.8% of patients included profited directly by the use of tcMEP monitoring due to the detection of an unintended clip stenosis. Considering these arguments and the consequences for the individual if a loss of motor function occurred, we felt, that a prospective, randomized study could not be justified.

6. SUMMARY

The aim of this retrospective study was the definition of the efficiency of tcMEP monitoring in the prevention of ischemic complications in the clipping of incidental, intracerebral aneurysms. Our motivation lay in the question of whether the disruptive factors observed inhibit the evaluation of tcMEP monitoring in aneurysm clipping in an extent to which its usage is of no further advantage to the surgical team.

We could reject this hypothesis on two considerations. Firstly, based on tcMEP monitoring, three cases of unintended clip stenosis could be identified and, by resetting the clip, a postoperative loss of motor function could be prevented in all of these cases (Tab. 4). We characterized these cases as a symptomatic tcMEP decline, in which an unintended deprive of blood supply to the motor cortex and hereby an ischemic mechanism caused the intraoperative change. Secondly, despite the positive impact of tcMEP monitoring on the postoperative outcome in these three cases, we found a statistically significant association between intraoperative tcMEP status and postoperative motor function at discharge (Tab. 5, Fig.8): The RR of any - transient or permanent - postoperative loss of motor function was significantly higher in a patient with a transient intraoperative tcMEP decline than in a patient with stable intraoperative tcMEP signals. This statistically significant difference depicts the accuracy of tcMEP in monitoring the motor pathway, which is furtherly confirmed by the calculation of sensitivity, specificity, NPV, and PPV (Tab. 7).

Nevertheless, we found various disruptive factors interfering with tcMEP monitoring in aneurysm clipping. We defined these as external influences manipulating tcMEP monitoring and hereby adding intraoperative events. As either intended or unspecific, these factors do not require intraoperative treatment or management. Consequently, tcMEP changes due to disruptive factors should theoretically not have a significant influence on postoperative motor function. We divided the disruptive factors observed into three main categories: positional, technical, and, circulatory causes (Fig. 7). Circulatory deficits included therapeutic hypotension, therapeutic cardiac arrest, and, most frequently, temporary clipping. We could not show a significant difference in the occurrence of intraoperative disruptive factors according to the site of the aneurysm treated (Tab. 6), which is, however partly, described in literature.

Concluding, a positive impact of the surgical action on the postoperative outcome can be expected by a correct and fast differentiation between a disruptive factor and a

symptomatic tcMEP decline (Fig. 9): A profound analysis of the pathomechanism responsible for an intraoperative decline seemed to be the key factor to reasonable tcMEP monitoring in aneurysm clipping. As tcMEP monitoring itself cannot provide a distinct cause-effect relationship, further intraoperative surveillance methods, such as ICG-Angiography or intraoperative microvascular Doppler- ultrasound, were considered to be necessary in achieving sufficient intraoperative reasoning.

To conclude, we stated that tcMEP monitoring in aneurysm clipping is a valuable device in the prevention of ischemic complications and postoperative neurological deficits.

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9. LIST OF TABLES

10. LIST OF FIGURES

11. CURRICULUM VITAE

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12. PUBLICATIONS

Oral presentations

Title The efficiency of transcranial motor evoked potential monitoring in the clipping of unruptured aneurysms
Meeting EANS Venedig, October 2017

Title The efficiency of transcranial motor evoked potential monitoring in the clipping of unruptured aneurysms
Meeting EANS Vasc. Section Nice, 2019

Posters

Title The efficiency of transcranial motor evoked potential monitoring in the clipping of unruptured aneurysms
Meeting ESMINT September 2019

13. APPENDIX

Complete illustration of patients included

Patient			aneurysm		intraOP Status	postOP status
no.	age	gender	size (mm)	site	tcMEP	motor deficit
1	41	f	4	MCA ri	0	0
2	48	f		MCA le	1	2
3	69	f	7	MCA	0	0
4	72	f		MCA ri	0	0
			CC	A. pericallosa le	0	0
6	40	m	CC	MCA ri	0	1
7	45	m	CC	MCA	0	0
8	67	m	4, Std. nascendi	ACI, A. ComA	0	1
9	48	m	CC	A. ComA	0	0
10	72	f	9	MCA	0	0
11	68	f	6	MCA	0	0
12	56	f	7	MCA ri, A. cerebri ant.	0	0
				MCA le	0	0
14	43	f	post Wrapping	MCA	0	0
15	64	f	15, Std. nascendi	2x ACI	0	0
			Std. nascendi	A. ophtalmica	0	0
17	58	f	28	A. cerebri ant.	0	0
18	54	f	CC	MCA ri	0	0
19	51	f	CC	MCA ri	0	0
20	44	f	2,5	ACI	0	0

21	57	f	4	MCA ri	0	0
22	61	f	9	MCA ri	0	0
			2	MCA le	0	0
24	56	f	2,5	A. ComA, ACI le	1	0
25	68	f	3	MCA ri	0	0
26	45	m	5,5	2x A. ComA	0	0
27	53	f	5; 2	MCA ri, ACI le	0	0
28	18	m	5; 2	MCA ri	0	2
29	41	f	6,5	MCA	1	0
30	48	m	4	Carotis-T.	0	0
31	56	m	1	A. pericallosa ri	0	0
32	47	m	5	MCA	0	0
33	57	f	9	A. cerebri ant.	0	0
34	47	f	8; 1	ACI ri u. le	1	0
			incomplete Clipping		0	0
36	46	f	CC	MCA	0	0
37	63	f	8	ACI	0	0
			incomplete Clipping		0	0
39	60	f	11	A. vertebralis	0	0
40	49	f	CC	P. Com	0	0
41	60	f	12	ACI	0	0
42	56	f	5	MCA	0	0
43	59	f	5,5	A. vertebralis	0	0
44	69	f	10	MCA, P.com ri	0	0
				P. Com li	1	0

46	71	m	8	MCA le	0	0
			3,5	MCA ri	0	0
48	44	w	5	MCA	0	0
49	54	w	Std. nascendi	MCA ri	0	0
50	50	f	3	A. pericallosa ri	0	2
51	53	m		MCA ri	0	0
52	64	f	6,5	MCA ri	0	0
53	58	f	2	A. cerebri ant.	0	0
54	47	m	std. nascendi	P. Com	0	0
				A. ComA, A. choroidea, MCA ri	0	0
56	48	f	7	MCA ri	0	0
			4	PICA le	0	0
58	51	f	7	ACI	1	0
59	47	f	3,5	MCA le	0	0
60	60	f	1,5; 1	MCA le, P. Com le	0	0
			1,5	MCA ri	0	1
62	61	f	7	MCA ri	0	0
63	46	f	7	ACI	0	0
			clipstenosis		0	0
65	72	f	7	MCA ri	0	0
66	57	m	8	A. ComA	1	0
			incomplete Clipping		0	0
68	50	m	1	2x MCA ri	0	0
69	57	f	8	P. Com ri	0	0
70	48	f	5	MCA ri	0	0

			after webbing	MCA le	0	0
72	71	f	4	MCA le	0	0
73	69	f	4; 11	MCA ri, MCA le.	1	0
74	76	f	6,4	A. ComA	0	0
75	63	f	7,5	MCA ri	0	0
76	69	f	6,5	MCA le	0	0
77	54	f	CC	A. vertebralis	0	2
78	75	m	CC	A. basilaris	0	2
79	69	f	7	MCA le	0	0
80	53	m	7	ACI le, P. Com le	0	0
81	75	w	6	MCA ri	0	0
82	29	f	6	MCA le	0	0
83	75	m	CC	A. ComA	0	0
84	53	f	Blisterlike	MCA ri	0	0
85	53	m		MCA le	0	0
86	57	f	6	A. pericallosa le	0	0
87	53	f	8	MCA ri	0	0
			1	MCA le	0	0
89	72	m	5	MCA ri	0	2
90	61	f	7	ACI le, MCA le	0	0
91	65	m	7; 6	ACI le, MCA le	0	0
			4	ACI ri	0	0
93	55	m	6	MCA le	0	0
94	60	f	5,5	MCA le	0	0
95	52	m	CC	A. choroidea ant.	1	0

96	48	m	4	MCA ri	0	0
97	61	f	14	ACI ri	1	0
98	35	f	CC	MCA ri	0	0
99	67	f		AICA le	0	0
100	45	f	9	MCA le	0	0
101	73	f		ACI le	0	0
102	68	f	4	MCA le	0	0
103	66	m	8	MCA ri	0	0
104	62	m	8	A. ComA	0	0
105	67	f	7; 2; 4; 5; 7	4x MCA ri, P. Com ri	0	0
106	52	f	8,5	MCA ri	0	0
			3	MCA le	0	0
108	62	f	4; 3	2xACI le	0	0
109	69	f	12; 3	ACI ri, A. pericallosa le	1	1
110	50	f	3	A. pericallosa ri	0	2
111	34	f	5	MCA ri	0	0
112	59	f	6,4	A. ComA	0	0
113	52	f	CC	ACI le	0	0
114	35	m	6	MCA ri	0	0
115	38	f	3	ACI le	0	0
116	48	f	6	MCA ri	0	0
117	57	f	9	P. Com ri	0	0
118	55	m	3	MCA le	0	0
			3	MCA ri	0	0
120	44	f	1,5	2xMCA ri	0	0

121	64	f	3,2	A. pericallosa	0	0
122	49	f	6; 2	2xMCA ri	0	0
123	37	m	7,5	MCA ri	0	0
124	60	f	7; 5	MCA ri	0	1
125	49	f	13	MCA le	1	0
			5; 2	MCA ri	0	0
127	73	f	7	MCA le	0	1
128	74	f	10	A. ComA	0	0
129	56	m	6	A. ComA	0	0
130	68	f	CC	A. ComA	0	0
131	52	f	10	ACI ri	0	0
			incomplete Clipping	ACI ri	0	0
133	66	f	2	MCA ri	0	0
134	55	f	7; 3	ACI ri, MCA le	0	0
135	41	m	Blisterlike	A. ComA	0	0
136	68	f	6	MCA le	0	0
137	48	f	3	A. pericallosa	0	0
138	43	f	5	A. ComA	1	0
139	44	f	1,5; 1,5	A. ComA, MCA le	0	0
140	72	f	3,5	PICA le	0	0
141	47	f		2xMCA ri	0	0
142	54	m	9	MCA ri	0	0
143	35	m	CC	A. ComA	0	0
144	60	m	18	MCA ri	0	0
			incomplete Clipping		0	0

146	59	f	3	MCA ri	0	0
147	48	m	CC	Carotis-T.	1	0
148	25	m		MCA ri	0	0
149	55	f	5,5	MCA le	0	0
150	38	f	8	ACI	1	0
151	44	f	5; 6	Carotis-T., ACI	0	0
152	69	f	7	MCA ri	0	0
153	41	f	2; 4; 1	ACI ri, A. choroidea ant le, MCA le	0	0
154	51	f	4	MCA le	0	0
				MCA ri	0	0
156	55	m	3; 10	A. ComA, MCA le	0	0
157	41	m	2	A. basilaris	0	0
158	54	f	29	A. ComA	0	0
159	27	f	CC	A. ComA	0	0
160	77	m		A. ComA	0	0
161	68	f		AICA	0	0
162	34	m	8	A. vertebralis	0	0
163	67	f	3	MCA ri	0	0
164	50	f	8	MCA ri	0	0
165	52	f	5	MCA ri	0	0
166	55	f	7	MCA ri	0	0
167	22	m	14	A. cerebri ant.	0	0
168	43	f	2,6	MCA le, A. choroidea ant le	0	0
169	65	f	12	A. ComA	0	0
170	50	m	7; 2,5	MCA ri, Truncus inferior	0	0

171	77	f	15	MCA ri	1	0

Table 8: Complete Illustration of patients included

f=female, m=male, n.a.= not available, CC= Coil compaction, MCA= A. cerebri media, A, ComA= A. communicans anterior, ACI= A. cerebri interna, P.Com= A. communicans posterior, ri= right, le=left, IntraOP status: 0= stable tcMEP, 1= transient decline, postOP status: 0= intact motor function, 1= transient postoperative hemiparesis, 2= permanent postopererative loss of motor function.