



Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: <http://ees.elsevier.com>

Median somatosensory evoked potential as a predictor of clinical outcome after urgent surgical extracranial internal carotid artery recanalization

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ARTICLE INFO

Article history:

Accepted 27 November 2020

Available online xxx

Keywords

Somatosensory evoked potentials

Evoked neuronal activity

Amplitude ratio

Outcome prediction

Ischemic stroke

Urgent recanalization

ABSTRACT

Objective: Changes in the N20/P25 amplitude of somatosensory evoked potentials (SEP) of the median nerve have been found to correlate with those in cortical regional cerebral blood flow (rCBF). Our study presents the use of median nerve SEP amplitude in predicting the clinical outcome of urgent surgical internal carotid artery (ICA) recanalization.

Methods: A total of 27 patients suffering an acute ischemic stroke (AIS) with extracranial ICA occlusion within 24 h were prospectively recruited. The primary preoperative endpoints included the SEP amplitude absolute value (SEP-amp) and the SEP amplitude side-to-side ratio (SEP-ratio). Clinical outcome at 3 months postoperatively was assessed using the modified Rankin scale (mRS-3M).

Results: The positive predictive values (PPVs) for SEP-amp and SEP-ratio were 95.5% and 100%, respectively, with the negative predictive values (NPVs) being 60.0% and 100%, respectively. The SEP-ratio correlated fully with mRS-3M.

Conclusion: The median SEP side-to-side N20/P25 amplitude ratio seems to be a very strong positive and negative predictor of the clinical outcome of urgent recanalization of an extracranial ICA occlusion.

Significance: The results suggest that cortical evoked activity may help in selection patient for surgical recanalization and predict clinical recovery after an acute ischemic stroke.

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Abbreviations: AIS, acute ischemic stroke; ACA, anterior cerebral artery; CBF, cerebral blood flow; CEA, carotid endarterectomy; CMRO₂, cerebral metabolic rate of oxygen; CCA, common carotid artery; CST, corticospinal tract; DWI, diffusion weighted image; FLAIR, fluid-attenuated inversion recovery; DNT, median door-to-needle time; DTF, door-to-flow time; ICA, internal carotid artery; IQR, interquartile ratio; IVT, intravenous; LAO, large artery occlusion; MEP, motor; MRC, Medical Research Council score; MRC-UE, Medical Research Council score upper extremity; MRC-LE, Medical Research Council score lower extremity; MCA, middle cerebral artery; mRS, modified Rankin scale; mRS-3M, modified Rankin scale 3 months after surgery; MT, mechanic thrombectomy; MTT, mean transit time; NIHSS, National Institute of Health Stroke Scale; NIHSS-door, National Institute of Health Stroke Scale on admission; NIHSS-CEA, National Institute of Health Stroke Scale before surgery; NPV, negative predictive value; OTF, onset-to-flow time; PMC, primary motor cortex; PPV, positive predictive value; rCBF, regional cerebral blood flow; SEP, somatosensory evoked potential; SEP-amp, somatosensory evoked potential amplitude; SEP-ratio, somatosensory evoked potential amplitude side-to-side ratio; TIA, transient ischemic attack.

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1. Introduction

A major factor affecting the clinical outcome of an acute ischemic stroke (AIS) caused by large artery occlusion (LAO) is early recanalization of the occluded artery. Based on prospective, randomized trials, there is a very strong recommendation for endovascular recanalization. (Jauch et al., 2013, Powers et al., 2018, Šaňák et al., 2016, Turc et al., 2019) However, endovascular mechanical thrombectomy (MT) fails in 3–13% of AIS with LAO. (Goyal et al., 2016) A persistent LAO is a predictor of early clinical deterioration. (Rajajee et al., 2006)

Once MT has failed, a proportion of patients is likely to be in the salvageable “tissue window” for recanalization. Some data are available for successful surgical embolectomy procedures for intracranial occlusion of the middle cerebral artery (MCA) as well as urgent recanalization of extracranial internal carotid artery (ICA) occlusion. (Benes et al., 2014, Fiedler et al., 2019)

At present, surgical recanalization – carotid endarterectomy (CEA) – of the extracranial ICA is not sufficiently supported in current guidelines because of outcomes of acute recanalization treatment of stroke with documented LAO. (Jauch et al., 2013, Powers et al., 2018, Turc et al., 2019)

Surgical recanalization can only be undertaken responsibly if endovascular recanalization is either unavailable or has failed. This means time to surgery would be always longer than time to endovascular MT. Because of longer time to recanalization clinical outcome can hardly be better after surgery than after MT. But clinical outcome can be better after surgical recanalization than in persisting acute ICA occlusion. As a result, there is a need for a reliable marker capable of identifying patients who would benefit from surgical recanalization as a last-ditch effort and who would not.

Preservation of cortical neuronal activity of the sensorimotor cortex is the main prerequisite for maintaining motor function. Regarding the extracranial ICA, neurophysiological markers might be useful in indicating early flow recovery (intraluminal shunt) to preclude development of definitive ischemia and/or a permanent defect. (Florence et al., 2004, Stejskal et al., 2007)

Surviving neurons in rolandic area are critical for functional recovery. Somatosensory evoked potential (SEP) elicibility on the side of ICA occlusion is a manifestation of surviving neurons in the symptomatic rolandic area. Urgent ICA recanalization will increase cortical rCBF and avert the development of definite ischemia and potentially disabling hemiparesis. In cases where the SEP are preoperatively non-elicible or abnormally reduced, cortical ischemia in rolandic area has already developed and the clinical deficit will not be offset by ICA recanalization.

Given the above, urgent CEA should be undertaken only in patients with surviving cortical neurons in the occluded artery territory. Median nerve SEP elicibility could thus serve as a marker of “tissue window” for a recanalization procedure in AIS.

1.1. Aim of study

To establish the feasibility of preoperative assessment using median nerve SEP prior to urgent recanalization of an acute extracranial ICA occlusion.

To determine the reliability of clinical outcome prediction based on the amplitude of the primary cortical somatosensory response.

To compare the reliability of prediction of selected clinical variables with SEP amplitude.

2. Material and methods

Patients were enrolled prospectively in the period from May 2015 through October 2019.

The inclusion criteria are consistent with the current recommendations for recanalization treatment in an AIS with documented LAO in its anterior circulation. (Powers et al., 2019) Additionally, we sought to assess SEP changes caused exclusively by the current acute ICA occlusion as some conditions in a patient’s history may have affected SEP elicibility undistinguishably from a currently evolving cortical ischemia.

2.1. Inclusion criteria

Symptoms of acute stroke involving the carotid territory within ≤ 24 h of symptom onset or most recent information about normal clinical status. Nonenhanced CT scan with a normal finding or with early signs of ischemia and/or MRI diffusion-weighted image and fluid-attenuated inversion recovery (DWI/FLAIR) mismatch with evidence of acute ischemia. (Thomalla et al., 2011) A CT angiogram revealed a unilateral symptomatic occlusion of the extracranial segment of the ICA accessible surgically. Unfeasibility of MT (proximal vascular territory anatomy, contraindication by the interventional radiologist) or MT failure or symptom duration > 6 h. Pre-stroke functional independence by the modified Rankin scale (mRS) ≤ 2 .

2.2. Exclusion criteria

Hemorrhagic stroke, stroke involving the posterior territory, pre-stroke disability (mRS > 2), stroke in the patient’s history. Subacute ischemia documented by CT or MRI scan, contralateral ICA occlusion. Known coagulopathy and/or INR > 1.7 , anticoagulation therapy not allowing acute reversal of the anticoagulant effect, tandem intracranial occlusion, common carotid artery (CCA) located high behind the angle of the mandible, other anatomically high-risk factors as defined by the SAMMPRIS study, (Yadav et al., 2004) advanced cancer.

All patients or their next of kin (in the case of patients having a speech disorder or impaired consciousness) gave their consent with urgent surgical recanalization. The study protocol was approved by the Ethics Committee of České Budějovice Hospital, České Budějovice, Czech Republic, in 2015.

2.3. Somatosensory evoked potentials (SEP)

Stimulation was performed using superficial bipolar electrodes on the volar aspect of the wrist over the course of the median nerve bilaterally, with the cathode placed proximally. Stimulation: monophasic square pulse, direct current, intensity 30 mA, pulse width 200 μ s, frequency 4.3 Hz.

Median SEP were recorded using subdermal corkscrew-like or subdermal monopolar needle electrodes placed on the scalp using the 10–20 system. Active electrodes were placed on C3 and C4 locations for monitoring cortical, and Cv5 spinal responses, with common reference at Cz. Registration: sensitivity 2 μ V/div, time base 10 ms/div, with 150–300 runs averaged. To shorten acquisition time, the number of averaging was reduced whenever the recording was evaluable and consistent. Alternating side stimulation was used, with the averaging done in parallel and synchronized on either side. Recording was started immediately upon anesthesia induction for surgical recanalization, with the response baseline set after the first three consistent recordings, prior to skin incision. Preceding MT was performed under local anesthesia in all cases.

All surgical procedures were performed under general intravenous anesthesia induced by continuous infusion of 1% propofol and remifentanyl with atracurium used for muscle relaxation.

Measurements included the absolute value and side-to-side ratio of the N20/P25 amplitude (symptomatic/asymptomatic). Normal outcome values were consistent with general recommendations: N20/

P25 $\geq 0.8 \mu\text{V}$ and side-to-side ratio of ≥ 0.5 , (Cruccu et al., 2008, Mauguiere et al., 1999) trial-to-trial amplitude variability $< 20\%$. ((Cruccu et al., 2008) Buchner, 2017, Facco et al., 2002) SEP were further monitored throughout the procedure until wound closure using a Cadwell Cascade system (Cadwell Instruments, Kennewick, WA, U.S.A.)

2.4. Clinical picture

Admission and preoperative finding were evaluated by a fully trained neurologist on duty, skilled in acute stroke management. Follow-up evaluation was done by one of two senior neurology consultants skilled in stroke management N.M. or R.M. at physical patient visit.

The following variables were evaluated and recorded: within several minutes of admission, NIHSS was scored (NIHSS-door) and pre-stroke functional status according to mRS. Right before transfer to the operating theatre, there were scored NIHSS again (NIHSS-CEA) and muscle strength according to the Medical Research Council (MRC) score separately for each extremity (upper extremity, MRC-UE and lower extremity, MRC-LE). The MRC scores apply to the most affected extremity segment.

Overall functional status according to mRS, as an independent outcome measure, was assessed 3 months after surgery (mRS-3M).

2.5. Statistical analysis

Analyzed outcomes included the following variables: NIHSS-door, NIHSS-CEA and MRC-UE, MRC-LE, absolute value of SEP amplitude (SEP-amp) and the side-to-side amplitude ratio of symptomatic/asymptomatic side (SEP-ratio). The 3-month outcome (outcome measure) was dichotomized into a favorable one defined as mRS 0–2, and an unfavorable one defined as mRS 3–6.

For the test of agreement, the group was dichotomized in electrophysiological parameters by the respective standard limits; regarding clinical variables (NIHSS, MRC), post-hoc analyses were performed for all possible dichotomizations. Only results with maximum robustness of the ϕ test are presented. The parts of dichotomized subgroups with lower NIHSS values, and higher MRC and SEP values were classified as positive ones, with the remaining parts of groups classified as negative ones. A favorable outcome was classified as a positive whereas an unfavorable one as a negative outcome.

Analyses were performed using the non-parametric Mann-Whitney U test, Spearman's correlation coefficient, and Pearson χ^2 test with Yates' correction. The limit of statistical significance was set at a $p = 0.05$. The analyses were performed using Statistica CZ v.12 software (TIBCO Software Inc., Palo Alto, CA, USA).

3. Results

Inclusion criteria were met by a total of 31 patients, of which number 4 (12.9%) were excluded due to neurophysiologist unavailability; hence, the group included 27 patients (92.6% males) with a mean age of 71.3 ± 8.3 years (range, 52–88 years).

3.1. Clinical findings in admission

In 19 (70.4%) cases, symptoms were apparent on their left side. Clinical presentations included transient ischemic attack (TIA) in 4 (14.8%), evolving stroke in 3 (11.1%) whereas a completed stroke was diagnosed in 20 (74.1%) cases. Objective findings on admission and immediately prior to surgery according to NIHSS criteria were as follows: median = 5.0; interquartile ratio (IQR) (2.0–10.0) or 6.0 and IQR (2.0–12.0), respectively both within a score range of 0–26. An unstable clinical deficit was observed in 12 (44.4%) patients. Muscle strength values in the affected upper extremity (MRC-UE) and lower extremity

(MRC-LE) were as follows: median 4.0, IQR (1.0–5.0) and 4.0, IQR (2.0–5.0), respectively. A speech disorder was diagnosed in 17 (63.0%) patients. A pre-stroke condition (classified as mRS 2) was only noted in 2 (7.4%) patients whereas the remaining 25 (92.6%) patients were asymptomatic (mRS 0).

3.2. Treatment

Intravenous thrombolysis (IVT) was undertaken in 16 (37.0%) patients, with a median door-to-needle time (DNT) of 35.0 (IQR, 32.0–36.0) minutes. Door-to-needle time is the time elapsed between the patient entering the first door of the hospital and start of thrombolytic therapy. It is an indicator of the in-hospital logistic process in AIS management. Door-to-flow time (DTF) was 265 (IQR, 185–370) minutes. Door-to-flow time is the time elapsed between the patient entering the first door of the hospital and restoration of blood flow through occluded vessel. It is an indicator of the in-hospital logistic, diagnostic and treatment process in AIS with LAO. Onset-to-flow time (OTF) was known in 22 (81.5%) patients with a median of 330 (IQR, 220–550) minutes, while OTF was unavailable in the remaining 5 (18.5%) patients (See Table 1). Onset-to-flow time as the time between symptom onset and restoration of blood flow through the occluded vessel gives the overall duration of vessel occlusion and hypoperfusion in the occluded vessel territory.

3.3. Evoked potentials

The somatosensory evoked potentials of the median nerve were measurable bilaterally in all patients. The absolute values of and side-to-side differences in N20 wave latency were within normal in all patients. The absolute value of the N20/P25 amplitude (SEP-amp) was decreased ($< 0.8 \mu\text{V}$) in 5 (18.5%) whereas the SEP-ratio was decreased (< 0.5) in 4 (14.8%) patients.

3.4. Surgical internal carotid artery recanalization

Internal carotid artery recanalization was successful in 25 (92.6%) patients. One (3.7%) patient received a conventional extracranial-intracranial bypass in one session, with another one (3.7%) remaining non-recanalized due to the insufficient caliber of the superficial temporal artery.

Surgical complications occurred in a total of 5 (18.5%) patients including 3 (11.1%) cases of wound hematomas, all of which were treated by successful surgical revision. Shortly before the procedure, 2 of these patients had IVT, but their preoperative (after IVT and before

Table 1
Descriptive group statistics.

Variable	Average	CI \pm 95.0%	Median	IQR	SD
MRC-UE	3.0	(2.3–3.7)	4.0	(1.0–5.0)	1.9
MRC-LE	3.5	(2.8–4.2)	4.0	(2.0–5.0)	1.8
NIHSS-door	6.3	(3.8–8.8)	5.0	(2.0–10.0)	6.3
NIHSS-CEA	8.4	(5.4–11.4)	6.0	(2.0–12.0)	7.5
OTF	506.9	(313.3–700.3)	330	(220.0–550.0)	489.4
DTF	436.8	(249.6–624.6)	265	(185.0–370.0)	463.7
SEP-amp	1.5	(1.1–1.1)	1.4	(1.0–2.0)	0.9
SEP-ratio	0.9	(0.7–1.7)	0.9	(0.6–1.2)	0.4

MRC-UE, MRC-LE = muscle strength upper extremity, lower extremity, respectively; NIHSS-door, NIHSS-CEA = National Institute of Health Stroke Scale on admission, before carotid surgery, respectively; OTF = onset-to-flow time; DTF = door-to-flow time; SEP-amp, SEP-ratio = somatosensory evoked potentials amplitude absolute value on the symptomatic side, side-to-side amplitude ratio; CI = confidence interval; IQR = interquartile range; SD = standard deviation.

CEA) fibrinogen levels were within normal. Cranial nerve paresis developed in 3 (11.1%) patients (hypoglossal nerve in 2 and facial nerve in 1). There was no case of intracranial bleeding. All complications were managed successfully or normalized spontaneously within 3 months.

Total 3-month morbidity and mortality was 8 (29.6%). Permanent morbidity (lasting more than 3 months) and mortality rates reached 4 (14.8%).

3.5. Clinical follow-up

Two patients with negative NIHSS-CEA, SEP-amp and SEP-ratio values immediately after CEA required intensive post-resuscitation care.

Twenty-four (88.9%) patients had a follow-up visit at 3 months after stroke.

Functional independence (mRS 0–2) was achieved by 23 (85.2%) patients. One (3.7%) patient remained severely disabled (mRS 5). Remaining three (11.1%) patients died (mRS 6) within one month. The cause of death was multiorgan failure developing during intensive post-resuscitation care. Two of these patients experienced recurrence of stroke involving the ipsilateral vascular territory.

Muscle strength (MRC-UE and MRC-LE) values were as follows: median = 5.0 (IQR, 4.0–5.0) and 5.0 (IQR, 5.0–5.0), respectively. A speech disorder was noted in 6 (22.2%) patients.

Major comorbidity and risk factors occurrence did not differ between outcome groups (see Table 2).

3.6. Clinical outcome prediction

Both the Mann-Whitney U test and Spearman's correlation consistently revealed statistically significant differences and/or correlations for two clinical (NIHSS-CEA and MRC-UE) and two electrophysiological (SEP-amp and SEP-ratio) variables. Statistically the most significant for the SEP-ratio were a $p = 0.0001$ and/or an $r_s = 0.616$ (see Table 3).

Table 2
Comorbidities and pre-stroke risk factors.

Comorbidity / risk factor	3 month outcome groups (mRS-3M)				Statistical significance ($p = 0.05$)
	0–2		3–6		
	(n = 23)	(n = 4)			
Age	median (IQR)	82.0 (70.5–84.5)	70.0 (67.0–76.0)	1513	(NS)
Hypertension	No (%)	17 (73.9)	3 (75.0)	1.0000	(NS)
Diabetes	No (%)	9 (39.1)	1 (25.0)	0.6247	(NS)
Dyslipidemia	No (%)	15 (65.2)	2 (50.0)	0.5961	(NS)
Chronic kidney disease	No (%)	2 (8.7)	1 (25.0)	0.3804	(NS)
Congestive heart disease	No (%)	5 (21.7)	2 (50.0)	0.2613	(NS)
Atrial fibrillation	No (%)	2 (8.7)	0 (0.0)	0.5987	(NS)
Previous acute coronary syndrome	No (%)	1 (4.3)	1 (25.0)	0.1760	(NS)
Previous stroke	No (%)	4 (17.4)	1 (25.0)	0.7610	(NS)
Current smoking	No (%)	8 (34.8)	1 (25.0)	0.7383	(NS)

mRS-3M = modified Rankin scale 3 months after surgery; IQR = interquartile range.

Table 3

Mann-Whitney U test with correction to ties and Spearman's correlation (r_s) depending on mRS at 3 months (mRS-3M). Statistical significance and correlation of both neurophysiological variables, and SEP-ratio in particular, were higher compared with the other variables.

Variable	Z value	p	r_s
MRC-UE	-2.443	0.0107	0.486
MRC-LE	-1.317	0.2158	0.265
NIHSS-door	0.413	0.6688	0.088
NIHSS-CEA	2.544	0.0060	0.506
OTF	0.171	0.8693	0.040
DTF	0.036	0.9716	0.014
SEP-amp	-2.902	0.0008	0.576
SEP-ratio	-3.105	0.0001	0.616

CI = confidence interval; DTF = door to flow time; IQR = interquartile range; MRC-UE, MRC-LE = muscle strength upper extremity, lower extremity, respectively; mRS-3M = modified Rankin scale 3 months after stroke; NIHSS-door, NIHSS-CEA = National Institute of Health Stroke Scale on admission, before carotid surgery, respectively; OTF = onset-to-flow time; SD = standard deviation; SEP-amp, SEP-ratio = somatosensory evoked potentials amplitude absolute value on the symptomatic side, side-to-side amplitude ratio, respectively.

Except for NIHSS-door, all selected variables had a very high positive predictive value (PPV) for a favorable outcome $\geq 95\%$. Negative predictive values (NPVs) (except for the SEP-ratio) were within the range of 25–60%.

Among our 23 patients with a normal SEP-ratio, 9 of them (39.1%) had an unstable deficit, with the NIHSS value prior to CEA > 10 and with upper extremity muscle strength < 3 in 6 each, of which number upper extremity plegia was found in 2 patients (patients 15 and 25) (See Figs. 1, 2, 3). After a successful recanalization procedure, all patients with a normal SEP-ratio were capable of pursuing self-care activities and vice versa.

The SEP-ratio correlated fully with mRS-3M, that is, both PPV and NPV reached 100%. The phi coefficient (Matthews correlation coefficient) likewise showed full agreement between SEP-ratio and mRS-3M implying most accurate prediction of the clinical outcome by the preoperative SEP-ratio.

The sensitivity, specificity and ϕ values are shown in Table 4.

A false negative error (NIHSS ≥ 10 , MRC-UE 0, MRC-LE ≤ 2 , SEP-amp $< 0.8 \mu\text{V}$ as well as functional independence at 3 months (mRS-3M 0–2) occurred by NIHSS-door criteria in 5 (18.5%), NIHSS-CEA in 6 (22.2%), MRC-UE in 2 (7.4%), MRC-LE in 4 (14.8%), and SEP-amp in 2 (7.4%) cases. Only with SEP-ratio was no false negative error found. A summary of results is shown in Fig. 1.

4. Discussion

The present paper assessed the neuronal cortical activity of the sensory motor region prior to urgent surgical recanalization for acute extracranial ICA occlusion following systemic and/or endovascular recanalization.

4.1. Neuronal activity and perfusion

As both native and evoked neuronal activity and pathway conductivity are dependent on regional cerebral blood flow (rCBF), (Boysen, 1973, Branston et al., 1974, Florence et al., 2004, Hossmann and Kleihues, 1973, Hossmann et al., 1973, McPherson et al., 1986, Sharbrough et al., 1973) evoked activity decreases or even disappears with decreasing cerebral metabolic rate of oxygen (CMRO₂). (Nakagawa et al., 1984) Cortical neuronal activity correlates closely with brain perfusion and is a reliable marker of the development of fo-

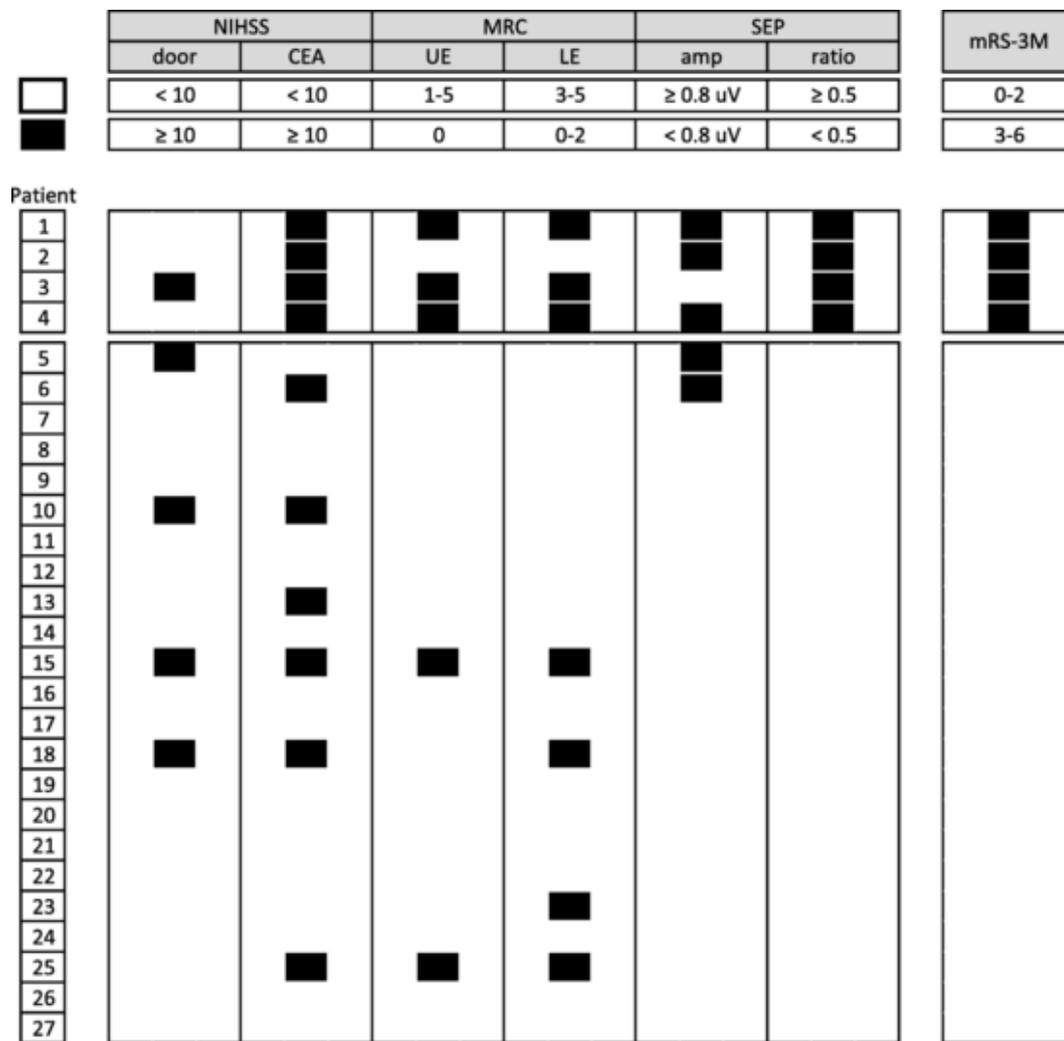


Fig. 1. Schematic representation of predictive factor values in our group of patients. Normal/favorable values are represented by white squares and abnormal/unfavorable values as black squares. Black squares (abnormal variables) associated with mRS-3M white square (favourable outcome) represent false negatives. Arranged by mRS-3M in descending order. (MRC-UE, MRC-LE = muscle strength upper extremity, lower extremity, respectively; mRS-3M = modified Rankin scale 3 months after stroke; NIHSS-door, NIHSS-CEA = National Institute of Health Stroke Scale on admission, before carotid surgery, respectively; SEP-amp, SEP-ratio, somatosensory evoked potentials amplitude absolute value on the symptomatic side, side-to-side amplitude ratio, respectively.)

cal brain ischemia. (Symon, 1980) The penumbra (also referred to as the “misery perfusion” region) is characterized by an rCBF of 15–20 ml/100 g/min, whereby neuronal activity also tends to decrease or even vanish, with neurons potentially surviving 3–4 h and longer in the penumbral region. (Baron, 1999, Markus, 2004) Neuronal activity resumption correlates inversely with the duration and depth of a preceding episode of hypoperfusion. (Hossmann and Kleihues, 1973, Hossmann et al., 1973, Lipton, 1999) While there have been reports of neurons surviving 30–48 h and longer in the penumbral region, (Heiss et al., 1992, Kalvach and Keller, 2007, Wise et al., 1983) the number of surviving neurons and/or tissue volume correlates inversely with the duration of hypoperfusion. Long-term survival of electrically silent neurons in the sensory motor cortex in the presence of a chronic ICA stenosis/occlusion has not been authoritatively documented. (Jussen et al., 2016, Ostry et al., 2007)

4.2. Hypoperfusion and evoked potentials

Somatosensory evoked potentials are a reliable marker of surviving neurons in mammals. (Branston et al., 1974, Hossmann et al., 1973, McPherson et al., 1987, Mizoi et al., 1987, Sharbrough et al., 1973) In a SEP response, a reduction in rCBF is associated, first,

with disappearance of late waves and a decrease in amplitude and, finally, disappearance of the primary somatosensory response to the N20/P25 potential. Median nerve SEP are generated in the posterior wall of the central sulcus, area 3b, receiving inputs from the hand, and projected to the scalp about 7 cm laterally from its midline (C3'/C4' electrodes). Both the primary somatosensory and motor hand cortical regions are located in the border zone of the MCA. The thalamocortical radiation is supplied by deep MCA branches. (Stejskal et al., 2001) SEP furnish direct information about somatosensory cortex integrity and thalamocortical radiation. Additionally, SEP may inform, though indirectly yet reliably, about neuronal activity of the neighboring primary motor cortex. Both the SEP amplitude and EEG frequency and amplitude correlate closely with changes in rCBF. (Florence et al., 2004) The technique of monitoring evolving brain ischemia by SEP measurement and EEG during CEA performed under general anesthesia is well established. (Florence et al., 2004, Stejskal et al., 2007) Compared with EEG, SEP are easier and quicker to measure as well as assess; besides, they are less sensitive to environmental interference.

Selective shunting during CEA is undertaken based on an ipsilateral decrease in SEP amplitude following ICA cross-clamping. (Ostrý and Stejskal, 2010, Stejskal et al., 2007) Motor evoked potentials (MEP) measurement during CEA is only marginally helpful in terms of

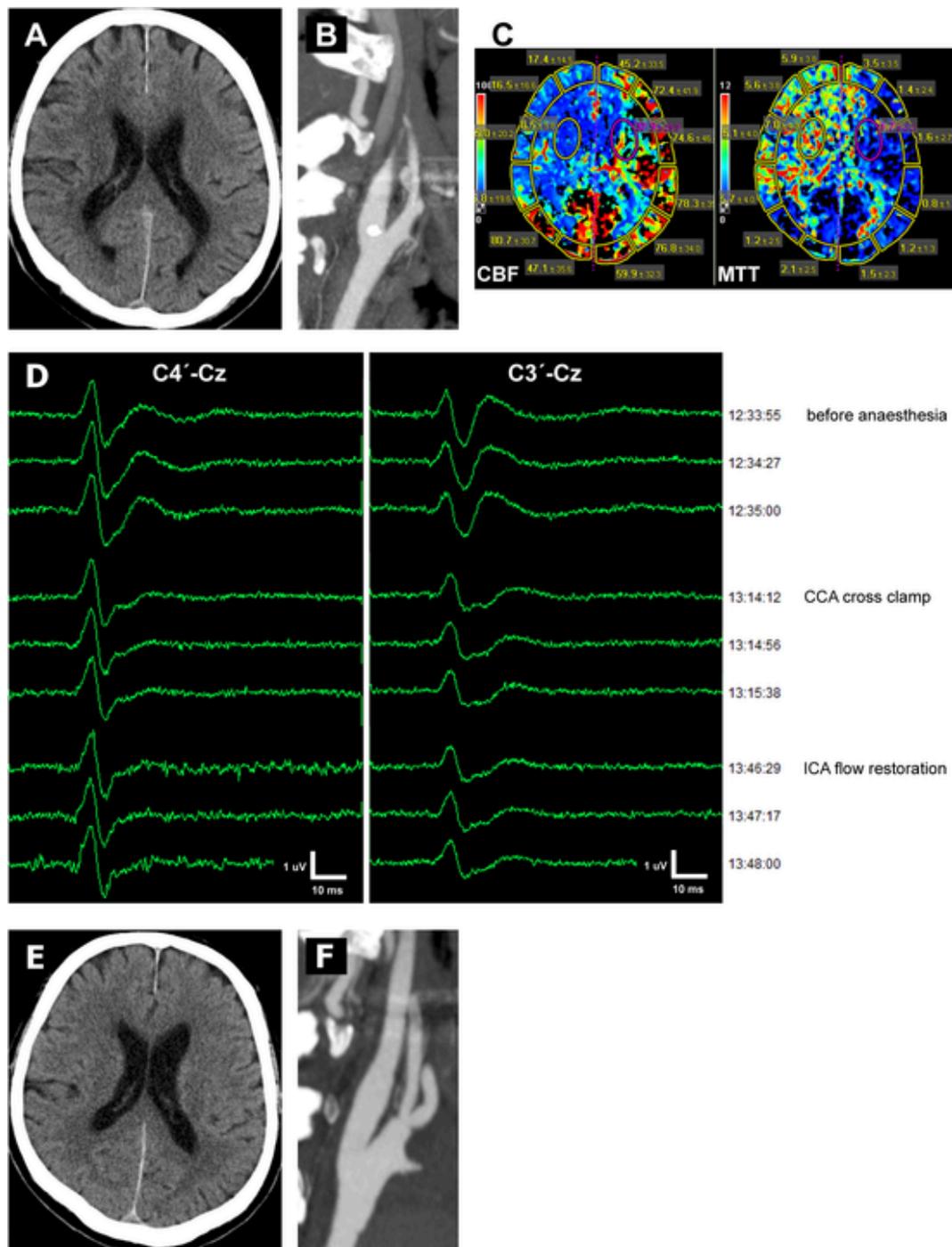


Fig. 2. Preserved preoperative SEP, NIHSS 19 before surgery (patient 15). Acute ischemic stroke with right ICA occlusion (A, B), right MCA, ACA hypoperfusion with CBF decrease and MTT prolongation (C) and preserved SEP on symptomatic side (D). **24 h after surgery:** nonenhanced brain scan without any ischemic changes (E) and patent right ICA (F). **3-month functional recovery** to minor symptoms (mRS 1) – very mild left arm paresis. (ACA = anterior cerebral artery; CBF = cerebral blood flow; DWI = diffusion weighted image; FLAIR = fluid-attenuated inversion recovery; ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin scale; MTT = mean transit time; NIHSS = National Institute of Health Stroke Scale; SEP = somatosensory evoked potentials.)

identifying “pure hemiplegia”, (Malcharek et al., 2013, Szelenyi et al., 2003) which develops, unlike territorial MCA hypoperfusion, due to perforator embolization/occlusion. As a result, SEP or, alternatively, EEG are more suitable tools for cortical perfusion quantification. (Florence et al., 2004, Stejskal et al., 2007) By contrast, MEP are more suitable for monitoring perfusion and motor pathway conductivity in white matter. (Neuloh and Schramm, 2004)

4.3. Internal carotid artery occlusion and somatosensory evoked potentials

Two main scenarios may occur following acute extracranial ICA occlusion: (1) The result is deep hypoperfusion with a severe clinical deficit and either decreased or non-elicitable SEP. To avoid ischemia development, reperfusion should be performed very quickly. (2) Hypoperfusion may be mild, with the degree of paresis likely to fluctuate and/or to gradually deteriorate, while SEP may be normal or insignifi-

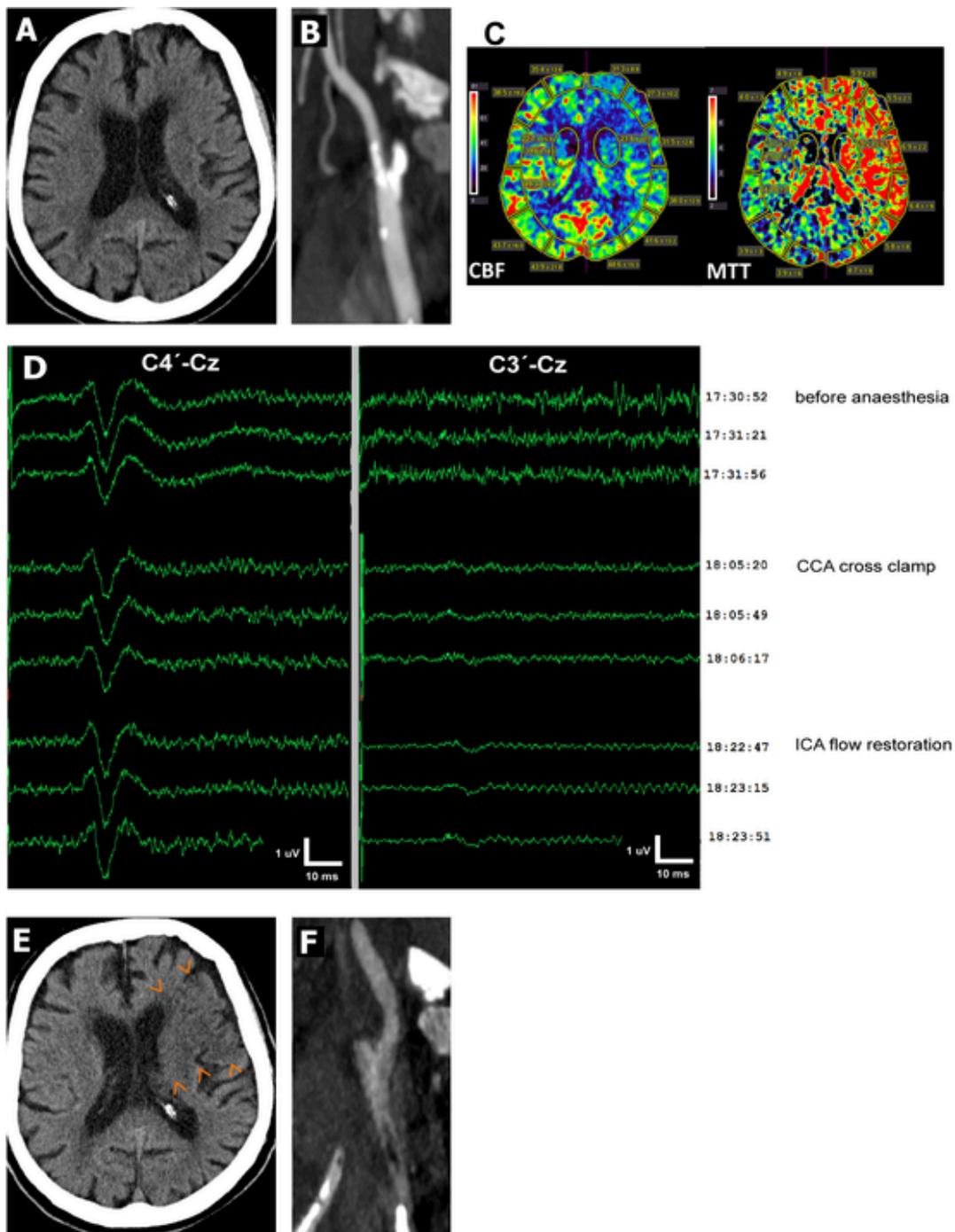


Fig. 3. Unilateral absent preoperative SEP, NIHSS 19 before surgery (patient 2). Acute ischemic stroke with left ICA occlusion (A, B), left MCA, ACA hypoperfusion with CBF decrease and MTT prolongation (C) and severely decreased median nerve SEP on symptomatic side (D) before and during surgery with no recovery after flow resumption. 24 h after surgery: left frontotemporal hypodensity (orange arrowheads) (E) and patent left ICA (F). 3-month functional outcome: severe disability (mRS 5) – severe right hemiparesis global speech disorder, bedridden and fully dependent. (ACA = anterior cerebral artery; CBF = cerebral blood flow; DWI = diffusion weighted image; FLAIR = fluid-attenuated inversion recovery; ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin scale; MTT = mean transit time; NIHSS = National Institute of Health Stroke Scale; SEP = somatosensory evoked potentials.)

cantly decreased to later disappear completely. The time window for recanalization is extended.

A characteristic feature of the first scenario is very quick insertion of an intraluminal shunt because of the ipsilateral decrease in SEP amplitude following ICA cross-clamping during CEA. (Stejskal et al., 2007) The second scenario should be opted for in an effort to manage an acute ischemic stroke secondary to ICA occlusion in a meaningful manner; otherwise ischemia develops before the patient has reached the hospital.

Second scenario probably took place in those nine patients with unstable and moderate neurological deficit and normal SEP-ratio that recovered after recanalization. All patients with a normal SEP-ratio recovered to self-sufficiency.

The difference in results between SEP-amp and SEP-ratio may be due to several causes: (1) The inter-individual variability of responses is much greater than the intra-individual one. (Buchner, 2017, Cruccu et al., 2008, 2008a, Facco et al., 2002, Chatrian, 1984) The ratio

Table 4

Robustness of clinical outcome prediction is high in terms of a positive outcome for all variables; it is, however, lower in terms of a negative predictor. Full correlation with functional status at 3 months post-stroke was achieved only with the SEP-ratio.

	Sens	Spec	PPV	NPV	χ^2	ϕ
MRC-UE < 1	91.3%	75.0%	95.5%	60.0%	6.02	0.6461
MRC-LE < 3	82.6%	75.0%	95.0%	42.9%	3.27	0.5375
NIHSS-door > 10	86.4%	25.0%	86.4%	25.0%	0.03	0.3182
NIHSS-CEA > 10	73.9%	100.0%	100.0%	40.0%	5.13	0.5437
SEP-amp < 0.8	91.3%	75.0%	95.5%	60.0%	6.02	0.6461
SEP-ratio < 0.5	100.0%	100.0%	100.0%	100.0%	19.66	1.0000

MRC-UE, MRC-LE = muscle strength upper extremity, lower extremity, respectively; NIHSS-door, NIHSS-CEA = National Institute of Health Stroke Scale on admission, before carotid surgery respectively; NPV = negative predictive value; PPV = positive predictive value; SEP-amp, SEP-ratio = somatosensory evoked potentials amplitude absolute value on the symptomatic side, side-to-side amplitude ratio, respectively.

of extreme values of the SEP-amp interval is > 10. The asymmetry of the SEP-ratio > 0.5 does not necessarily imply an abnormal decrease in amplitude on the symptomatic side, that is, a false positive result is more likely in SEP-amp than in SEP-ratio. (2) Anesthetics decrease SEP amplitude bilaterally. As SEP were measured after anesthesia induction, the anesthesia-related decrease in the N20/P25 amplitude, SEP-amp, may have produced a false negative more readily compared with the SEP-ratio. (See Table 3).

Shiban et al. suggested the possibility of predicting the clinical defect through SEP and upper extremity MEP measurement and monitoring prior to and during endovascular recanalization. (Shiban et al., 2016) The above authors reported complete agreement (NPV = 100%) in predicting an unfavorable outcome due to failure of ipsilateral SEP resumption (only 2 observations). This is fully consistent with our data for the SEP-ratio (with a standard limit of up to 0.5) (4 cases). The negative predictive value of SEP-amp was significantly lower (NPV = 60%). By contrast, the PPV (whereby a normal finding predicts a favorable outcome) was remarkably high, with a SEP-amp of 95.5% and SEP-ratio as high as 100%.

In cases of intracranial occlusion of the first MCA segment and basilar artery investigated by Shiban et al., one should also take into account – unlike ICA occlusion – impaired white matter perfusion, explaining the need for combining SEP and MEP but making the study protocol more difficult to be adhered to.

No time delay related to lead placement was observed or, worse still, to be a reason for failure to perform an examination.

Urgent CEA for an unstable or disabling deficit is not conclusively supported by earlier or recent guidelines. (Jauch et al., 2013, Powers et al., 2019) The morbidity and mortality rates after an urgent CEA are often in excess of 20%. (Benes et al., 2014) A significant proportion of reported unfavorable outcomes includes patients with ischemia completed already preoperatively as demonstrated by the SEP-ratio. Our group contains only 14.8% of patients with preoperative ischemia predicted by SEP-ratio.

Every effort should thus be made to perform urgent CEA only in cases whereby cortical neurons survive in the occluded artery territory. Indicating a patient for urgent CEA based on the status of neuronal survival in the Rolandic area may significantly improve the safety of the procedure while also likely improving the clinical outcome of patients with preoperatively completed ischemia, that is, an abnormal preoperative SEP-ratio, as they would not be exposed to the risks and complications associated with urgent CEA.

A similar, or even identical, technique of prediction could probably be applied to occlusions in the more distal ICA segments accessible

only to endovascular treatment. Intracranial occlusions involving also the posterior circulation affect blood flow through both grey and white matter at different rates and grades depending on the localization and length of the occlusion. Determination of the neuronal activity and axonal conductivity would likely require simultaneous verification of the integrity of several eloquent zones, their interface and projection pathways. The main limitation of multimodal evoked potentials and functional imaging by functional magnetic resonance is that it is time consuming.

4.4. Predictive outcome models

The most important and most often used clinical outcome predictors include age, NIHSS and time to recanalization. (Chen and Winstein, 2009) In our group of patients, clinical outcome was not shown to be dependent on OTF or DTF. The closest correlation between clinical factors and outcome measures was found with the SEP values.

Electrophysiological predictors of motor function recovery usually include corticospinal tract (CST) integrity or excitability of the primary motor cortex (PMC). (Hendricks et al., 2003, Pizzi et al., 2009) Some techniques have been reported to induce neuronal plasticity resulting in improved function. (Di Lazzaro et al., 2010) The value of this technique of prediction lies in selecting the strategy of the rehabilitation program and treatment. Multiple prediction neurophysiology-based techniques using EEG have emerged to be used in acute stroke. (Shiban et al., 2016, Wu et al., 2016) These techniques can provide more precise information compared with imaging techniques. (Wu et al., 2016) The potential of these examinations is believed to be in aiding the decision-making process regarding recanalization treatment.

The SEP-ratio may also be another contribution to Rolandic cortex assessment, which could help support and increase caution in urgent occluded artery recanalization.

5. Advances, limitations, and perspectives future lines of research

The main strength of our study is the direct assessment of neuronal activity in the hyperacute stage of stroke just before ICA recanalization. Preoperative measurement of SEP furnishes information about the status of the target brain function while not extending time to recanalization. To the best of our knowledge, ours is the first study predicting the clinical outcome prior to urgent surgical recanalization of acute ICA occlusion while showing that inclusion of SEP measurement is not associated with any delay. Our data independently and consistently document a correlation between direct evidence of neuronal function/activity and clinical outcome. (Shiban et al., 2016)

A limitation of the present study is that it included a relatively small and highly selected group of patients enrolled in a single center. Our strict criteria were selected to reduce the heterogeneity of the group to better allow for testing our hypothesis. Use of softer criteria could potentially affect SEP values by other factors not associated with stroke and, hence, data bias. Our post-hoc clinical variables (NIHSS and MRC) dichotomization into mild/severe symptoms is just another limitation. However, any consistent clear definition of mild or minor stroke based on the clinical picture does not exist yet. (Fischer et al., 2010) Nonetheless, the study was a prospective one with only 4 patients excluded due to the unavailability of a neurophysiologist to perform urgent preoperative SEP measurement. Our data should therefore be tested for robustness in a larger and more heterogeneous group of patients.

Evidence of neuronal cortical activity in the vascular territory of the occluded artery could serve as a “tissue window” prior to recanalization and could thus significantly contribute to further specifying the indication for urgent ICA recanalization, which could possibly become a “third line” treatment for acute ischemic stroke. (Fiedler et al., 2019,

Klugar et al., 2020) The permanent morbidity and mortality rates of 14.8% are lower by half compared with the risk of early deterioration associated with persisting LAO. (Rajajee et al., 2006)

6. Conclusion

Measurement of the median nerve SEP is feasible and provides for reliable assessment before urgent surgical ICA recanalization without extending time to recanalization. The side-to-side amplitude ratio of preoperative scalp median SEP with a limit of 0.5 seems to be promising and an exceptionally reliable both positive and negative predictor of clinical outcome after urgent surgical recanalization of acute internal carotid artery occlusion.

Surgical urgent ICA recanalization based on the preoperative SEP-ratio might become a safe and effective third-line option in acute ischemic stroke therapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Footnotes

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