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学位論文

Intraoperative transcranial facial motor evoked potential monitoring in surgery of cerebellopontine angle tumors predicts early and late postoperative facial nerve function

（小脳橋角部腫瘍手術における経頭蓋刺激顔面運動誘発電位モニタリングを用いた術後早期および長期の顔面神経機能予測）

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論　文　内　容　要　旨（和　文）

学位論文題名	Intraoperative transcranial facial motor evoked potential monitoring in surgery of cerebellopontine angle tumors predicts early and late postoperative facial nerve function (小脳橋角部腫瘍手術における経頭蓋顔面運動誘発電位モニタリングを用いた術後早期および長期の顔面神経機能予測)

【目的】脳幹と小脳の間に位置する小脳橋角部には、聴神経腫瘍や髄膜腫などが発生するが、これらに対する摘出術では顔面神経機能の温存が大きな課題である。その原因の一つとして、顔面神経の状態を術中にリアルタイムに把握することが困難な点が挙げられる。一方、これまで上下肢の機能については、経頭蓋電気刺激により運動野を興奮させて活動電位（MEP）をモニタリングする方法が普及・実用化している。しかし、Facial MEP (FMEP)は刺激する頭皮と記録する顔面筋が近いため安定した波形を得ることが難しい上、術後顔面神経機能との十分な相関も確立されておらず普及には至っていなかった。本研究では、我々が新たに考案した刺激法を用いて、術中の FMEP が安定的に評価可能かどうか、ならびに、その振幅の変化と術後顔面神経機能の関係を後方視的に検討することを目的とした。

【方法】2011 年から 2018 年までに当科で FMEP モニタリング下に小脳橋角部腫瘍摘出術を施行した 73 症例を対象とした。顔面神経機能は House-Brackmann (HB) 評価法を用い、grade I-II を機能良好、grade III-VI を機能不良群とし、術後早期（術後 1 週間以内）および術後長期（術 1 年後）に評価を行った。刺激電極は Cz を陰極、C3/C4 を陽極とし、記録電極は口輪筋に設置した。今回新たに考案した刺激法として、二相性・定電流・閾値上刺激強度を組み合わせた刺激設定を用いた。手術開始後に基準となる振幅を設定し、それに対する術中振幅の変化率（振幅比）を評価した。術中の最小振幅比 (MBR)、手術終了時振幅比 (FBR)、術中の回復値 (RV = FBR-MBR) を指標にして、術後早期および長期の顔面神経機能との相関を統計学的に調査した。

【結果】73 例中 62 例で評価が可能だった。改良した刺激法により刺激アーチファクトが排除され基線の安定した FMEP 波形が得られ、振幅評価の正確性が向上した。刺激による体動も抑制でき顕微鏡操作を中断する必要はなかった。術後早期における顔面神経機能不良群は 22 例で、そのうち 8 例は術後長期でも改善が見られなかった。術後早期に顔面神経麻痺が出現するか否かは術中最少振幅比と強い相関があり、振幅比が 35%以下までの低下をカットオフとすると感度 0.91、特異度 0.95 で予測が可能であった。振幅比が 35%を下回った場合でも手術操作を中止すると回復することが多く、その回復値と長期的な顔面神経機能(HB グレード)の改善度に相関 (r = 0.68, P = 0.001)が見られた。

【結語】新たな FMEP の刺激法は、正確な評価可能な波形が得られた。新たな指標として、術後早期の予測には MBR が、術後長期の顔面神経麻痺の回復度合いの推定には RV が有用であった。本研究で得られた知見を、手術の際の判断に生かすことで、小脳橋角部の腫瘍における顔面神経機能温存につながることが期待される。

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Abstract

Objective: Preserving facial nerve function (FNF) during tumor resection surgery is crucial in the cerebellopontine angle (CPA), a space between the brainstem and the cerebellum. Facial motor evoked potential (FMEP) can help to monitor the FNF continuously. However, it is difficult to steadily elicit FMEP due to the short distance between the stimulating and the recording electrodes. Also, there is no clear evidence about the relationship between intraoperative FMEP changes and postoperative FNF, which has limited its practical application. Here, we aimed to determine whether a special stimulation method can improve FMEP monitoring accuracy and to propose a novel method that predicts FNF calculated from drop and recovery of FMEP amplitude ratio during the CPA tumor surgery.

Methods: We enrolled 73 patients with a CPA tumor and used a biphasic, constant current, and suprathreshold stimulation (BCS) protocol to record FMEP of the orbicularis oris. We classified FNF into two groups using House–Brackmann (HB) grading system into satisfactory (HB grades I and II) and unsatisfactory (HB grades III to VI), according to the early and the late (1year later) postoperative period. We measured the intraoperative minimum-to-baseline amplitude ratio (MBR), the final-to-baseline amplitude ratio (FBR), and the recovery value (RV). RV was measured by subtracting MBR from FBR. We statistically evaluated FNF both at early postoperative (EP) and late postoperative (LP) periods using those values.

Results: We successfully obtained 62 FMEP readings. Using the BCS protocol, we obtained FMEP with a better-stabilized waveform baseline than the previous method. Facial palsies occurred in 22 patients during the EP period and persisted in eight patients during the LP period. Both MBR and FBR showed a significant correlation; however, the MBR had a superior correlation with FNF in the EP period. The number of optimal cutoff MBR was at

35%, with a sensitivity of 0.91 (95% CI 0.78–0.96) and a specificity of 0.95 (95% CI 0.88–0.98). There was a good relationship between RV and FNF (i.e., improving HB grade) during the LP period ($r = 0.68$, $P = 0.001$).

Conclusions: MBR can be an intraoperative predictor of FNF in the EP period. RV is a new and useful predictor of FNF recovery. The new findings can help in surgical decision-making that can lead to the preservation of FNF in CPA tumor surgery.

Abbreviations

AUC	Area under the curve
BCS	Biphasic, constant current, and suprathreshold stimulation
CI	Confidence intervals
CMAP	Compound muscle action potentials
CPA	Cerebellopontine angle
CSF	Cerebrospinal fluid
DES	Direct electrical stimulation
EP	Early postoperative
FBR	Final-to-baseline amplitude ratio
FMEP	Facial motor evoked potential
FNF	Facial nerve function
HB	House–Brackmann
ISI	Inter-stimulus interval
MBR	Minimum-to-baseline amplitude ratio
LP	Late postoperative
ROC	Receiver operating characteristic
RV	Recovery value
TES	Transcranial electrical stimulation
VS	Vestibular schwannoma

1. Introduction

The cerebellopontine angle (CPA) is a deep and narrow space between the brainstem and the cerebellum. Neurosurgeons consider this area as one of the most challenging operative areas that required sophisticated surgical approaches. A variety of tumors, such as vestibular schwannomas, meningiomas, and epidermoid cysts, can develop in the CPA (Fig. 1-1), where several cranial nerves, including the facial nerve, exist within this narrow space. The CPA's tumors can displace, encase, or stretches the cranial nerves. The severity of stretching can be so significant to the level where the nerve turns into a translucent membrane, often invisible and difficult to find by neurosurgeons, even with the help of an operative microscope. Preserving the facial nerve function (FNF) after CPA tumor surgeries is necessary for the patient's quality of life. Advanced neurosurgical training will not be enough alone to preserve the facial nerve structure, but also the development and validation of intraoperative electrophysiological monitoring protocols of the facial nerve are of great importance.

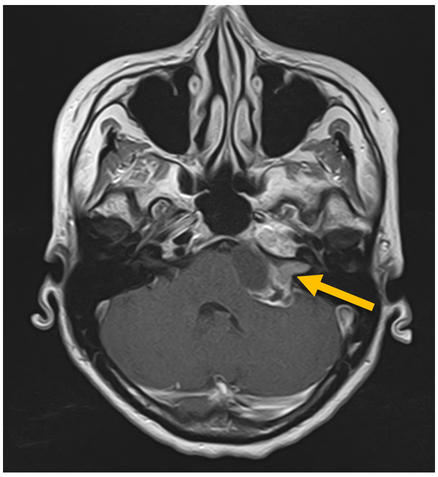

Fig. 1-1. An axial T1-weighted magnetic resonance imaging scan with contrast administration, showing a vestibular schwannoma in the left cerebellopontine angle (arrow).

1.1 Direct electrical stimulation

Direct electrical stimulation (DES) is the standard, most straightforward, and most widely used facial nerve monitoring technique. During CPA surgery, the operator using a probe applies a direct electrical stimulation to the nerve's surface to elicit compound muscle action potentials (CMAP) recorded through a paired electrodes inserted on the patient's ipsilateral facial muscles (Fig. 1-2). It allows us to identify the anatomical locations of the facial nerve in the vicinity of the tumor. This step represents the first step to guard against facial nerve dysfunction. However, identification of the facial nerve is not always achieved in the early stages of the surgery.

Many reports attempted to predict FNF outcome after tumor removal through evaluating the amplitude of evoked CMAP (Harner et al., 1988; Selesnick et al., 1996), stimulation threshold (Sughrue et al., 2010), and proximal-to-distal amplitude ratio (Taha et al., 1995). However, these methods can only be applied after identifying the nerve near the brainstem (Romstock et al., 2000; Acioly et al., 2013).

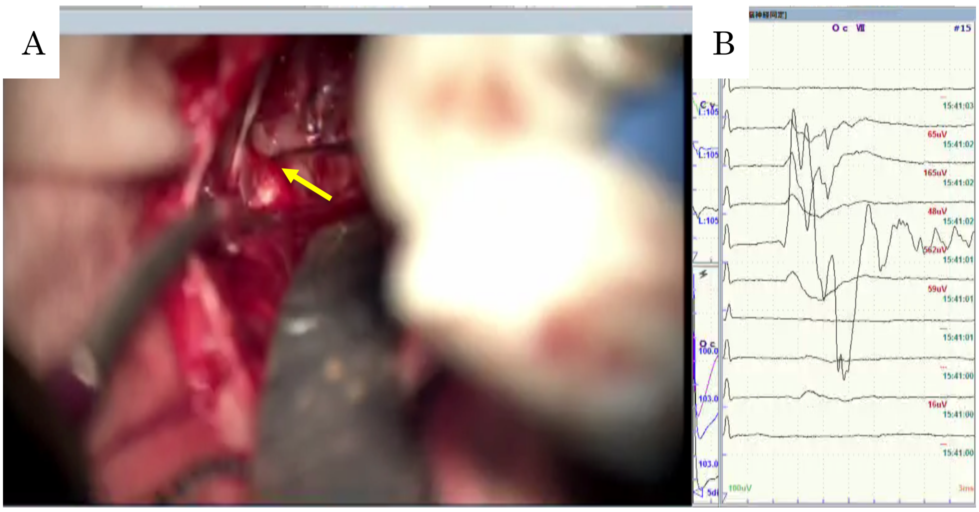

Fig. 1-2. (A) An intraoperative surgical microscope image showing stimulation of the facial nerve next to the tumor using mono-probe (arrow). (B) A screenshot showing the evoked compound muscle action potentials (CMAP) recorded from the ipsilateral facial muscles.

1.2 Transcranial electrical stimulation

Facial motor evoked potential (FMEP) monitoring by transcranial electrical stimulation (TES) was introduced by Dong et al. (2005); it provides information on the integrity of the whole facial nerve pathway (Macdonald, 2006; Sala et al., 2007) and allows the monitoring of FMEP before the identification of the facial nerve around its root exit zone in the brainstem, even in cases of surgery where it is difficult to identify the nerve. However, FMEP still has some limitations due to the short distance between the stimulating and the recording electrodes. It can be problematic to accurately read and measure FMEP waveforms that are contaminated with stimulation artifacts, especially when the baseline of the MEP recording is drifted by a monophasic electrical stimulation (Fig. 1-3). In addition, a high stimulation intensity, such as a supramaximal intensity, may induce patient body shaking (Amano et al., 2011), and significant stimulation artifacts in FMEP waveforms (Dong et al., 2005). Here, we introduce a novel FMEP monitoring technique with biphasic, constant current, and suprathreshold stimulation (BCS) to overcome the aforementioned issues.

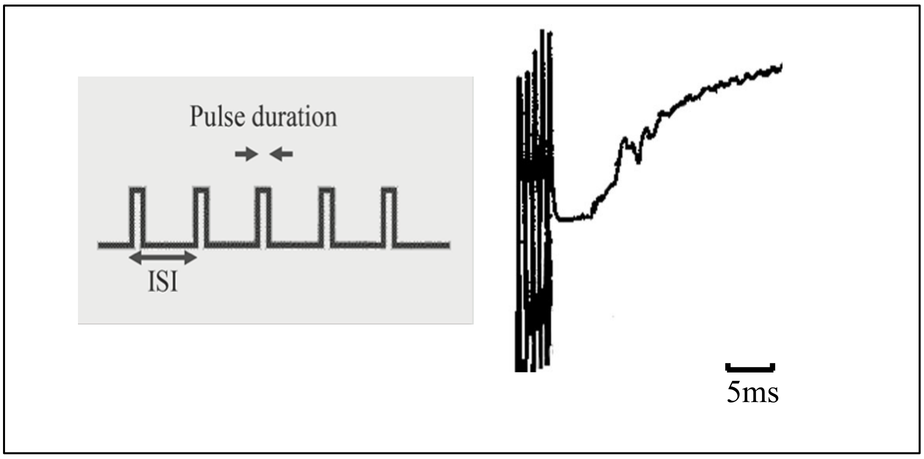

Fig. 1-3. Monophasic stimulation pulse (left) and waveform of facial motor evoked potential (right). The monophasic stimulation affects the waveform drifting; thus, it is hard to measure the amplitude accurately. (ISI, inter-stimulus interval.)

Most previous studies have estimated FNF using the final-to-baseline amplitude ratio (FBR) of FMEP, which represents the final MEP amplitude value measured in the surgery; however, only a few studies have reported the association between intraoperative FMEP and FNF not only in the early postoperative (EP) period but also in the late postoperative (LP) period (Acioly et al., 2011). These studies have predicted the long-term recovery of facial palsy if observed immediately after surgery. In this study, we attempted to clarify the capability of postoperative facial palsy prediction using a novel protocol of FMEP (BCS) and to identify predictive indices associated with facial palsy during the EP or LP period. We evaluated previously reported indices, such as FBR and minimum-to-baseline amplitude ratio (MBR), which represents the lowest value during surgery. We also evaluated a new index, recovery value (RV), which is calculated by subtracting MBR from FBR, representing the extent of amplitude recovery during surgery.

2. Methods

2.1. Study design and patient selection

We conducted a retrospective study by reviewing records of the patients. We enrolled 73 patients undergoing CPA and petro-clival region tumor resections under intraoperative FMEP monitoring, from September 2011 to May 2018 at the Fukushima Medical University Hospital. They did not have preoperative facial nerve palsy and were not subjected to reoperation within one year after the first surgery. We categorized FNF of the patients using the House–Brackmann (HB) grading system (Table. 2-1) (House et al., 1985) within one week of the surgical resection (i.e., during the EP period) and 1 year after (i.e., during the LP period). Expert faculty neurosurgeons assessed the FNF.

Table 2-1. The House-Brackmann's (HB) facial nerve grading system.

Grade	Description	Characteristics
I	Normal	Normal facial function in all areas
II	Mild dysfunction	Gross: slight weakness noticeable on close inspection; may have very slight synkinesis At rest: normal symmetry and tone Motion Forehead: moderate to good function Eye: complete closure with minimum effort Mouth: slight asymmetry
III	Moderate dysfunction	Gross: obvious but not disfiguring difference between two sides; noticeable but not severe synkinesis, contracture, and/or hemifacial spasm At rest: normal symmetry and tone Motion Forehead: slight to moderate movement Eye: complete closure with effort Mouth: slightly weak with maximum effort
IV	Moderately severe dysfunction	Gross: obvious weakness and/or disfiguring asymmetry At rest: normal symmetry and tone Motion Forehead: none Eye: incomplete closure Mouth: asymmetric with maximum effort
V	Severe dysfunction	Gross: only barely perceptible motion At rest: asymmetry Motion Forehead: none Eye: incomplete closure Mouth: slight movement
VI	Total paralysis	No movement

2.2. Ethical statement

The Fukushima Medical University research ethics committee approved the study (approval number 1390), and all patients provided written informed consent before their enrollment.

2.3. Anesthesia

Anesthesia induction was performed using a bolus injection of propofol (1.5–2.0 mg/kg) and remifentanil (2 mg/kg) under bispectral index monitoring; the target control infusion of propofol was maintained at a concentration of 2.5–3.0 μg/ml in the brain. All patients received rocuronium bromide bolus injection (0.6 mg/kg) before intubation. Additional muscle relaxant agents were not infused during surgery.

2.4. Transcranial Electrical Stimulation

We used the MEE 1200 series system (NIHON KOHDEN, Tokyo, Japan) for intraoperative monitoring. We placed corkscrew electrodes subdermally on the scalp at the C3, C4, and Cz locations, in accordance with the international 10 to 20 electrode placement system (Fig. 2-1). The cathode was in the Cz location and the anode in the C3 or C4 location to stimulate the corresponding facial motor area contralateral to the tumor side.

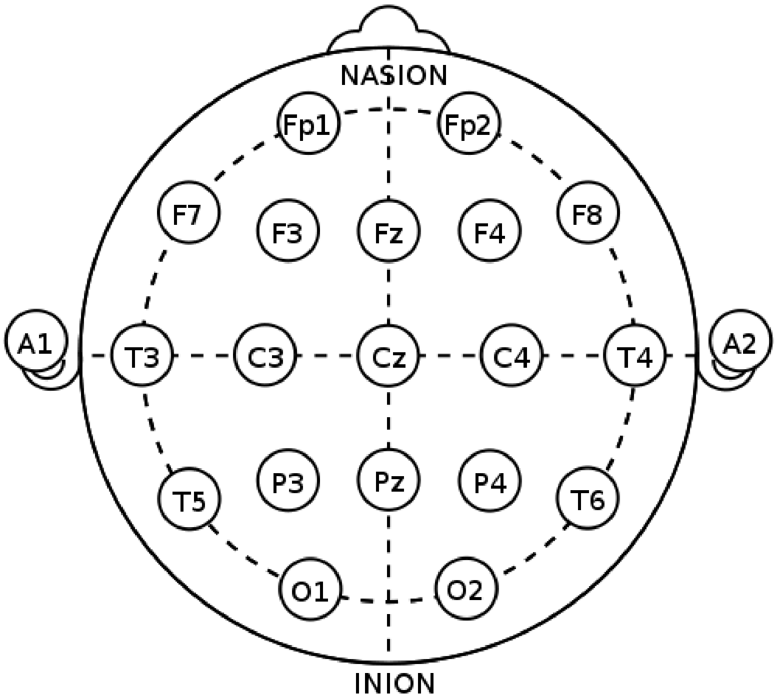

Fig. 2-1. The international 10-20 system is seen from above the head. (Abbreviations: A, Ear lobe; C, central; P, parietal; F, frontal; Fp, frontal polar; O, occipital; T, temporal.)

We applied the stimulation with a constant current of rectangular symmetrical biphasic pulses in trains of five to eight pulses (Fig. 2-2). The pulse duration was 0.2 ms (for each of the negative and positive phases) with an inter-stimulus interval of 1.4–1.6 ms. When FMEP was difficult to induce, we used a multi-train (double or triple) TES at an inter-train interval of 50–100 ms. We set the stimulation intensity to a suprathreshold level that could elicit an FMEP with at least 100 μV. In most cases, we were able to elicit FMEP amplitude of approximately 300 μV at baseline and calibrated the thenar muscle MEP amplitude ipsilateral to the tumor side to avoid a significant difference from FMEP amplitude. The baseline amplitude was recorded while opening the dura. The stimulation intensity was 200 mA at its maximum. To avoid a false negative reading due to peripheral facial nerve excitations by subcutaneous electrical current leaks (Ulkatan et al., 2007; Tellez et al., 2016), we applied a single pulse stimulus to confirm the absence of elicited waveforms (Fig. 2-3 and 2-4).

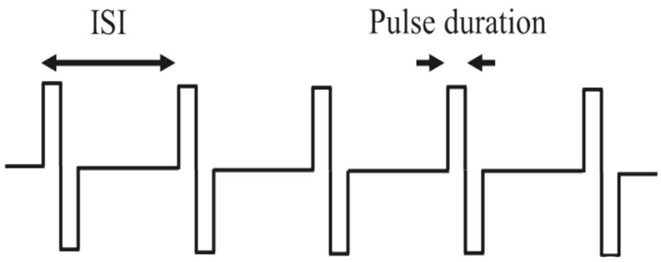

Fig. 2-2. Biphasic stimulation is composed of rectangular symmetrical biphasic pulses. The pulse duration was 0.2 ms (for each of the negative and positive phases) with an inter-stimulus interval (ISI) of 1.4–1.6 ms.

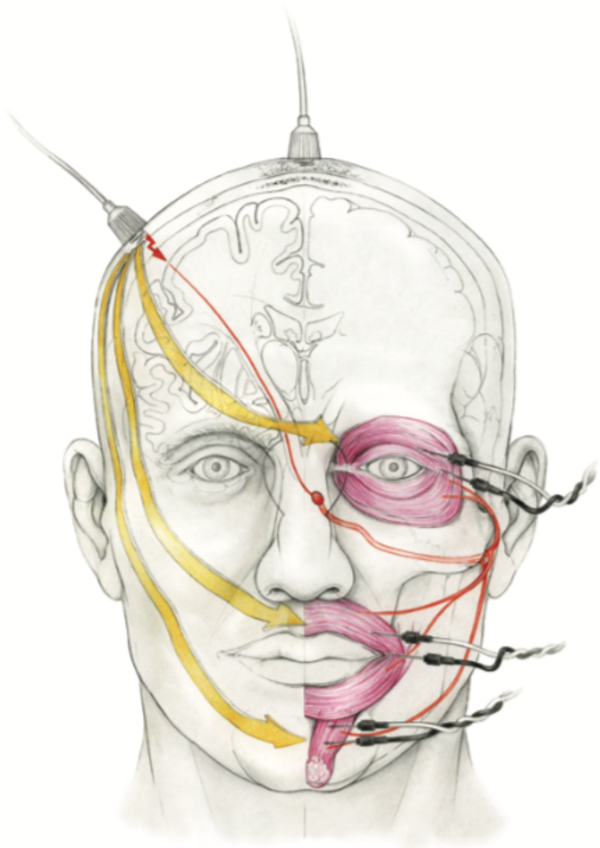

Fig. 2-3. Illustration showing the activation of the corticobulbar tract versus peripheral facial nerve excitation of facial nerve target muscles. During activation of the corticobulbar tract, anodal stimulation of the motor cortex (*red arrow*) elicits activation of lower motor neurons in the facial nerve nucleus of the brainstem, from which facial nerve target muscles are activated. As a confounder, peripheral stimulation (yellow arrows) may also active facial nerve target muscles, albeit at shorter latencies and already in response to single stimulation pulses. This may lead to false negative reading. *Reprinted with permission from (Sarnthein et al.).*

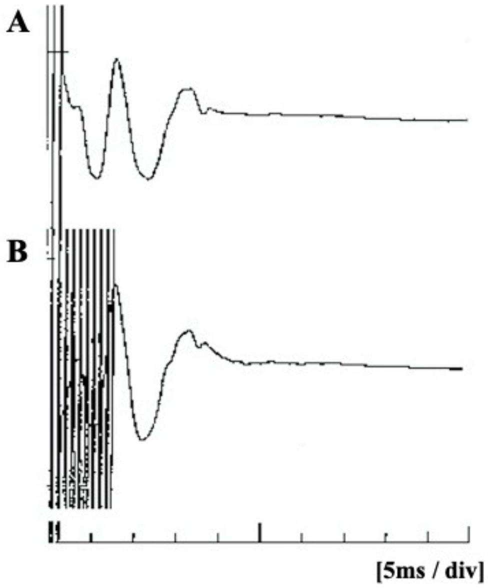

Fig. 2-4. FMEP waveform elicited by a single and train pulse stimulus
Example of Facial motor evoked potential waveform response to single stimulation pulses (i.e., current leaks) (A). Even with train stimulation, the same latency waveform is elicited the same as with the single stimulation and masked in the train stimulation artifact (B).

2.4. Motor Evoked Potential Recording

We used a pair of needle electrodes to record FMEP from the orbicularis oris muscle. We set the filter at 20 Hz (low-bandpass) and 1.5 kHz (high bandpass). As a control, we simultaneously recorded the ipsilateral thenar muscle MEP to detect FMEP changes due to factors unrelated to surgery (anesthetic fading, body temperature changes, and CSF leaks) (Lyon et al., 2005; MacDonald, 2017). When any of these changes were observed, we adjusted the stimulation intensity for FMEP by 5%–15% to maintain constant thenar muscle MEP amplitude. Because FMEP amplitude was variable in each recording, we considered FMEP amplitude change as significant when it disappeared or the amplitude ratio decreased to <50% in three consecutive recordings. When this occurred, an initial alarm was raised to the operating surgeon by the monitoring technician. FMEP recording using TES was usually performed intermittently with other intraoperative monitoring (see below) at intervals of 5 min. We recorded FMEP more frequently during the microsurgical stages while in proximity to the facial nerve or a presumption of an impending drop in FMEP amplitude. Moreover, the surgeon interrupted the procedure or changed the operative region whenever facial nerve damage was suspected.

2.5. Other intraoperative monitoring

In this study, all patients with CPA tumors underwent brainstem auditory evoked potential monitoring. In addition, the free-running electromyography was monitored continuously in all patients. Furthermore, we evoked the compound muscle action potential (CMAP) using DES for safer surgical exploration of the facial nerve when the anatomy of the facial nerve was unclear (e.g., vestibular schwannoma or large petroclival meningioma).

2.6. FNF outcome prediction indices

The first indices used for FMEP assessment during surgical procedures are the amplitude ratios (amplitude ratio (%) = intraoperative amplitude/baseline amplitude × 100). These ratio indices include 1) MBR and 2) FBR. MBR was the lowest value during surgery, and FBR was usually recorded after closing of the dura. If the intraoperative FMEP was higher than the baseline amplitude, the amplitude ratio could be more than 100% (Fig. 2-5). Furthermore, we established a new index for evaluating the degree of FMEP recovery at the end of the operation as RV and calculated it by subtracting MBR from FBR.

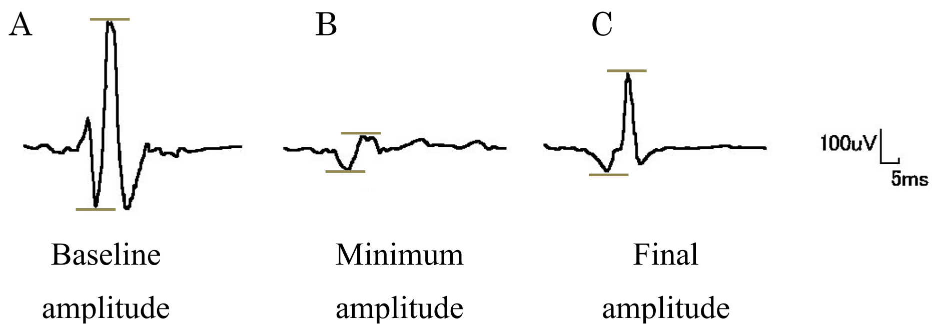

Fig. 2-5. Example of waveforms from baseline after dura opening (A), the minimum (B), and the final after tumor resection (C). The ratio of baseline amplitude to minimum amplitude was defined as MBR; the ratio of baseline amplitude to final amplitude, as FBR.

2.7. Statistical analysis

We classified FNF into two groups according to the EP period: satisfactory (HB grades I and II) and unsatisfactory (HB grades III to VI). We followed up with patients of the unsatisfactory group in the EP period and further categorized their FNF into either recovery (HB grades I and II) or persistent (HB grades III to VI) groups in the LP period.

I. *Prediction of FNF in the EP period*. We compared the calculated MBRs, FBRs, and RVs between the FNF-satisfactory and -unsatisfactory groups using Spearman correlation coefficients. In addition, logistic regression analysis was performed using a forced entry method to ascertain the associations of prospective confounders preserving FNF: MBR, FBR, gender, age, tumor size (maximum diameter on axial image of an MRI at the level of internal acoustic canal), and surgical approach. If any multicollinearity existed between any two variables, they were not included together in the same logistic regression analysis. Moreover, the optimal cutoff points of MBR and FBR were investigated.
II. *Prediction of FNF in the LP period.* We compared the calculated MBRs, FBRs, and RVs between the recovery and persistent groups using Spearman's correlation coefficients and calculated the optimal cutoff value of the highly correlated indices using a contingency table analysis. Moreover, we analyzed the correlation between the improvement degree of HB grade and the three indices without classification into the FNF-outcome groups using Spearman's correlation coefficients in the group of patients with facial nerve palsy in the EP period.

We evaluated the area under the curve (AUC) using the receiver operating characteristic (ROC) curve analysis for significant factors to obtain an optimal cutoff value, and we calculated 95% confidence intervals (CI) for ratios. We found no defective data and included all outliers in our statistical analysis. We set the significance in all our tests at $P < 0.05$ and used the IBM SPSS Statics 25.0 software (Mac client version, IBM, Armonk, NY, USA) to conduct all statistical analyses.

3. Results

3.1. Feasibility of FMEP with the BCS protocol

Using the BCS protocol, we obtained FMEP with better-stabilized waveform baseline than the monophasic stimulation method (Fig. 3-1); we could assess compound muscle action potentials in 62 patients (Fig. 3-2). We excluded 11 patients because of FMEP-related problems, such as peripheral facial nerve activation by a current leak (7 patients) and difficulty in eliciting stable waveforms due to high stimulation threshold (4 patients). Table 3-1 represents a summary of the patients' characteristics. The data for 62 patients are summarized and displayed in Appendix: Supplementary Table 1.

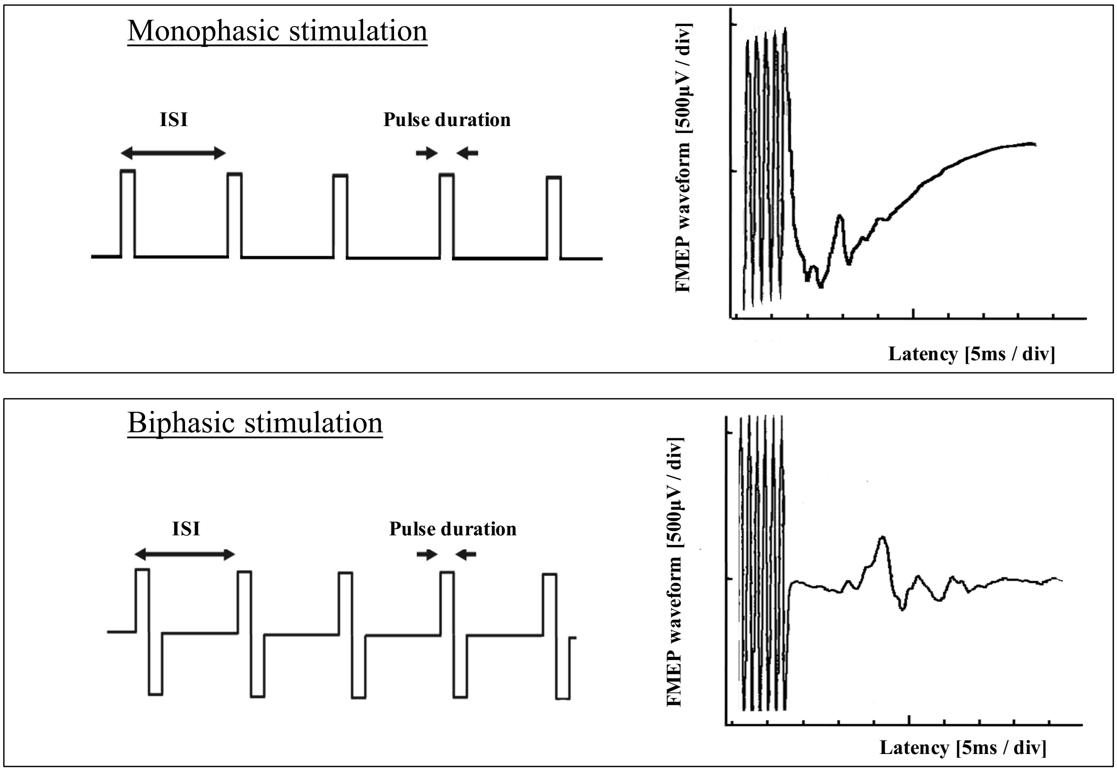

Fig. 3-1. Stimulation pulse and waveform types.
Facial motor evoked potential waveform differences between the monophasic (upper) and biphasic stimulation (lower). The biphasic stimulation shows a semi-horizontal baseline waveform pattern.

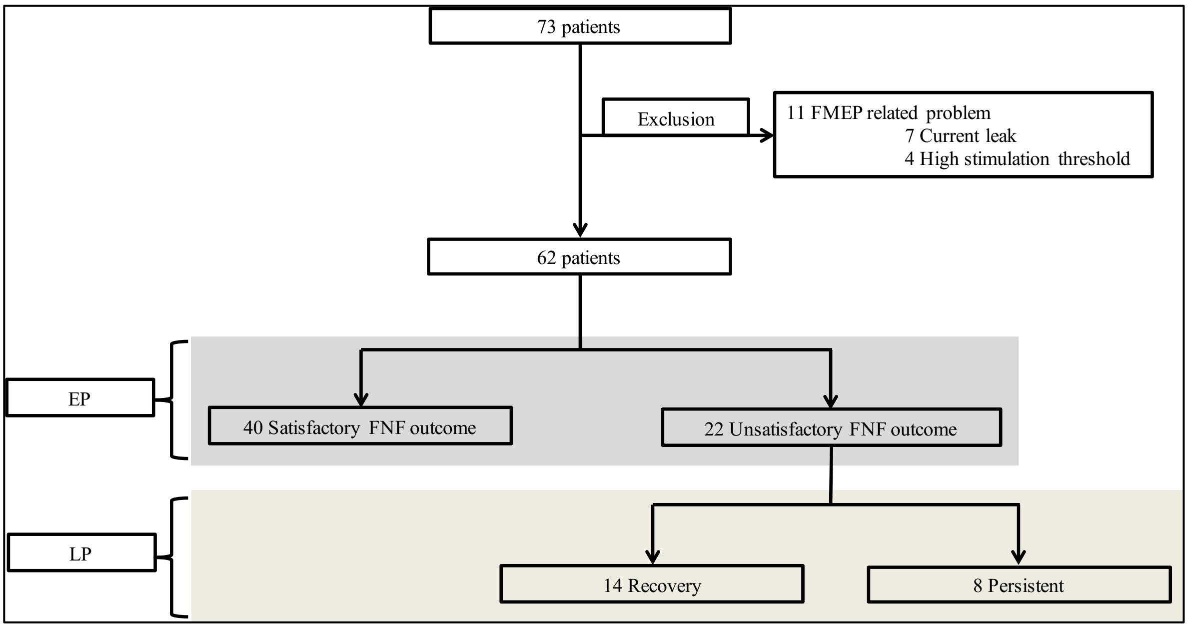

Fig. 3-2 Flowchart of the patient selection criteria and summary of the facial nerve function outcome groups

Table 3-1

Summary of patients' characteristics

Variable	Value
Number of patients	62
Men	21 (34%)
Women	41 (66%)
Age (years)	
Median	59
Range	18–80
Tumor size (mm)	
Median	32.5
Range	15-57
Surgical approach	
Trans-petrosal	14 (23%)
Lateral suboccipital retrosigmoid	48 (77%)
Diagnosis	
Vestibular schwannoma	35 (56%)
Meningioma	18 (29%)
Others	9 (15%)
Minimum-to-baseline amplitude ratio	
Median	53
Range	1–148
Final-to-baseline amplitude ratio	
Median	86
Range	2–198
HB grade in early postoperative period	
Satisfactory group (HB I–II)	40 (65%)
Unsatisfactory group (HB III–VI)	22 (35%)
HB grade in late postoperative period	
Recovery group (HB I–II)	54 (87%)
Persistent group (HB III–VI)	8 (13%)

3.2. Prediction of FNF in the EP period

We allocated 22 patients to the unsatisfactory group in the EP period (Fig. 3-2). Table 3-2 summarizes data for these patients. Table 3-3 shows that MBR and FBR were significantly correlated with FNF; MBR had a higher Spearman's rho (rho = 0.79) than FBR. Figure 3-3 describes the differences between the satisfactory and unsatisfactory groups based on their MBR. In the ROC curve (Fig. 3-4A), the numbers denote the points on the curve where the optimal cutoff MBR was at 35%, with a sensitivity of 0.91 (95% CI 0.78–0.96) and a specificity of 0.95 (95% CI 0.88–0.98). The AUC value was 0.97 (95% CI 0.93–1.00). Regarding FBR, the number denoted that the optimal cutoff on the ROC curve was at 60% (Fig. 3-4B), with a sensitivity of 0.82 (95% CI 0.67–0.91) and a specificity of 0.90 (95% CI 0.82–0.95). In addition, the AUC value was 0.94 (95% CI 0.89–0.99) for FBR. We confirmed the existence of collinearity between MBR and FBR. The simultaneous inclusion of the two factors in the logistic regression analysis is inappropriate. We considered the factor with the greater value in the clinical practice and chose MBR for the analysis, rather than FBR since MBR can be interpreted and applied in the surgical decision by surgeons during surgery, while FBR can be obtained only at the end of the surgery. Table 3-4 shows that MBR is significantly correlated with FNF status ($P < 0.001$).

Table 3-2

Summary of 22 patients with unsatisfactory postoperative facial nerve function in the early period

No.	Diagnosis	Tumor size (mm)	MBR (%)	FBR (%)	RV	FNF in EP period (HB grade)	FNF in LP period (HB grade)
1	VS	26	34	44	10	3	1
2	VS	27	12	30	18	3	1
3	VS	24	56	76	20	3	1
4	meningioma	50	22	47	25	3	1
5	meningioma	33	31	62	31	3	1
6	meningioma	54	51	93	42	3	1
7	VS	31	9	59	50	3	1
8	VS	30	17	35	18	4	1
9	VS	35	18	52	34	4	1
10	meningioma	50	4	49	45	4	1
11	VS	48	23	90	67	4	1
12	VS	36	2	22	20	5	1
13	VS	32	13	33	20	5	2
14	VS	42	14	44	30	5	2
15	VS	32	12	22	10	4	3
16	VS	32	10	21	11	3	3
17	ependymoma	36	2	2	0	5	4
18	VS	25	7	8	1	5	4
19	VS	22	10	14	4	5	4
20	VS	33	1	9	8	5	4
21	VS	34	22	30	8	4	4
22	VS	30	10	18	8	6	4

Table 3-3

Correlation of index with facial nerve function in the early postoperative period

Index	Spearman's correlation coefficient
Minimum-to-baseline ratio	$rs = -0.79$, $P < 0.001$
Final-to-baseline ratio	$rs = -0.74$, $P < 0.001$
Recovery value	$rs = -0.21$, $P = 0.095$

Table 3-4

Logistic regression of facial nerve palsy (early postoperative period) in 62 patients

			95% Confidence interval	
Variable	P-value	Odds ratio	Lower	Upper
Gender	0.845	0.758	0.047	12.176
Age	0.192	1.056	0.973	1.145
Tumor size	0.512	1.048	0.911	1.205
Approach	0.848	0.723	0.026	20.128
Minimum-to-baseline ratio	**<0.001**	0.855	0.784	0.934

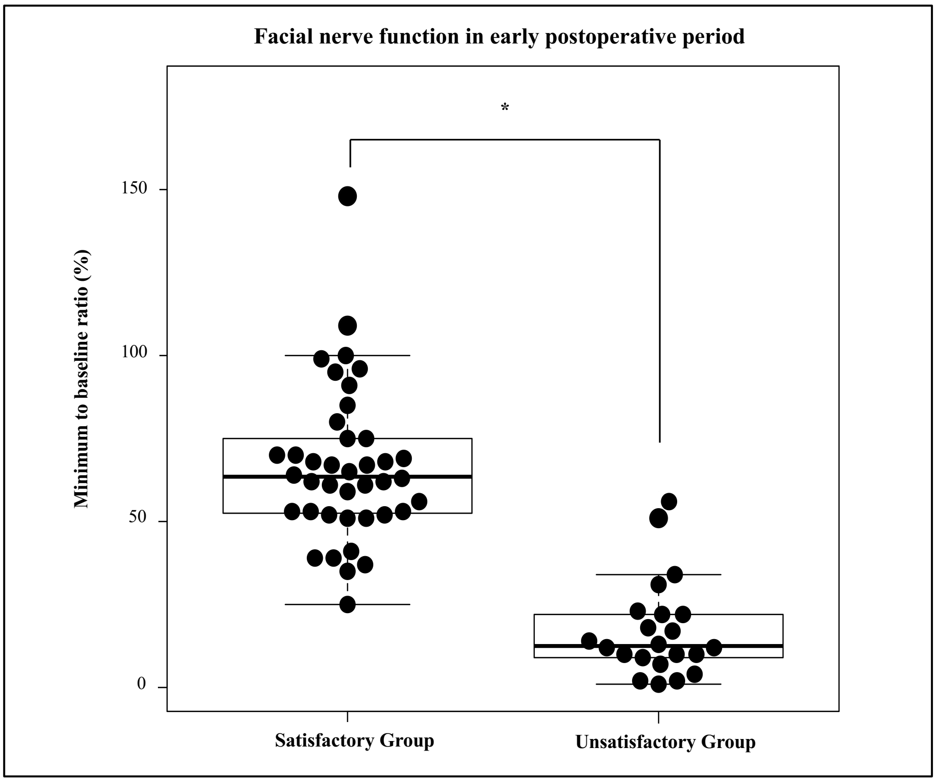

Fig. 3-3. Facial nerve function in the EP. Box plots showing the Mann-Whitney U test result with a significant difference in the MBR between the satisfactory and unsatisfactory groups in the EP (*p < 0.001).

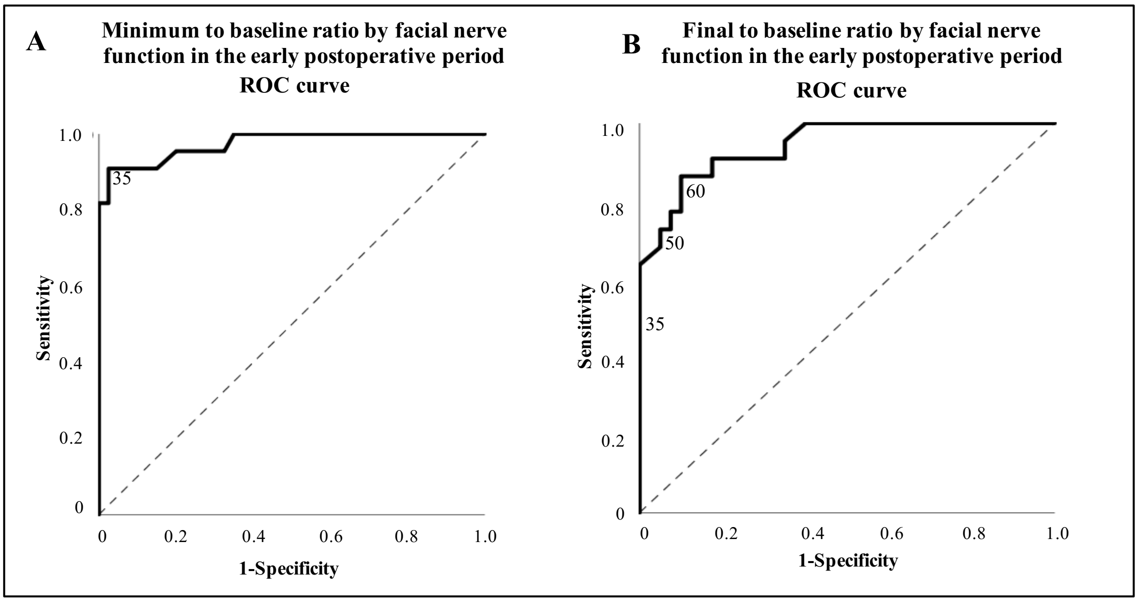

Fig. 3-4. (A) The ROC curve shows the predictive power of MBR for the facial nerve function in the early postoperative period. The numbers denote the point on the curve at which MBR was set to 35% as an optimal cutoff. The area under the curve is 0.97. (B) The ROC curve shows the predictive power of FBR. The numbers denote the point on the curve at which FBR was set to 35%, 50%, and 60%. The area under the curve is 0.94.

3.3. Prediction of FNF in the LP period

Of the 22 patients allocated into the unsatisfactory group, 14 recovered their FNF, and we re-allocated them to the recovery group, but the facial nerve dysfunction persisted in 8 patients whom we kept in the persistent group throughout the LP period (Fig. 3-2). Table 3-5 shows that both FBR and RV were significantly correlated with FNF in the recovery groups during the LP period, and RV showed the strongest correlation among the indices. Figure 3-5 describes the differences between the satisfactory and unsatisfactory groups based on their RV, and according to this figure, we created a contingency table analysis of the cutoff RVs of 10%, 15%, and 20% (Table 3-6). With RV set to 15% cutoff, the sensitivity of FNF prediction was 0.93 (95% CI 0.80–0.93), and specificity was 1.00 (95% CI 0.77–1.00). The 22 patients in the unsatisfactory group presented various courses of HB grade recovery (Table 3-2), and RV showed a significant positive correlation with the degree of improving HB grade (Fig. 3-6).

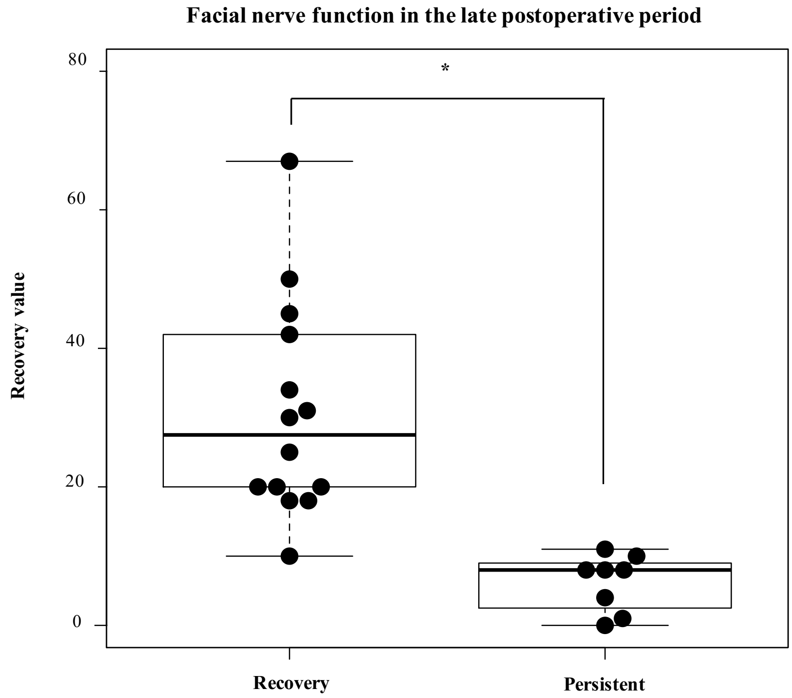

Fig. 3-5. Facial nerve function in the late postoperative (LP) period
Box plots showing significant differences in the recovery value between the recovery and persistent groups in the LP period (*$P < 0.001$).

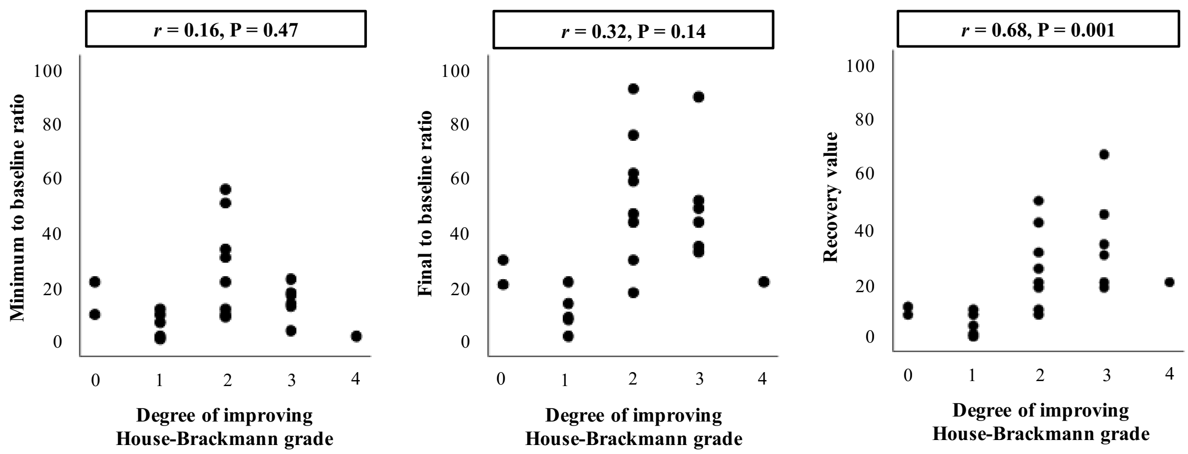

Fig. 3-6. Scatter plots showing the correlation between the degree of improving House–Brackmann grade and three parameters (minimum-to-baseline ratio, final-to-baseline ratio, and recovery value). The recovery value has a significant positive correlation with the degree of improving House–Brackmann grade.

Table 3-5

Correlation of index with facial nerve function in the late postoperative (LP) period

Index	Spearman's correlation coefficient
Minimum-to-baseline ratio	$rs = -0.49$, $P = 0.022$
Final-to-baseline ratio	$rs = -0.81$, $P < 0.001$
Recovery value	$rs = -0.84$, $P < 0.001$

Table 3-6

Comparison of RV and FNF values in the LP period in each cutoff value

Cutoff RV (%)	True positive (No.)	False positive (No.)	True negative (No.)	False negative (No.)	Sensitivity (95% CI)	Specificity (95% CI)
10	14	2	6	0	1.00 (0.87–1.00)	0.75 (0.52–0.75)
15	13	0	8	1	0.93 (0.80–0.93)	1.00 (0.77–1.00)
20	11	0	8	3	0.79. (0.65–0.79)	1.00 (0.75–1.00)

True positive: RV is equal or greater than the cutoff value accompanied by a satisfactory FNF in the late postoperative period (HB I or II); false positive: RV is equal or greater than the cutoff value accompanied by unsatisfactory FNF (HB III–VI); true negative: RV is lesser than the cutoff value accompanied by unsatisfactory FNF (HB III–VI); false negative: RV is lesser than the cutoff value accompanied by satisfactory FNF (HB I or II).

4. Discussion

FMEP by TES has been an effective method for intraoperative monitoring of FNF, and it also can predict the postoperative status of facial nerve palsy using specific indices, such as FBR and MBR. However, in actual clinical practice, it is possible to encounter difficulty in distinguishing between FMEP waveform and stimulation artifacts because of the short latency of FMEP (Goto et al., 2010). Moreover, the waveform baseline can drift because of stimulation artifacts, making it difficult to accurately measure FMEP amplitude. Thus, we introduced the BCS protocol to overcome these drawbacks and obtain a stable baseline with fewer artifacts that can be reproduced. This facilitated the reading and measuring of the wave more consistently than with monophasic stimulus protocols.

Most studies on FMEP using TES have evaluated FNF using FBR (Table 4-1). These reports have shown that FNF in the EP period can be predicted based on FBRs with a cutoff value <35% or <50% (Akagami et al., 2005; Dong et al., 2005; Fukuda et al., 2008; Tokimura et al., 2014). Moreover, the event-to-baseline amplitude ratio for intraoperative evaluation has been reported to be an important index (Acioly et al., 2011). However, no studies have reported whether intraoperative FMEP findings can predict the recovery of facial nerve palsy.

This study has provided a designed protocol for stabilizing FMEP waveforms and the prediction possibility of FNF in the EP and LP periods not only using MBR and FBR but with an additional novel index, RV, which focused on the deepest drop and intraoperative FMEP amplitude recovery.

4.1. Prediction indices of FNF in the EP period

In this study, we reconfirmed the usefulness of FBR as an FNF predictor in the EP period, similar to previous reports. The sensitivity and specificity of 50% cutoff values in our study were comparable to those in other studies (Akagami et al., 2005; Dong et al., 2005; Acioly et al., 2010). Moreover, we showed that in the EP period, MBR could predict the occurrence of facial palsy as efficiently as FBR. Based on our results, MBR <35% would predict a severe postoperative facial palsy with high accuracy (sensitivity = 0.91 and specificity = 0.95). MBR or the event-to-baseline ratio has been documented only in few studies, whereas the use of FBR for the prediction of postoperative facial nerve palsy has been reported many times (Table 4-1). In the present study, the BCS protocol enhanced accurate and consistent FMEP amplitude measurements, even in low-amplitude waveforms. This may result in a better MBR evaluation and detection of its clinical relevance.

Our decision to choose MBR for logistic regression analysis was based on MBR practicality in the surgical course as well as our experience. MBR can be interpreted in an earlier stage of surgery than FBR. Thus, in an earlier surgical stage, the surgeon can decide whether to continue with the tumor excision or hold the procedure and avoid further damage to the nerve.

Table 4-1

Summary of published data on transcranial FMEP to predict FNF outcomes

Author, year	Cases (n)	Stimulus method & intensity	Recording part	Criteria	Predictor of FNF outcome	
					EP period	LP period
Dong, 2005	76	Suprathreshold 100–400 V	Oris	FBR	Cutoff ratio 50%, 35%, and 0%	N.A.
Akagami, 2005	71	N.A. 200–400 V	Oris	FBR	Cutoff ratio 50%	N.A.
Fukuda, 2008	26	Supramaximal 180–550 V	Oculi, oris	FBR	Cutoff ratio 50%	N.A.
Acioly, 2010	60	N.A. 200–600 V	Oculi, oris	FBR	Cutoff ratio oculi 80%, oris 35%	N.A.
Acioly, 2011	35	N.A. 200–600 V	Oculi, oris	EBR	Acute ratio deteriorations of >50%	Small number sizes
Tokimura, 2014	35 (20)	Supramaximal /during surgery: threshold+50 V	Oculi, oris	FBR	Cutoff ratio 50%	No facial palsy in 6 months
Bhimrao, 2016	367	N.A. 150–300 V	Oris	FBR	Cutoff ratio 62%	Cutoff ratio 59%
Ling, 2017	97	N.A. 132.7 V (SD 28.3)	Mentalis	FBR	Cutoff ratio 77%	Cutoff ratio 57%
Present study	57	Suprathreshold 35–170 mA	Oris	(i) MBR (ii) RV	(i) Cutoff ratio 35%	(ii) More than 15

4.2. Prediction indices of FNF in the LP period

Some studies (Bhimrao et al., 2016; Ling et al., 2018) have shown that FBR can predict long-term FNF (Table 4-1). This study is not an exception because it confirmed the correlation of FBR and FNF in the LP period. A study using CMAP showed that the recovery of facial nerve damage depended on the recovery of the monitoring amplitude (Nakatomi et al., 2015). This was also true for FMEP studies and our experience. Patients with facial palsy immediately after surgery who had an amplitude recovery after a transient drop in FMEP during surgery demonstrated improvement of facial palsy during a longer observation period (Samii et al., 2006; Ling et al., 2018). However, no reports verified a relationship between FNF improvement and intraoperative FMEP variation. In this study, we found that RV was a useful index for evaluating the tendency of FMEP improvement in association with long-term recovery among the unsatisfactory group in the EP period. In fact, both FBR and RV had a strong correlation with two FNF HB grade groups (satisfactory and unsatisfactory) in the LP periods (Table 3-5). However, only RV showed a significant correlation with the degree of improvement of HB grade (Fig. 3-6).

In CPA tumor surgery, a decrease in FMEP amplitude usually occurs during manipulation of the tumor and/or the facial nerve, affecting the nerve itself, rather than damaging the nucleus of the facial nerve at the brainstem or its upper motor neurons. Nerve injuries were classified by Seddon in 1942 as neurapraxia, axonotmesis, or neurotmesis based on the severity and extent of injury to the neural components (Fig. 4-1). Neurapraxia is a conduction block caused by a focal demyelination without axonal loss; thus, complete recovery can be achieved within a few hours at the earliest. In contrast, axonotmesis and neurotmesis are caused by axonal damage, which might require a long time to recover or may end with no regeneration (Seddon, 1942). It is conceivable that intraoperative damage to facial nerve fibers can be due to a mixture of the above three conditions.

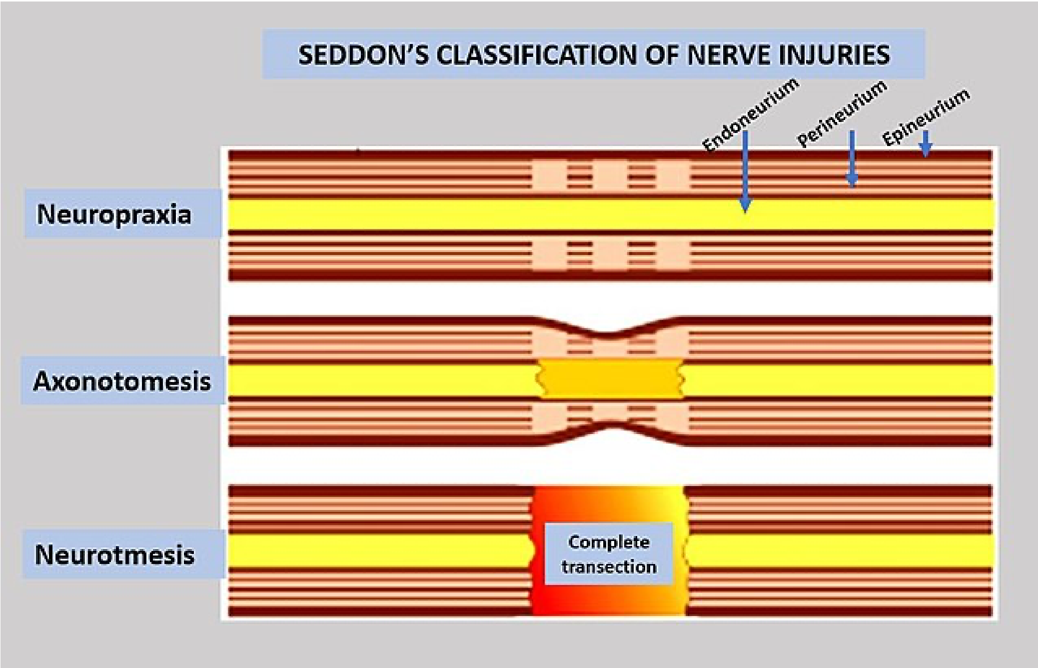

Fig. 4-1. Seddon's classification of nerve injuries. Neurapraxia is the lowest degree of nerve injury with focal demyelination. Axonotmesis involves loss of the continuity of axon but preservation of connective tissue. Neurotmesis is a total disruption of the nerve fiber.

The underlying neurophysiological phenomenon indicated by RV is most likely a short-term recoverable neuropathy (neurapraxia). RV reflected relatively milder forms of nerve injury; thus, a higher RV value may be associated with good recovery of facial palsy. The clinical significance of RV, not just FBR, is that it allows prediction of the extent of improvement in a more accurate manner based on the intraoperative FMEP data. The time course of recovery from surgical nerve damage can vary depending on the volume of the nerve fibers involved, extent and/or duration of the injurious stress, and patient's ability to recover. Because RV is calculated from two different time points and evaluates the recovery extent of the amplitude of FMEP, as opposed to FBR, which evaluates only one time point, RV shows stronger correlations with FNF recovery than that with FBR.

It should be noted that RV is an evaluation index for a patient with existing facial nerve palsy in the EP period. In other words, RV would be useful as an intraoperative index when a certain degree of FMEP drop (MBR < 35%) is observed.

4.3. A new BCS protocol

We selected a unique stimulation method (BCS) to improve the accuracy of FMEP monitoring. We chose a biphasic configured rectangular symmetrical cathodic and anodic stimulation within one pulse. This stabilized the waveform baseline compared with the monophasic stimulation method (Fig. 1). It is known and practiced that increasing the low-bandpass filter (100–200 Hz) is also an effective way to reduce a stimulation artifact (Dong et al., 2005; Fukuda et al., 2008; Acioly et al., 2011; Ling et al., 2018). However, if the low-bandpass filter is set higher, FMEP amplitude might reduce. The BCS method minimizes this phenomenon, and we set the low-bandpass filter at 20 Hz. Sarnthein et al. (2013) obtained good waveforms using similar stimulation methods and evaluated correlations between the threshold-level elevation and the postoperative FNF.

We also used a constant current stimulator, different from the usual constant voltage stimulator (Table 4-1). During surgery, the electric resistances are affected by factors, such as CSF leaks, operating procedures, and body temperature changes. Hence, in cases with constant voltage stimulation, each differing current can alter the electric charge, which is the most significant factor for stimulation (Macdonald et al., 2013). Studies have used the suprathreshold stimulation method (Dong et al., 2005; Tokimura et al., 2014) that requires stimulation intensity adjustments during the surgery but has the advantage of suppressing the head movement caused by the stimulation and avoiding interruptions during the surgical procedure. In addition, body shaking during surgical procedure can be avoided by using the BCS protocol. Moreover, the technician applied frequent stimulations while observing the microscope video monitor.

4.4. Application of FMEP to future CPA tumor surgeries

In practice, if FMEP drops due to surgical damage, the surgeon receives an alarm from the monitoring technician to stop the procedure. The surgeon will comply with the notification and waits for few minutes. Considering the degree of recovery of the FMEP, the surgeon decides whether to continue the tumor resection or abort the surgery to preserve the FNF. In this case series, we did not administer steroids during surgery or in the postoperative period.

4.5. Limitations

This study has a few limitations. For the analysis of the prediction of FNF in the LP period, the sample size (only eight subjects in the persistent group) was small. Moreover, we conducted a single-center study, and the results might vary in another facility if a similar study model is utilized. The MBR, FBR, or RV cutoff values might differ due to various kinds of biases, such as surgeon's skill level and the type of anesthesia protocol. Although the study results showed the usefulness of MBR and RV, both single and multi-center validation studies should be conducted. Furthermore, leaked currents may be misidentified as a true FMEP if they activate the waveform of the peripheral facial nerve. These false negatives are a common problem and a major limitation in FMEP measurements. Effective monitoring was possible in 62 out of our 73 patients (84%), and the successful monitoring rate was comparable to those of other reports (Acioly et al., 2010; Verst et al., 2012; Sarnthein et al., 2013). For this study, we analyzed FMEP recorded from the orbicularis oris muscle only, because data from other facial muscles, such as the orbicularis oculi muscle, were not recorded simultaneously in all of the patients. FMEPs recorded and analyzed from other facial muscles may have their own cutoff points and probably their own outcome measures.

5. Conclusion

In summary, FMEP monitoring with BCS stimulation produces waveforms with few baseline artifacts. In the EP period, MBR during surgery is useful for predicting facial palsy. We believe that RV can predict long-term FNF recovery better than FBR. Our technique may help increase the FNF preservation rate and may reassure patients with postoperative facial palsy and good indices that FNF will eventually recover.

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8. Appendix

Supplementary Table 1

Summary of 62 patients" details of correlation between facial MEP change and postoperative facial nerve function outcome.

No.	Gender	Age	Disease	Surgical Approach	Tumor size	MBR	FBR	RV	FNF in EP	FNF in LP
1	M	40	VS	LSR	40mm	53	100	47	1	1
2	F	48	Meningioma	TP	32mm	91	96	5	1	1
3	M	62	Meningioma	TP	40mm	63	150	87	1	1
4	F	53	VS	LSR	24mm	95	115	20	1	1
5	F	65	Meningioma	TP	37mm	53	134	81	1	1
6	F	53	VS	LSR	29mm	61	156	95	1	1
7	F	76	hemangioblastoma	LSR	40mm	62	93	31	1	1
8	F	76	Malignant lymphoma	LSR	24mm	65	80	15	1	1
9	F	18	neurinoma	LSR	31mm	51	51	0	1	1
10	M	46	VS	LSR	33mm	39	47	8	1	1
11	F	69	VS	LSR	27mm	59	86	27	1	1
12	F	56	VS	LSR	20mm	68	85	17	1	1
13	F	64	VS	LSR	24mm	39	63	24	1	1
14	F	56	SFT	LSR	30mm	52	161	109	1	1
15	F	49	Meningioma	TP	55mm	75	100	25	1	1
16	F	34	neurinoma	TP	57mm	67	183	116	1	1
17	M	65	SFT	LSR	45mm	68	104	36	1	1
18	F	38	VS	LSR	23mm	56	112	56	1	1
19	F	72	Meningioma	LSR	22mm	100	108	8	1	1
20	M	35	Meningioma	LSR	21mm	69	108	39	1	1
21	M	72	VS	LSR	45mm	109	113	4	1	1
22	F	63	epidermoid	LSR	36mm	85	107	22	1	1
23	F	65	Meningioma	LSR	24mm	35	173	138	1	1
24	F	65	Meningioma	LSR	41mm	51	89	38	1	1
25	F	59	VS	LSR	48mm	67	118	51	1	1
26	M	44	Meningioma	LSR	15mm	53	82	29	1	1
27	F	44	VS	LSR	17mm	70	71	1	1	1
28	F	65	Meningioma	LSR	20mm	96	112	16	1	1

29	F	78	Meningioma	LSR	52mm	62	102	40	1	1
30	M	33	epidermoid	TP	51mm	61	72	11	1	1
31	F	62	VS and Meningioma	TP	22mm	99	108	9	2	1
32	M	53	VS	LSR	24mm	64	77	13	2	1
33	F	42	Meningioma	TP	35mm	75	105	30	2	1
34	F	55	VS	LSR	38mm	41	47	6	2	1
35	F	18	VS	LSR	53mm	37	86	49	2	1
36	F	65	VS	LSR	20mm	70	198	128	2	1
37	M	32	VS	LSR	19mm	148	155	7	2	1
38	F	68	Meningioma	TP	40mm	25	57	32	2	1
39	F	40	Meningioma	TP	48mm	52	93	41	2	1
40	M	61	VS	LSR	35mm	80	118	38	2	1
41	M	74	VS	LSR	31mm	9	59	50	3	1
42	F	61	Meningioma	TP	50mm	51	93	42	3	1
43	F	67	VS	LSR	32mm	10	21	11	3	3
44	F	65	VS	LSR	26mm	34	44	10	3	1
45	F	80	VS	LSR	24mm	56	76	20	3	1
46	M	58	Meningioma	TP	50mm	22	47	25	3	1
47	F	43	VS	LSR	27mm	12	30	18	3	1
48	F	76	Meningioma	TP	33mm	31	62	31	3	1
49	M	63	VS	LSR	32mm	12	22	10	4	3
50	F	63	Meningioma	TP	50mm	4	49	45	4	1
51	M	25	VS	LSR	30mm	17	28	11	4	1
52	F	61	VS	LSR	34mm	22	30	8	4	4
53	M	39	VS	LSR	48mm	23	90	67	4	1
54	F	19	VS	LSR	35mm	18	52	34	4	1
55	M	67	VS	LSR	33mm	1	9	8	5	4
56	M	48	ependymoma	LSR	36mm	2	2	0	5	4
57	M	79	VS	LSR	22mm	10	14	4	5	4
58	M	55	VS	LSR	36mm	2	22	20	5	1
59	M	77	VS	LSR	25mm	7	8	1	5	4
60	F	53	VS	LSR	32mm	13	33	20	5	2
61	F	38	VS	LSR	42mm	14	44	30	5	2
62	F	49	VS	LSR	30mm	10	18	8	6	4