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ORIGINAL ARTICLE

Blink reflex excitability in patients with Hemifacial spasm exhibiting different abnormal discharge patterns: from early isolated discharges to later grouped bursts or tonic spasms

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Abstract

Objective We studied blink reflex (BR) and BR excitability recovery (BRER) in patients with hemifacial spasm (HFS) exhibiting different abnormal discharge patterns. We hypothesized that patients with groups of clonic or tonic burst activities appear later in the disease course and may have more excitability of the BR circuit at the brainstem compared to patients with isolated twitchings, which occur earlier.

Methods We included 124 patients with botulinum toxin-naive HFS (mean age 50.6 ± 13.3 years) and 40 healthy subjects. We performed surface polymyography on facial muscles in patients and classified them according to the abnormal discharge pattern: isolated discharges, grouped bursts forming random sequences, tonic spasms, and a combination of these activities. Then, we recorded BR and BRER at 200, 600, and 1000 ms interstimulus intervals. We compared disease duration, R1 and R2 latencies, R2 area-under-the-curve (AUC), and BRER% (i) between healthy subjects and patients and (ii) among groups of patients with different abnormal discharge patterns.

Results There were isolated discharges in 28 patients, grouped bursts forming random sequences in 42, and continuous muscle activity with tonic spasms in one. The remaining patients had combinations. Mean R1 and R2 latencies were significantly longer, and mean R2 AUC was significantly higher on the symptomatic side of patients compared to healthy subjects. The mean BRER was enhanced on both sides in patients than in healthy subjects ($p < 0.001$). However, it was similar among patient groups with different abnormal discharge patterns ($p > 0.05$). The mean disease duration in patients with isolated discharges was shorter (3.3 ± 2.0 years) than those with grouped bursts or tonic spasms ($p = 0.002$; Kruskal–Wallis test).

Conclusion Our study observed that excitability at the brainstem was similar in HFS patients with different abnormal discharge patterns, suggesting that the difference in discharge patterns in HFS may be due to a reason other than the difference in BR excitability.

Keywords Hemifacial spasm · Blink reflex · Blink reflex excitability recovery

Introduction

Hemifacial spasm (HFS) is characterized by involuntary, repetitive, and irregular movements of facial muscles on one side of the face [1, 2]. It is considered due to an irritating lesion in the facial nerve at its root exit zone in the posterior fossa. It is generally attributed to a blood vessel compressing the facial nerve at the brainstem.

The first symptom is usually the intermittent twitching of the eyelid muscle that can lead to the forced closure of the eye, whereas patients with full-blown HFS generally present with paroxysmal muscle discharges, consisting of rapid, irregular clonic or tonic bursts of electromyography activity that involve lower and upper facial muscles simultaneously [3, 4].

The R2 component of the blink reflex (BR) is hyperexcitable on the affected side more than on the unaffected side [5, 6]. A well-accepted method to measure the excitability of the BR pathway is the BR excitability recovery (BRER) study [7]. In the BRER studies, two consecutive stimuli of the same intensity are applied to the supraorbital nerve at interstimulus intervals (ISIs) between 100 and 1500 ms. The

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sizes of the responses to the conditioning (first) and test (second) stimuli are measured, and a percentage of the responses is calculated. In healthy individuals, the R2 component of the BR after the test stimulus is usually completely abolished from 0 to 200–300 ms, slowly recovering to 70–90% at the 1500 ms interval [8]. However, enhanced and earlier BRER, i.e., the appearance of responses to the test stimulus at short interstimulus intervals, develops in many disorders, mainly attributed to the basal ganglia [9, 10]. In HFS, the BRER also increases on the affected and clinically healthy sides [5]. Among clinical findings, longer disease duration correlated slightly with enhanced BRER [5].

Keeping in mind that HFS starts with isolated discharges and irregular clonic or tonic bursts may appear in patients with a longer duration of disease [4], and BRER is more enhanced in patients with a longer duration of HFS; we, here, hypothesized that patients with groups of clonic or tonic burst activities, which appear later in the disease course may have more enhanced BRER compared to patients with isolated twitchings. Thus, we studied BR and BRER in patients with HFS exhibiting different abnormal discharge patterns.

Method

Patient selection

We included all consecutive patients diagnosed with HFS admitted to our movement disorders outpatient clinic between January 2010 and January 2019. The HFS was diagnosed with clinical and surface polymyography findings.

The exclusion criteria were as follows: (i) the presence of an intracranial tumor or demyelinating lesion, (ii) having a botulinum toxin injection in the last six months, (iii) having a history of peripheral facial palsy, and (iv) having a contraindication for the electrophysiological assessments such as a pacemaker.

We also enrolled 40 healthy subjects in the study for electrophysiological comparisons. The age and gender of patients and healthy subjects were similar (Table 1).

The participants gave informed consent, and we obtained approval from the local ethics committee.

Clinical assessments

We retrieved the demographics, age at onset, duration, and side of involuntary movements from the medical records.

Table 1 Demographic and clinical findings of patients and healthy subjects

	Patients with hemifacial spasm $n=124$	Healthy subjects $n=40$	p
Mean age, year	50.6 ± 13.3	46.5 ± 12.2	0.085[a]
Gender (Male), *n* (%)	70 (56.4)	25 (62.5)	0.500[b]
Mean age at onset, year	46.4 ± 13.1	–	
Disease duration, year	4.4 ± 5.9	–	
Side (Left/Right), *n* (%)	62 (50)/62 (50)	–	
Type of discharges		–	
Isolated discharges	28		
Grouped bursts	42		
Tonic spasm	1		
Combination any of them	53		

[a]Mann–Whitney *U* test

[b]Chi-Square test

Electrophysiological assessments

All electrophysiological examinations were performed using a Neuropack Sigma MEB-5504k (Nihon Kohden Medical, Tokyo, Japan) and silver-silver chloride surface recording electrodes. All electrophysiological tests were performed comfortably and conveniently in a quiet room while patients were sitting after proper skin temperature was achieved (mean 32 °C). A single neurophysiologist (M.E.K.) performed all electrophysiological examinations.

Surface polymyography

Surface recording electrodes were placed on the bilateral orbicularis oculi and ipsilateral orbicularis oris in all patients and mentalis muscle or posterior auricular muscle in selected cases. The sensitivity was set to 200–500 µV/div, and the analysis time was 0.1 s/div. The frequency range was between 20 Hz and 5 kHz.

The recordings were done at complete relaxation or during simple and complex voluntary movements for 30 min. The recordings were done at rest for at least 20 min. Then, the recordings were captured during voluntary movements such as speaking, closing the eyes, and blowing to observe if voluntary movements triggered spasms and if there was a synkinetic spread of the voluntary movements.

The type, frequency, rhythmicity, amplitude, and duration of involuntary movements were evaluated. Patients were classified into four groups according to the abnormal discharge type: (i) isolated discharges, (ii) grouped bursts

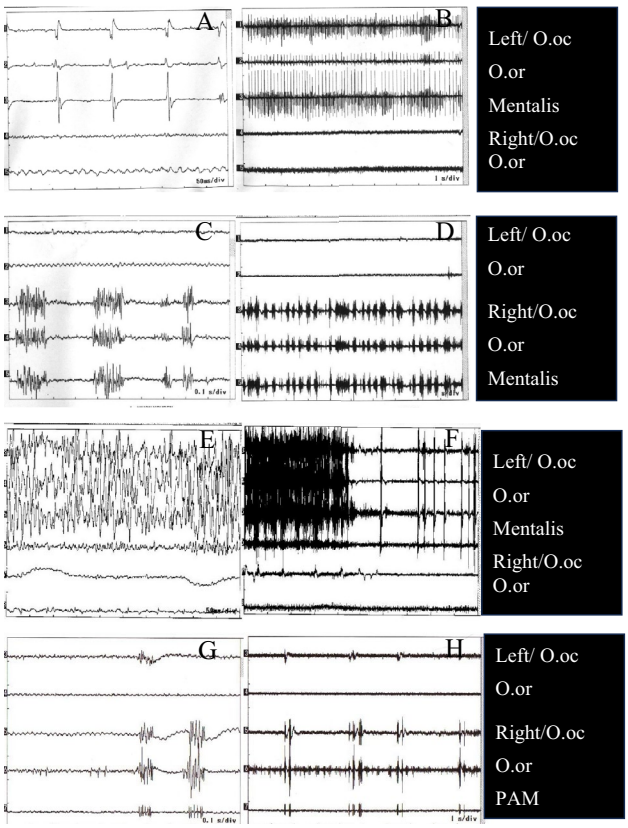

Fig. 1 **A**, **B** Isolated discharges on left-sided facial muscles in a 52-year-old male patient with left hemifacial spasm. **C**, **D** Grouped bursts on right-sided facial muscles in a 59-year-old male patient with right hemifacial spasm, **E**, **F** tonic spasm followed by grouped bursts in a 45-year-old male patient with left hemifacial spasm. **G**, **H** Blink bursts on right-sided facial muscles in a 69-year-old female patient with right hemifacial spasm. The bursts in the first trace in this patient were normal blink bursts. *PAM* posterior auricular muscle

forming random sequences, (iii) continuous muscle activity with tonic spasms, and (iv) a combination of these discharges.

We categorized discharge types based on the following criteria: (i) if there were single and isolated motor unit spikes, the type was isolated discharges (Fig. 1A and B), (ii) if clusters of multiple motor unit spikes formed bursts 50–100 ms in duration, the patient was considered to have grouped bursts (Fig. 1C and D), and (iii) if the abnormal activity was formed by continuous motor unit potential activity in succession, generally longer than 500 ms and sometimes turning into an interference pattern, it was grouped as a tonic spasm (Fig. 1E and F). Group bursts triggered by the synkinetic propagation of the spontaneous blinks (Fig. 1G and H) were excluded from the analysis.

Blink reflex and recovery excitability of BR recordings

The BR and BRER at 200, 600 ms, and 1000 ms interstimulus intervals were recorded in patients and healthy subjects. The BR and BRER were recorded bilaterally in the patients but only on the right side in healthy subjects. The recording electrodes were placed on the orbicularis oculi muscle. We also placed recording electrodes on the orbicularis oris muscle on the spasm side to measure the magnitude of synkinetic spread in patients.

The R2 threshold was determined by 0.2 increases in stimulus intensity to record BR. The R2 threshold was the intensity that produced the first acceptable response (larger than 50 μV at acceptable latency). Then, the test stimulus, a transcutaneous square-wave electrical stimulus with a duration of 0.2 ms and an intensity of 5 times the R2 threshold, was applied to the supraorbital branch of the trigeminal nerve. To record BRER, we used paired stimuli with ISIs of 200 ms, 600 ms, and 1000 ms. Both stimuli were applied at the supraorbital foramen, and the intensities of both stimuli were the same as in BR recordings.

The sequence of blocks was randomly changed in each subject. Recordings in each trial were repeated five times. All five recordings were rectified and averaged before the measurements. The filters were set to 3 kHz low-pass and 20 Hz high-pass. Analysis time and amplitude sensitivity were adjusted to 20 ms/div and 200 μV, respectively.

Data and statistical analysis

We measured

- The latency of R1 and R2 responses, and
- The area-under-the-curve (AUC) of R2

We calculated the recovery percentage at each ISI using the following formula:

$$\text{R2 AUC after test stimulus} / \text{R2 AUC after conditioning stimulus} \times 100$$

We compared the parameters above

(i) Between asymptomatic sides of patients with HFS, symptomatic sides of patients with HFS, and healthy subjects

(ii) Among patients with isolated discharges, patients with grouped bursts forming random sequences, and patients having continuous muscle activity with tonic spasm.

We used SPSS 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY) for statistical analysis. First, we determined the normality of the group using Kolmogorov–Smirnov test. There was a nonhomogeneous distribution. Then, comparisons were made using the Kruskal–Wallis test for numerical data and the chi-square test for categorical data. For post hoc analysis, we used the Mann–Whitney *U* test. Using Pearson correlation analysis, we performed a correlation analysis between age, disease duration, and BRER%. Numerical data were presented as mean ± SD (minimum–maximum) and categorical variables n (%). A p value < 0.05 was deemed significant.

Results

Clinical findings

There were 126 patients with HFS. We excluded one patient with a tumor at the cerebellopontine angle and one with a T2-FLAIR hyperintense lesion at the middle cerebellar peduncle. We included 124 patients diagnosed with HFS (mean age 50.6 ± 13.3 years). The mean age at onset was 46.4 ± 13.1 years. The mean duration of the disease was 4.4 ± 5.9 years. Sixty-two patients (50%) had left-sided HFS. The details are given in Table 1.

Electrophysiological findings

Surface polymyography

There were isolated discharges in 28 patients, grouped bursts forming random sequences in 42 patients, and continuous muscle activity with tonic spasms in one patient. The remaining patients had any combination of these discharges. Patients with isolated discharges (48.7 ± 7.5 years) were younger than those with grouped bursts (52.2 ± 8.2 years) or tonic spasms (50.5 years; $p = 0.040$, Kruskal–Wallis test). The mean duration of HFS was shorter in patients with isolated discharges (3.3 ± 2.0 years) compared to patients with grouped bursts (4.7 ± 2.2 years) or tonic spasms (5.6 years; $p = 0.002$, Kruskal–Wallis test).

BR and BR excitability recovery

Mean R1 and R2 latencies were longer on the symptomatic side of patients compared to healthy subjects. The mean R2 AUC was significantly higher on both sides of patients compared to healthy subjects (Table 2).

Table 2 Findings of blink reflex and BRER

	Symptomatic side of HFS	Asymptomatic side of HFS	Healthy subjects	p[a]
R1 latency, ms				
Ipsilateral	10.9 ± 1.6	9.5 ± 1.5	8.7 ± 1.2	< 0.001
R2 response				
Latency, ms	33.0 ± 5.7	32.1 ± 4.9	26.9 ± 4.2	< 0.001
AUC, μV ms	5.1 ± 3.1	4.7 ± 3.2	3.2 ± 1.4	< 0.001
BRER of R2				
200 ms, %	28.9 ± 24.1	22.6 ± 21.4	11.0 ± 11.5	< 0.001
600 ms, %	54.9 ± 14.2	52.1 ± 22.8	40.7 ± 20.1	< 0.001
1000 ms, %	72.6 ± 28.0	71.3 ± 28.4	57.1 ± 25.1	0.002

Mean ± SD

HFS hemifacial spasm, *AUC* area-under-the curve, *BRER* blink reflex excitability recovery, *R1 latency and R2 latency post hoc analysis* symptomatic side of HFS vs. healthy subjects $p < 0.000$, *R2 AUC post hoc analysis* symptomatic side of HFS vs. healthy subjects $p < 0.000$; normal side of HFS vs. healthy subjects $p < 0.000$, *BRER, 200 ms posthoc analysis* symptomatic side of HFS vs. healthy subjects $p < 0.001$; normal side of HFS vs. healthy subjects $p < 0.05$, *BRER, 600 ms posthoc analysis* symptomatic side of HFS vs. healthy subjects $p < 0.001$; normal side of HFS vs. healthy subjects $p < 0.001$, *BRER, 1000 ms posthoc analysis* symptomatic side of HFS vs. healthy subjects $p < 0.005$

[a]Kruskal–Wallis test

The mean BRER at each ISI was also higher on both symptomatic and asymptomatic sides of patients with HFS than on healthy subjects (Table 2). When patients with different types of discharge were compared, no significant difference in recovery excitability of BR on the symptomatic side (Fig. 2A), on the asymptomatic side (Fig. 2B), or recorded on the orbicularis oris was found. There was a slight and positive relationship between the age of patients and BRER% ($r = 0.252$, $p = 0.000$). There was no correlation between disease duration and BRER ($p = 0.802$).

There was no significant difference in iR2/cR2 among patients with different types of discharge (Table 3).

Discussion

Our study analyzed the BRER in patients with HFS and compared it between different abnormal discharge patterns. The major findings in this study were as follows: (i) there was enhanced BRER on both symptomatic and asymptomatic sides in patients with HFS, (ii) isolated discharges appeared earlier in the disease course than grouped bursts or tonic spasms, and iii. BRER was similar in patients with different abnormal discharge patterns.

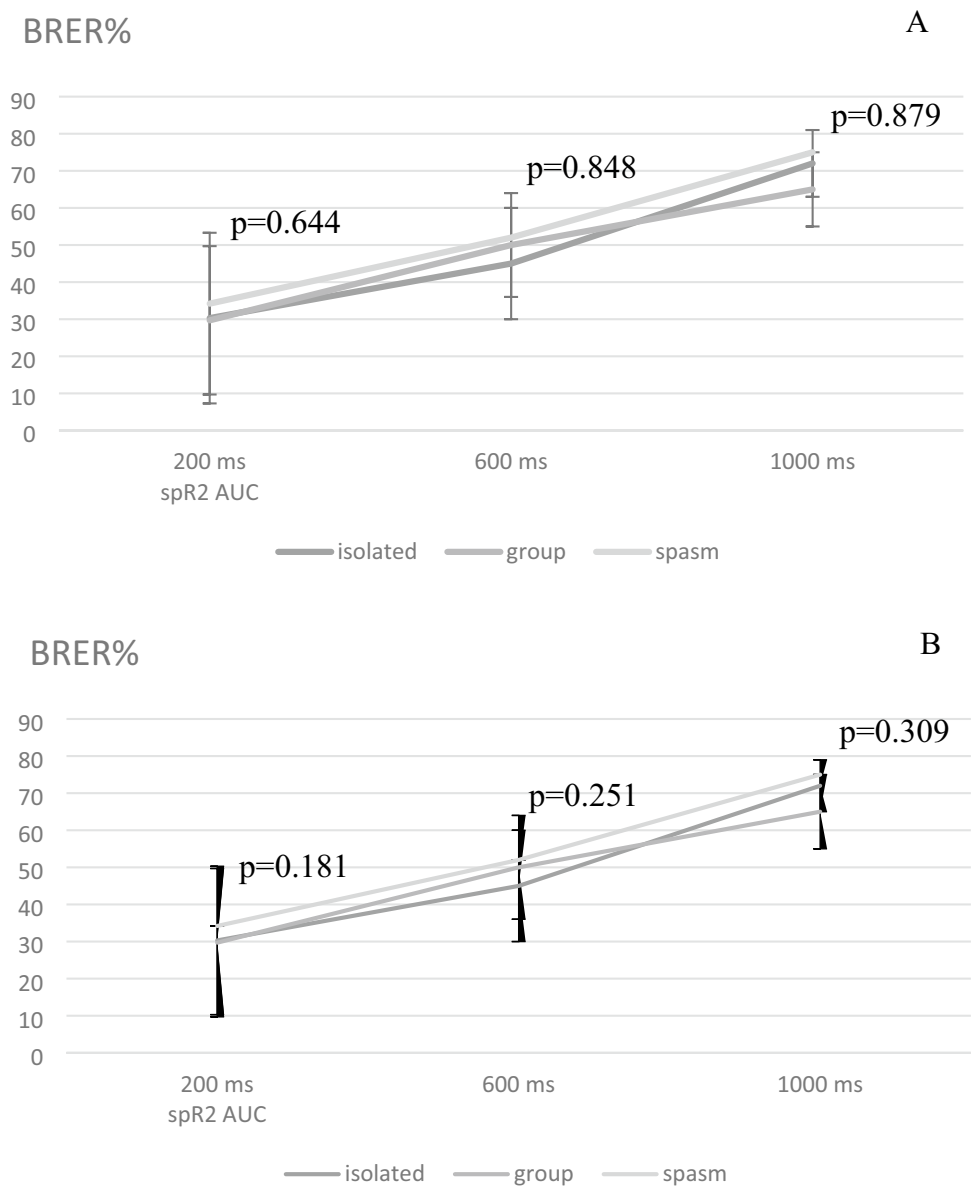

Fig. 2 Comparisons of patients with different types of discharge regarding blink reflex excitability recovery were recorded from the orbicularis oculi muscle on the spasm side or the asymptomatic side and recorded on the orbicularis oris muscle. *asymp* asymptomatic side, *AUC* area-under-the curve, *BRER%* recovery excitability of R2 component of blink reflex, *group* patients with grouped bursts forming random sequences, *isolated* patients with isolated discharges, *O.or* orbicularis oris muscle, *sp* symptomatic side, *spasm* patients with continuous muscle activity with tonic spasm

Table 3 Comparison of the ratio of R2 AUC after ipsilateral stimulation to contralateral stimulation between patients with different bioelectrical spasm activity

	Isolated discharges	Grouped bursts	Tonic spasm	p^a
iR2 AUC/cR2 AUC	1.3 ± 0.7	1.2 ± 0.9	1.2	0.990

c contralateral, *i* ipsilateral, *AUC* area-under-the-curve

[a]Kruskal–Wallis test

Hemifacial spasm is associated with increased excitability of the BR pathway [5, 6, 11]. We also replicated similar findings on both symptomatic and asymptomatic sides of the patients, which indicates increased excitability of the BR pathway in patients with HFS in this study. However, as reported in various studies, enhanced BRER abnormalities are not specific to HFS. An enhanced BRER may be seen in extracranial dystonia syndromes or in other movement disorders, such as idiopathic Parkinson's disease, multiple system atrophy, or progressive supranuclear palsy [12] or even in a subgroup of patients with multiple sclerosis having asymmetric hemispheric involvement [13]. BRER from 100 to 300 ms in idiopathic Parkinson's disease after stimulation of the less affected side was higher than BRER obtained after stimulation of the more affected side, whereas no differences were found in atypical parkinsonism syndromes [14]. The asymmetry index calculated using stimulations of more and less affected sides could discriminate idiopathic Parkinson's disease from atypical parkinsonism syndromes

except for corticobasal degeneration. Because in corticobasal degeneration, the involvement of abnormal BRER was symmetrical despite the asymmetrical cortical atrophy or asymmetrical parkinsonism [15]. We did not observe asymmetric involvement in HFS despite the clinical asymmetric findings. HFS is considered a facial nerve disorder caused by an irritating lesion in the facial nerve at its root exit zone. Previous findings of bilateral BRER enhancement in HFS were attributed to the increased excitability of the interneuron pool [5]. However, it may also suggest a suprasegmental modulation of BRER.

In line with our hypothesis, we classified patients into four groups using polymyography: patients with isolated discharges, patients with grouped bursts forming random sequences, patients with continuous muscle activity with tonic spasms, and any combination of these discharges. We excluded the patients with combinations of the discharges from the analysis. Previously, there was information that isolated discharges appeared earlier in the clinical course of the disease, and other forms of bursts develop in time with disease progression [4], which was also confirmed by our findings. Patients with isolated discharges were younger and had shorter disease duration than those with grouped bursts or tonic spasms. Considering these findings, our hypothesis was the emergence of an enhanced BRER in patients with longer disease duration or patients with grouped bursts or tonic spasms. In contrast to our main hypothesis, we found no difference in enhanced BRER among HFS patients with different discharges. This is an important finding as it implies that the increased BRER in HFS patients is unrelated to the type of discharge patients experience. Furthermore, it suggests that the underlying pathophysiology of HFS may be more complex than previously thought [3, 5, 16] and that the mechanisms causing increased excitability may be multifaceted. Brainstem and cortical networks are in close communication. Similar abnormalities across different discharge patterns suggest the various types may be related to basal ganglia–brainstem connections. We should also emphasize that BRER does not express whole brainstem excitability. Although the increased excitability at the motoneuron or interneuron pool is supposedly responsible for HFS, other brainstem pathways, which are not measured by BRER, may play a role.

In the normal population, BRER is inversely correlated with age [17]. The BRER is generally significantly influenced by age but not by sex. It shows an inverse correlation with age, indicating reduced BRER with aging [17]. In HFS, it is clear that BRER is mildly higher among elderly patients. In our study, there was a direct relationship with aging, suggesting that this effect may result from chronicity of the disease. A previous cohort study also showed a slight correlation between BRER and disease course [5]. However, the analysis between disease duration and BRER in our study did not confirm such a relation.

We acknowledge certain limitations of the study. The major limitation of the study was the need for longer surveillance. This was a cross-sectional study. We did not have the opportunity to investigate a more extended period of these patients since we chose to analyze in the botulinum toxin naïve period. All the patients were examined before treatment, and as a matter of fact, they were treated after the analysis. However, the high number of patients included in the analysis is the superiority of our study. One patient group included only one patient. Thus, the comparisons were practically a comparison of two main groups. Although nerve conduction studies are reported to be relatively safe [18], caution was recommended for repetitive nerve stimulation and proximal nerve stimulations under certain conditions [19]. Therefore, in our laboratory, we traditionally avoid giving repetitive stimulations or head, neck, or Erb point stimulations in patients with pacemakers. However, no patients were excluded due to this criterion.

Conclusion

In conclusion, our findings of increased neural excitability in the BR pathway in HFS patients occur regardless of the discharge type. However, further follow-up studies with larger sample sizes will confirm these results.

Data availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Conflict of interest Authors report no conflict of interest.

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