HEMIFACIAL SPASM: AN ELECTROPHYSIOLOGICAL EVIDENCE OF FACIAL MOTOR NEURONS HYPEREXCITABILITY

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ชื่อวิทยาศาสตร์	โรคหน้ากระตุกครึ่งซีก: หลักฐานทางสรีรวิทยาไฟฟ้าที่แสดงถึงภาวะไวเกินต่อการกระตุ้นของเซลล์ประสาทสมองคู่ที่เจ็ด
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บทคัดย่อ

กลไกการกระตุกของกล้ามเนื้อในผู้ป่วยโรคหน้ากระตุกครึ่งซีกยังเป็นที่โต้แย้งกันอยู่ว่า เกิดจาก ephaptic transmission หรือ เกิดจากภาวะไวเกินต่อการกระตุ้นของเซลล์ประสาทสมองคู่ที่เจ็ด

<u>วัตถุประสงค์</u>

เพื่อพิสูจน์ว่ากลไกในการกระตุกของกล้ามเนื้อในผู้ป่วยโรคหน้ากระตุกครึ่งซีกเป็นผลมาจาก ภาวะไวเกินต่อการกระตุ้นของเซลล์ประสาทสมองคู่ที่เจ็ด และ brainstem interneurons

<u>แบบการทดลอง</u>

การศึกษาในครั้งนี้ใช้ paired-shock technique กระตุ้นให้เกิดการตอบสนองของ blink reflex ในผู้ป่วยโรคหน้ากระตุกครึ่งซีกจำนวน 20 รายและในคนปกติ

21 ราย โดยมีระยะห่างระหว่างตัวกระตุ้นตัวแรกและตัวกระตุ้นตัวที่สองอยู่ในช่วง 50-900 msec ซึ่งจะแสดงให้ทราบถึงการเปลี่ยนแปลงของภาวะไวต่อการกระตุ้นของเซลล์ประสาทในแต่ละราย โดยจะใช้ paired stimuli กระตุ้นหน้าทั้งสองซีกและบันทึกการตอบสนองที่กล้ามเนื้อ orbicularis oculi ทั้งสองซีกของใบหน้าพร้อม ๆ กัน

ผู้ถูกทดลอง

ผู้ป่วยโรคหน้ากระตุกครึ่งซีกจาก Movement Disorder Clinic สาขาวิชาประสาทวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล จำนวน 20 ราย และคนปกติ 21 ราย อายุระหว่าง 30-60 ปี

ผลการทดลอง

ในการศึกษาครั้งนี้พบว่าคนปกติค่า absolute refractory period ของ R_2 response อยู่ในช่วงระหว่าง 200-400 msec โดยมีค่าเฉลี่ยและส่วนเบี่ยงเบนมาตราฐานเท่ากับ 271.42 $\pm$ 64.36 msec แต่ในกลุ่มผู้ป่วยจะมีค่า absolute refractory period อยู่ในช่วงระหว่าง 100-200 msec ค่าเฉลี่ยและส่วนเบี่ยงเบนมาตราฐานเท่ากับ 160 $\pm$ 50.26 msec ทั้งในหน้าด้านกระตุกและด้านปกติไม่ว่าจะกระตุ้นจากด้านใดก็ตาม ซึ่งแสดงให้เห็นว่าค่า absolute refractory period ของผู้ป่วยโรคหน้ากระตุกครึ่งซีกได้ผลสั้นกว่าในบุคคลปกติอย่างมีนัยสำคัญทางสถิติ ($p<0.05$)

สรุปผลการทดลอง

ผลจากการศึกษาวิจัยครั้งนี้ชี้บ่งว่า กลไกการกระตุกของกล้ามเนื้อในผู้ป่วยโรคหน้ากระตุกครึ่งซีกนั้น เป็นผลมาจากภาวะไวเกินต่อการกระตุ้นของเซลล์ประสาทสมองคู่ที่เจ็ด และ brainstem interneurons ในวงจร blink reflex

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ABSTRACT

The underlying mechanism of muscle spasm in patients with hemifacial spasm (HFS) remains controversial; ephaptic transmission or facial nucleus abnormal hyperexcitability.

Objective

To prove the underlying mechanism of muscle spasm in HFS that was due to the hyperexcitability of facial motoneurons and brainstem interneurons .

Design

Paired-shock technique was performed to elicit blink reflex response in 20 HFS patients and 21 normal subjects. A

second shock delivered at a varying time interval between 50-900 msec after the first reveals excitability changes induced by a preceding impulse. In each case, paired stimuli were applied on both sides of the face and simultaneous recorded response from the orbicularis oculi muscles on both sides.

Subjects

Twenty HFS patients from the Movement Disorder Clinic, Division of Neurology, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University and 21 normal subjects were recruited. Age range between 30-60 years.

Results

In normal subjects, the absolute refractory period of R_2 response was found to lie between 200-400 msec with mean and standard deviation of 271.42 and 64.36 msec. On the other hand, in patient group, it was found to lie between 100-200 msec with mean and standard deviation of 160 and 50.62 msec on both the affected and the unaffected sides, irrespective the side of stimulation. These indicate that the absolute refractory period of HFS patients was significant shorter ($p<0.05$) than the absolute refractory period of normal subjects.

Conclusion

This findings suggest that the underlying mechanism of HFS is the enhanced excitability of facial motoneurons and brainstem interneurons mediating blink reflex.

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HFS	=	hemifacial spasm
CT	=	computed tomography
MRI	=	magnetic resonance imaging
AICA	=	anterior inferior cerebellar artery
PICA	=	posterior inferior cerebellar artery
Hz	=	Hertz
R_1	=	the early component of blink reflex
R_2	=	the late component of blink reflex
R_{2c}	=	the late component of blink reflex of contralateral side
G_1	=	active electrode
G_2	=	reference electrode
msec	=	millisecond
EMG	=	electromyogram
Na^+	=	sodium ion
C	=	degree of Celsius
cm	=	centimeter
p	=	probability
N	=	number
SD	=	standard deviation
yrs	=	years
M	=	male
F	=	female

CHAPTER I

INTRODUCTION

The facial muscles (Figure 1), or muscles of facial expression provide humans with the ability to express a wide variety of emotions, including frowning, surprise, fear and happiness. The muscles themselves lie within the layers of superficial fascia. As a rule, they arise from bones or fascia of the skull and insert themselves into the skin. Because of their insertions, the muscles of facial expression move the skin rather than a joint when they contract (Figure 2). All are supplied by the facial nerve (1, 2).

Hemifacial spasm (HFS) is a movement disorder of the face characterized by involuntary paroxysmal bursts of tonic or clonic movements of the facial muscles innervated by the seventh cranial nerve (3, 4, 5). It was first described by Schultze in 1875 (3). Hemifacial spasm is considered to be a form of segmental myoclonus, often starting as "twitches" in upper and lower eyelids, spreading gradually to involve the remainder of the orbicularis oculi and other facial muscles. In advanced cases, spasm increases in both severity and frequency, resulting in prolonged contraction of several muscles on the affected side of the face (Figure 3). This particular spasm was provoked by

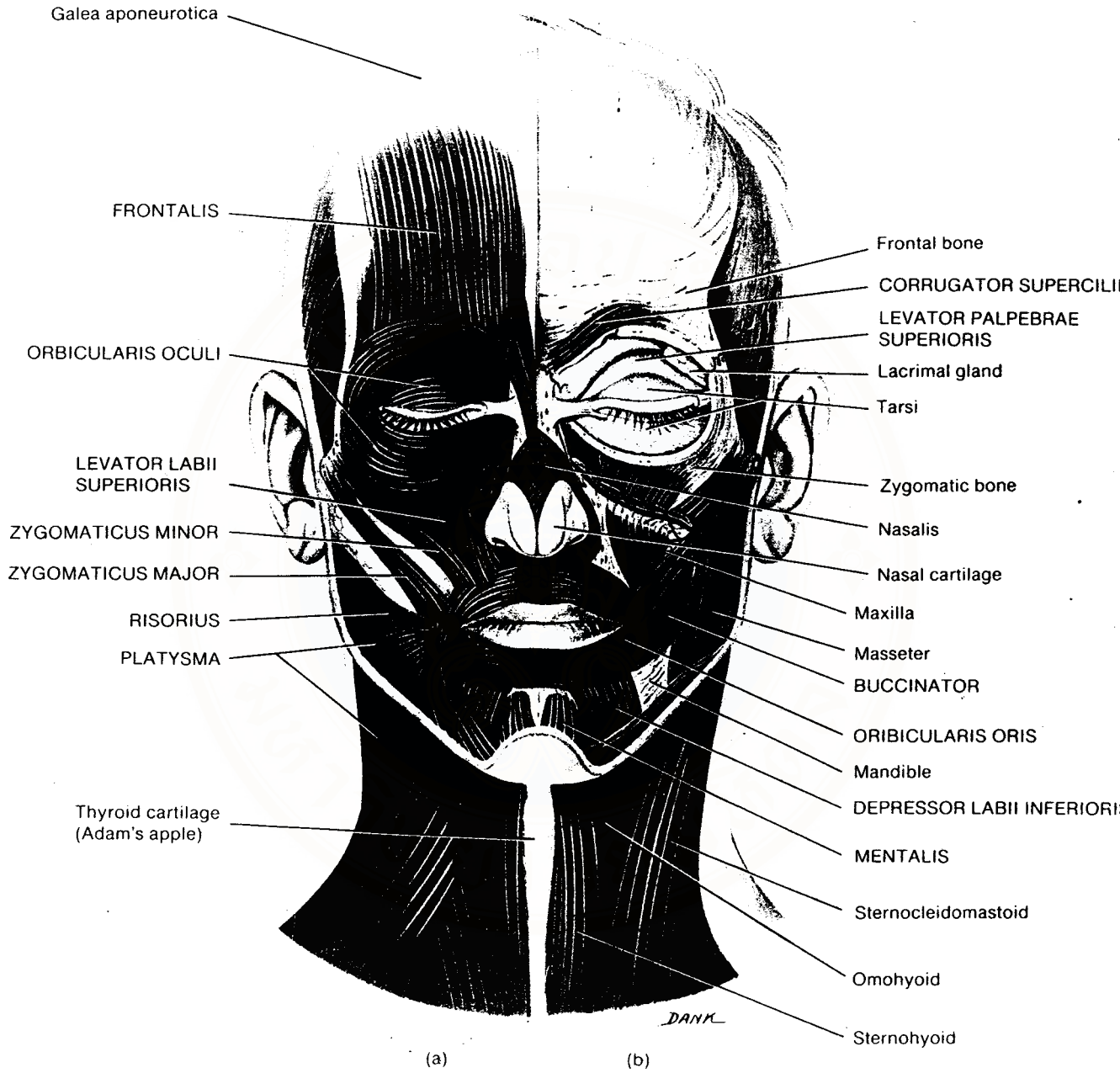
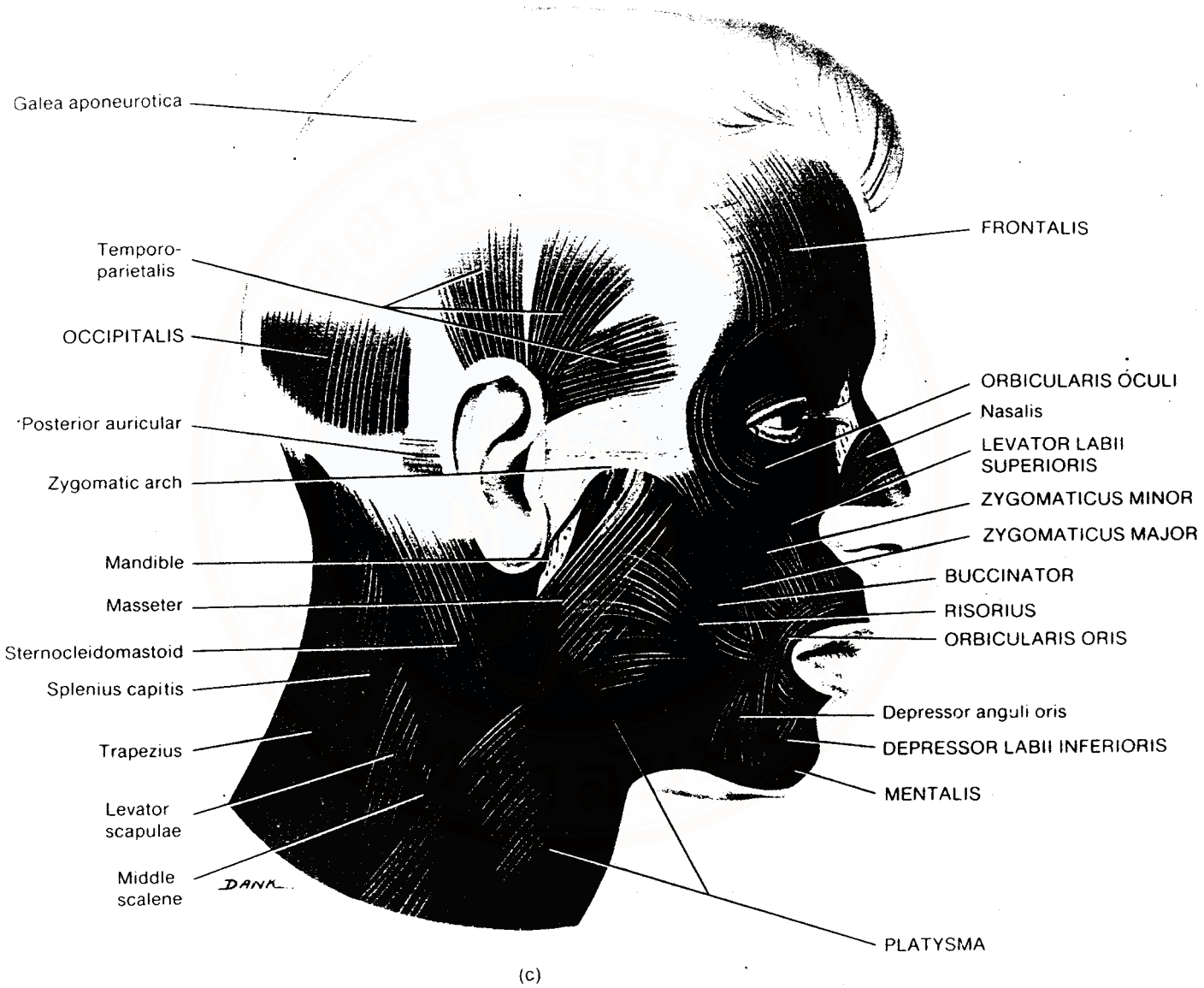


Figure 1. Muscles of facial expression

(a) anterior superficial view

(b) anterior deep view.



(c)

Figure 1. (continued)

(c) lateral superficial view.

Palpebral Part

Orbital Part

Orbicularis Oculi

Frontalis

Corrugator Supercilii

Procerus

Nasalis

Risorius

Depressor Anguli Oris

Orbicularis Oris

Zygomaticus Major

Mentalis

Figure 2. Muscles of expression in action.

Figure 3. Patient with hemifacial spasm.

tension and fatique and was relieved by relaxation. Volitional activation of one muscle results in synchronus involuntary contraction of other muscles. Many patients complain about persistence of the spasms at night, which prevent them from sleeping, and also their occurrence during sleep (3, 4, 5, 6). Occasionally, spontaneous remissions occur that last for weeks, months, or even years; but ordinarily, once begun, the condition remains permanent (7, 8).

Aside from involuntary muscle spasms described above, HFS patients may also have synkinesias in the affected side. These associated movements are not always present. A typically observed synkinesia consists in the simultaneous contraction of the orbicularis oris, mentalis or platysma when the subject blinks, especially after a burst of spasms. Although HFS patients rarely complain of pain, an aching sensation or "tightness" is experienced by some with predominantly tonic spasms. Besides the discomforting twitching nature of HFS, patients also complain of difficulty in concentrating in a variety of tasks, such as reading or sewing, which require mental concentration and accurate vision (7).

Although HFS may occur in all age group, it usually starts in middle age. Women outnumber men 3:2, and the left side is more frequently involved than the right side (3, 5, 7), which in some patients turn into bilateral HFS (4).

Etiology of Hemifacial Spasm

In the pre-CT era, HFS was commonly considered "idiopathic" because appropriate radiographic studies were not always performed (3). Many surgeons have reported vascular structures lying across the root entry zone (REZ) of the seventh cranial nerve and have treated it as the offending agent causing HFS. Indeed, once the compressing vessel is wrapped, or otherwise separated from the nerve, HFS usually improves or disappears (3, 7, 9, 10, 11, 12). According to surgeons who have reported abnormal vessels, those vessels thought to be the prime offenders in HFS are the anterior inferior cerebellar artery (AICA), posterior inferior cerebellar artery (PICA), and acoustic artery or internal auditory artery. Occasionally, veins that traverse this area will be found to compress the facial nerve. According to some surgeons an artery is the offending structure in about 92% of cases. Frequently, the basilar artery or vertebral arteries are shifted from the midline to lie in this region as well. In addition to a branch of the basilar artery or vertebral arteries being closely applied to the seventh cranial nerve, arteriovenous malformations have been reported to cause HFS (3, 5).

Although aberrant vessels or abnormal vasculature appears to be the most common cause of HFS, the most common tumor associated with HFS is an epidermoid or cholesteatoma of the

cerebellopontine angle. Neuromas and meningiomas of the cerebellopontine angle have also been reported, and bony abnormalities including basilar invagination or impression have occasionally been implicated (3, 7). In addition, families with autosomal dominant inheritance of HFS have been described (5, 13). Table 1 details the causes of HFS spasm in 1,688 cases reviewed in the 1988 study by Digre and Corbett (3).

Table 1. Etiology of hemifacial spasm in 1,688 reported cases.

Vascular (N=509)	
Abnormal vessels	475
Dolichoectatic-basilar artery	16
Aneurysm	9
Ateriovenous malformation	8
Persistent acoustic artery	1
Tumor (N=19)	
Cerebellopontine angle tumors	17
Petrous ridge meningioma	1
Parotid tumor	1
Bony abnormalities (N=7)	
Basilar impression	5
Cranio-occipital malformation	1
Paget's disease	1
Other (N=4)	
Multiple sclerosis	2
Peripheral injury	2
Not specified	986
Unknown (after confirmatory radiographic study, surgery, or at autopsy)	163

When computed tomography (CT) and magnetic resonance imaging (MRI) were applied to the study of HFS, it's etiology was determined to be mostly an abnormally large, long, displaced vessel, presumed to be a dolichoectatic basilar/vertebral artery which, by its configuration could predict the side of HFS 89% of the time. Because of the high percentage of diagnostic accuracy of CT and MRI studies, even more causes of HFS may yet be elucidated and the "idiopathic" classification will continue to shrink in size. Now, it is generally accepted that the cause of HFS is the cross-compression of the facial nerve where it enters the brainstem (9, 14, 15).

Pathophysiology of Hemifacial Spasm

Although it is not clear how the cross-compression of the facial nerve causes the symptoms of HFS, and the site of physiological abnormality causing those symptoms is also unclear, three different hypotheses have been proposed to explain the pathophysiological underlying mechanism of muscle spasm in HFS.

First, aberrant regeneration is thought to represent a sprout of nerve going to a muscle not normally innervated by that nerve (Figure 4) (3, 4). However, this explanation has not had much success in explaining the features of nontraumatic HFS, as these patients have no history of facial nerve injury.

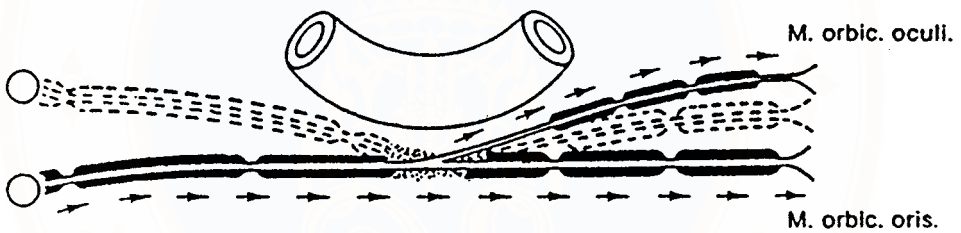


Figure 4. Aberrant regeneration.

The second is ephaptic transmission or "cross-talk" (Figure 5) which was proposed by Gardner in the early 1960s. The term comes from "ephapse" which means "to touch" or a point of contact. Theoretically, ephaptic contact can depolarize axons bidirectionally (orthodromically and antidromically), but usually only depolarizes axons unidirectionally (orthodromically) in the facial nerve. Nielsen suggests that the mechanism for HFS is the result of the formation of an artificial synapse between nerve fibers at the injury site. The ephaptic transmission is a "mass effort" of polarity charges in areas where decreased resistance lowers the firing threshold in damaged or ischemic nerve (10).

Finally, Moller in 1984 proposed an alternative electrophysiologic explanation for HFS. He suggested that the damaged site becomes a trigger zone which generates and transmits impulses orthodromically as well as antidromically. So, the antidromic impulses activate facial motoneurons, which cells in turn send impulses down the facial nerve, causing the HFS. He calls this phenomenon a "kindling" effect (Figure 6).

The pathophysiologic mechanisms underlying the spasm, though, are unclear. The ephapsis theory of Gardner and kindling mechanism of Moller are both attractive and both may have merit. However, there is no consensus regarding the interpretation of neurophysiologic data at this time.

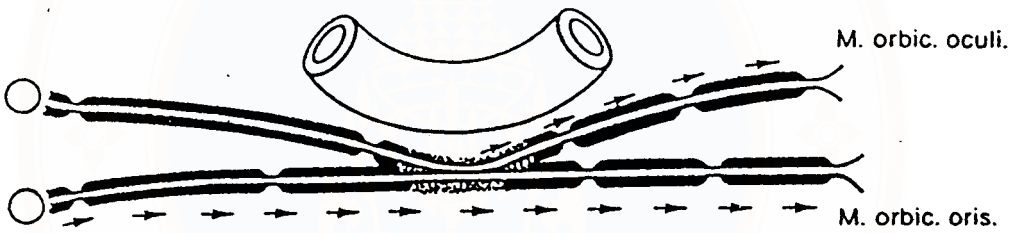


Figure 5. Ephaptic transmission or "cross talk".

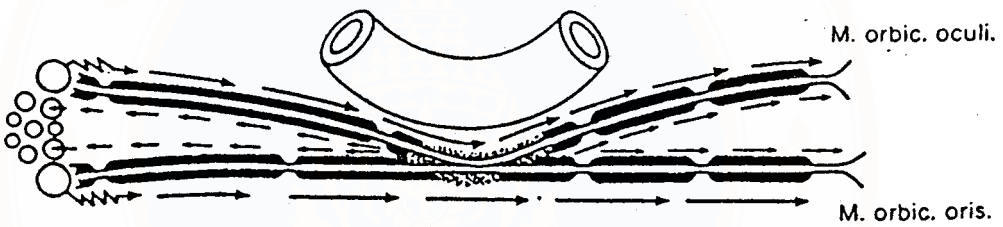


Figure 6. "Kindling" model.

The Hypothesis of This Research

Enhanced excitability of facial motoneurons and of those brainstem interneurons in patients with HFS is the underlying mechanism of muscle spasm.

The Aims of This Research

To prove the aforementioned hypothesis, the following electrophysiological measures were recorded

1. Absolute refractory period of blink reflex R_2 responses in patients with HFS and normal controls.

2. The mean values of absolute refractory period in patients and normals were compared.

Review Literature

Both the clinical and electrophysiologic measures were studied widely to explain the pathophysiological underlying mechanism of muscle spasm. Most researchers hold to one of two hypotheses on the underlying mechanism of HFS : either ephaptic transmission between injured nerve fibers at the site of compression or facial motoneurons. As an example, Sadjadpour (11) suggested that certain postfacial palsy phenomena (e.g.,

facial contracture, crocodile tears, etc) have been examined in relation to faulty misrouting of the nerve fibers, which thus far has been offered as an explanation for such phenomena. Analogy was made with the problem of HFS, occuring without antecedant facial palsy. Evidence was presented to support the thesis that both the HFS and postfacial palsy phenomena are due to formation of an "artificial synapse" (an ephapse) at the site of nerve injury. This would allow for crossing-over of impulses from one nerve fiber to another and interaction between afferent and efferent axons, analogous to the situation of bare, uninsulated electrical wires placed adjacent to each other.

Nielsen (17) studied 62 patients with HFS to test for the presence of ephaptic transmission an ectopic excitation. Following stimulation of zygomatic or mandibular branches of the facial nerve, simultaneous recording from the orbicularis oculi and mental muscles showed transmission of impulses between two branches involving a fraction of slow conduction motor nerve fibers. The after-activity and late-activity following the passage of an antidromic impulse indicated the presence of autoexcitation with an interspike frequency of 250 to 350 Hz. A similar result was obtained when studied the blink reflex, the latency and amplitude of the early (R_1) component of orbicularis oculi response were increased as compared with the unaffected side and controls, in keeping with pathologic findings of focal demyelination (18). Hypercalcemia, induced by hyperventilation,

gave rise to ectopic excitation, that in turn caused synchronous spasms of the facial muscles. These findings suggested that ectopic excitation and ephaptic transmission played an important role in the pathophysiology of HFS.

Spontaneous and associated hyperkinetic facial movements and contracture which follow injury to the seventh cranial nerve (postparalytic HFS) or arise without known previous injury (cryptogenic HFS) are pathological phenomena not found in the distribution of other cranial or somatic motor nerves. The commonly expressed hypotheses of pathogenesis -- aberrant regeneration and fiber excitation by false synapse formation (ephapses) at the sits of injury -- can not account for all aspects of these phenomena or for the uniqueness of such movements to the distribution of the seventh nerve. Ferguson (8) suggested that the diversity of facial motor behaviour, which encompasses voluntary, emotional, and especially automatic, associated, and reflexive movements, was based on a unique central organization that sets it apart from other motor groups. He hypothesized that because of this organization, the changes following axonal injury -- which include selective deafferentation, glial response, axonal sprouting, functional reconnection, and hyperexcitability from dendritic spike generation -- can unmask and augment automatic, associated and reflexive movements already present in the facial neuronal network to result in facial hyperkinesia.

Esteban et al (19) studied 53 cases of primary HFS by means of blink reflex and compared their results with a normal control group. Reflex responses were obtained by cutaneous electrical stimulus of both the supraorbital nerve (trigemino-facial reflex), and the facial nerve at the stylo-mastoid region (facio-facial reflex). The R_2 response was considered abnormal when its latency was shortened (hyperactivity) or delayed (hypoactivity). Thirty six out of 53 cases with primary HFS showed abnormal responses, with a combination of facial nerve impairment (delayed R_2 in the facio-facial reflex) and trigeminal facial hyperactivity (shortened R_2 in the trigemino-facial reflex). Five cases show hyperactivity in both the trigemino-facial reflex and the facio-facial reflexs. These results suggest a state of hyperexcitability, probably at the level of the facial nucleus, combined with a peripheral facial nerve involvement in a high proportion of patients with primary HFS.

Elmqvist et al (20) studying 20 patients with HFS noted no consistent synchronization between the motor unit discharges from different muscles. They found no synkinetic movements on the affected side of the face between spasms. Stimulation of individual branches of the facial nerve gave rise to a direct response in the muscle innervated by the branch but no lateral spread to any other muscles. However, stimulation on either side of the face elicited a late response on the affected side of the

face but not on the opposite side. This would be expected if the shocks intended for a branch of the facial nerve inadvertently activated the cutaneous branch of the trigeminal nerve. It would elicit R_2 in the orbicularis oculi muscle and in the presence of synkinesis, in other facial muscles on the affected side as the result of lateral spread. They interpreted these findings as indicative of a hyperexcitable facial nucleus rather than the existence of ephaptic transmission between fibers innervating different facial muscles.

Moller and Janetta (14, 15, 16) tested the validity of ephaptic transmission at the site of a lesion by measuring the latency of various responses intraoperatively. In HFS patients, stimulation of one branch of the facial nerve caused contraction of muscles innervated by a different branch of the facial nerve. If such a lateral spread results from ephapses, the onset latency of the delayed response should equal the antidromic and orthodromic conduction to and from the resumed site of lesion. However, the response from the orbicularis oculi muscle to electrical stimulation of the marginal mandibular nerve exceeded the sum by a few milliseconds. Obtaining similar results from the mental muscles after stimulation of the zygomatic branch, they concluded that synkinesias resulted from facial motoneurons rather than ephaptic transmission.

Sole and Tolosa (21) studied electrically elicited blink reflex responses in HFS patients by applying single and paired stimuli on both sides of the face. Responses after single stimuli were of larger size on the side of spasm compared with the uninvolved side and controls. With paired stimuli, the inhibitory effect of the conditioning stimuli upon the test stimuli late response (R_2), which was always observed in normals, was significantly less pronounced at short interstimuli intervals in patients. This resulted in an enhanced recovery curve of R_2 which was observed on the side of the spasm, as well as the contralateral, clinically normal side. Patients with longer disease duration showed more striking abnormalities of the recovery curve. They suggested that there was an enhanced excitability of facial motoneurons and of those brainstem interneurons that mediate the blink reflex pathway in HFS patients.

Although the pathophysiologic mechanism remained unclear, the recent results mentioned above tend to support a facial motoneuron hyperexcitability as being the underlying mechanism of muscle spasm. In this research, paired stimuli blink reflex with various interstimulus intervals were applied. This technique clearly demonstrates facial motoneuron excitability by the onset of recovery from twin pulses are basically dependent on neuronal excitability : the earlier the onset of recovery, the greater the excitability of motoneurons being tested. It is speculated that early onset of recovery should be obtained in HFS.

The Blink Reflex

Blinking in response to a tap on the face has been studied clinically since it was first described by Overend in 1896 (22, 23, 34). He described it as a new "cranial reflex" and considered that the afferent stimuli come from cutaneous rather than from deep structures such as periosteum, bone or muscle. After this original description, the blink reflex was described under a multitude of different names according to the area tapped, the muscles which responded, and the mechanism considered to be responsible. In 1945 Wartenberg reviewed the controversy over the nature of this response, which he termed the "orbicularis oculi reflex". He proposed that, in general, all reflexs be divided into "skin-muscle" (superficial or cutaneous) and "deep muscle" depending on where the receptors responsible for them were thought to lie. He felt that the corneal reflex was a superficial reflex of the orbicularis oculi muscle whereas the blink reflex was a "muscle reflex". Wartenberg had the "definite impression" that tapping was effective by its activation of intramuscular receptors directly or indirectly "by transmission of the concussion to the muscle" through bone or other tissues.

Studies of the corneal reflex, assessed as part of the clinical examination of neurologic disorder, fall short of providing accurate quantitative analysis. In contrast, the

electrically-or mechanically-elicited blink reflex allows one to record the evoked potential with an oscilloscope for precise determination of the reflex latency and amplitude. Stimulation of the supraorbital nerve elicits two temporally separate responses of the orbicularis oculi, an early (R_1) component and a late (R_2) component (Figure 7 a). The early component has a shorter latency and is more synchronized than the second. R_1 is evoked only on the side of stimulation via a pontine pathway. In contrast, unilateral stimulation elicits R_2 bilaterally, presumably relayed through a more complex route, including the pons and lateral medulla (Figure 7 b) (22, 23, 24, 25).

Stimulation of the trigeminal nerve elicits reflex contraction of the orbocularis oculi. The blink reflex reflects the integrity of the afferent and efferent pathways including the proximal segment of the facial nerve. As mentioned earlier, a single shock to the supraorbital nerve evokes two separate contractile responses of the orbicularis oculi. The latency of R_1 represents the conduction time along the trigeminal and facial nerves and pontine relay. R_2 is less reliable for this purpose, because of inherent latency variability from one trial to the next. Furthermore, the latency of R_2 reflects the excitability of interneurons and the delay for synaptic transmission in addition to the axonal conduction time.

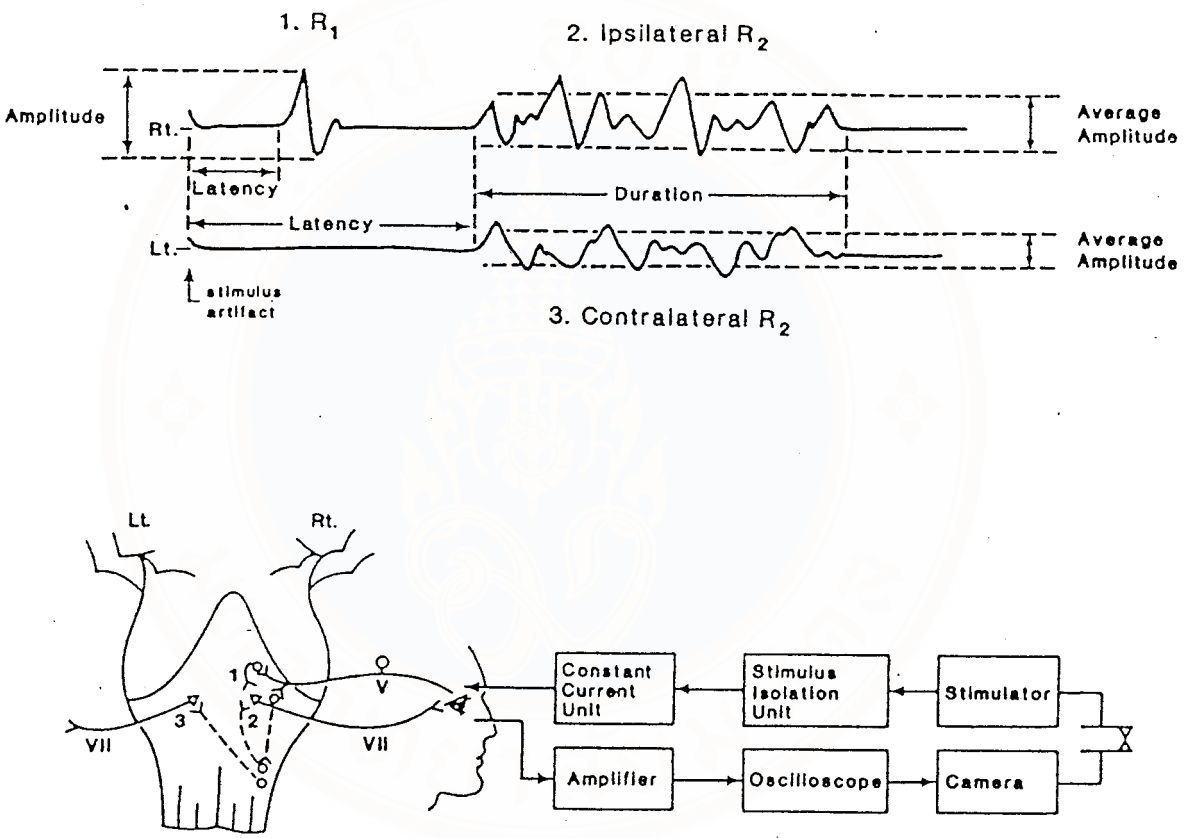


Figure 7. Blink reflex

(a) blink reflex response

(b) blink reflex pathway.

In most clinical studies, the subject lies supine on a bed in a warm room with eyes either open or gently closed. Surface electrodes suffice for stimulation of the nerve and recording of the evoked muscle action potentials. The recording leads consist of an active electrode (G_1) on the upper or lower lateral aspect of orbicularis oculi and a reference electrode (G_2) on the temple or the lateral surface of the nose, with a ground electrode under the chin or around the arm. The supraorbital nerve is stimulated with the cathode placed over the supraorbital foramen on one side. A two-channel osciloscope allows simultaneous recording from the orbicularis oculi on both sides (25).

In order to interpret results of blink reflex studies properly, it is important to recognize certain features which distinguish one of the two components from the other. The R_1 component is briefer in duration and relatively more constant in latency, size, and shape than the R_2 component. Also, R_1 is seen only on the side of stimulation, whereas R_2 is seen bilaterally. In different normal subjects, values for minimal latency range from 8 to 14 msec for R_1 and 23 to 44 msec for R_2 component produced by electrical stimulation over the supraorbital nerve (23). The minimal latency difference for R_1 on the two sides in the same individual in normally less than 1.5 msec. Apprehension results in a marked increase of the amplitude of the second component, with diminution in the size of R_1.

Similarly, there is a decrease in the amplitude or disappearance of R_1 in light sleep, whereas R_2 is then prolonged in its duration. With repeated stimulation in a relaxed subject, there is "habituation" of the R_2 component, i.e., successive stimuli result first in a decrease in the amplitude and duration of the response, which may finally completely disappear (23).

Recording of blink reflexes electromyographically is a simple, reproducible procedure which can be performed in any clinical EMG laboratory. Determination of values for the minimal latency of the two components on the ipsilateral side and the second component on the contralateral after stimulation of the supraorbital nerve can be useful in localizing a lesion in the trigeminal and/or facial nerves. Thus, a prolonged latency for first and second components on the ipsilateral side and the second component on the contralateral side suggests a lesion of the afferent arc, i.e., the ipsilateral trigeminal nerve. On the other hand, unilateral delay in the latency of the second component, regardless of the side of stimulation, suggests a lesion of the efferent arc, i.e., the facial nerve. Changes in latency as well as amplitude of the two components of the blink reflex can also be produced by lesions of the central nervous system, a fact which must be recognized whenever one is performing any reflex study for diagnostic purposes. Finally, as mentioned earlier, one must take into consideration verious physiological variables which influence reflex studies in a

clinical setting.

Paired-shock Technique

A second shock delivered at a varying time interval after the first reveals excitability changes induced by a precending impulse. In this method, called the paired-shock technique or the conditioning and testing technique, the first shock conditions the nerve, and the second impulse tests the resulting effect. The test stimulus, given during the absolute refractory period of the conditioning stimulus elicits no response. During the relative refractory period that follows, the test response shows reduced amplitude and increased latency (26).

The physiologic mechanism underlying the refractory period is inactivation of sodium (Na^+) conductance, following the passage of an impulse, sodium channels will close to initiate repolarization. Once closed or inactivated, they cannot open immediately, regardless of the magnitude of depolarization by a subsequent impulse. This constitutes the absolute refractory period. During the subsequent relative refractory period, only an excessive depolarization, far beyond the ordinary range, can reactivate sodium conductance. Here, the impulse propagates more slowly than usual, because it takes longer to each the elevated critical level required to generate the action potential. The

refractory period is prolonged with low temperature, advanced age, slow conduction velocity, and after experimental demyelination.

Studies of the blink reflex tended to overemphasized latency determination without due regard to the size of R_1 and R_2. A proper analysis of their amplitude, however, can estimate the level of brainstem reactivity, provided, of course, that the patient has intact trigeminal and facial nerves. Instead of applying single stimuli, paired shocks given in a conditioning and testing paradigm help differentiate the excitability of motor neurons and interneurons based on the differing recovery curves of R_1 and R_2.

CHAPETER II

MATERIALS AND METHODS

Subjects

Twenty one healthy subjects served as a normal control group, age range between 30-60 years. They had no history of neurological or muscular disease, drug abuse, alcoholism, diabetes mellitus and were without any medications for at least one week prior to the test.

Twenty HFS subjects from the Movement Disorder Clinic, Division of Neurology, Department of Medicine, Siriraj Hospital, ranging in age from 30-60 years were recruited. Every patient had been treated symptomatically, either by clonazepam, diclofenac or botulinum toxin injection.

Experimental Procedures

The study was performed at the Electromyographic Laboratory of Neurology Division, Department of Medicine, Siriraj Hospital. The technique used was paired-shock technique to elicit the blink reflex response as previously described by Kimura (19).

During the study, subjects lay supine on a couch in a quiet and warm room (27°C) with eyes gently closed. Recording leads consisted of an active electrode placed on the orbicularis oculi muscle (mid-lower eyelid) and a reference electrode on the temple, with the ground electrode wound around the arm. The cathode of the stimulating electrode was placed at the supraorbital foramen and the anode was 3 cm away over the skin of the frontal bone (Figure 8).

A two-channel computerized oscilloscope allows simultaneous recording from the orbicularis oculi muscles on both sides. The electrical stimulus from a Grass stimulator (model SD 9) was a 0.2 msec rectangular shock of appropriate intensity which was adjusted to obtain a well-defined R_1 (the early component) and a stabilized latency of the R_2 (the late ipsilateral component) and of the R_{2c} (the late contralateral component) of the blink reflex response. Action potentials were recorded by a Dantec Neuromatic 2000C with a frequency band pass of 20-2,000 Hz.

When the stimulus was adjusted to appropriate intensity, the same intensity shocks were delivered in pairs (paired-shock technique), with interstimulus intervals (delay times between conditioning and test stimuli) varying between 50 and 900 msec, with 100 msec increments between 100-900 msec. A rest period of not less than 30 seconds was allowed between each stimulation.

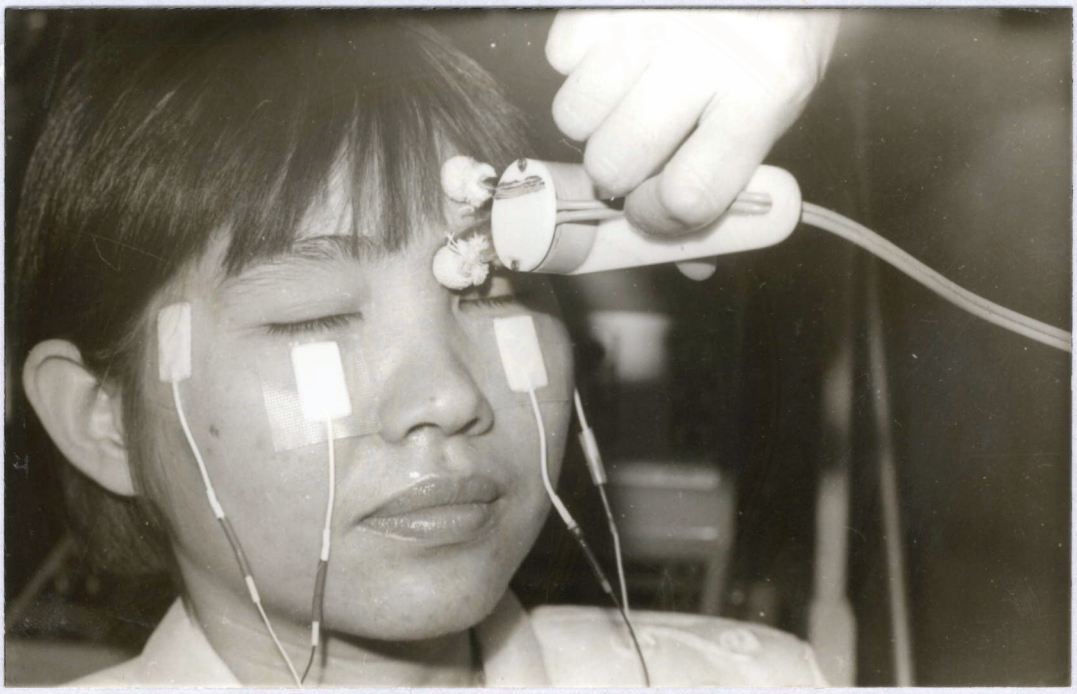


Figure 8. Technique for recording the blink reflex.

Testing at each interstimulus interval was repeated at least 4 times, to ensure reproducible responses. With both HFS patients and normal control subjects, paired stimuli were applied on both sides of the face.

Measurements

In each case, The shortest interstimulus interval which evoke R_2 response of test stimuli was recorded. The latencies of ipsilateral and contralateral R_2 response which obtained following pair stimuli was measured from stimulus artifact to the initial deflection of the evoked potential response (Figure 9).

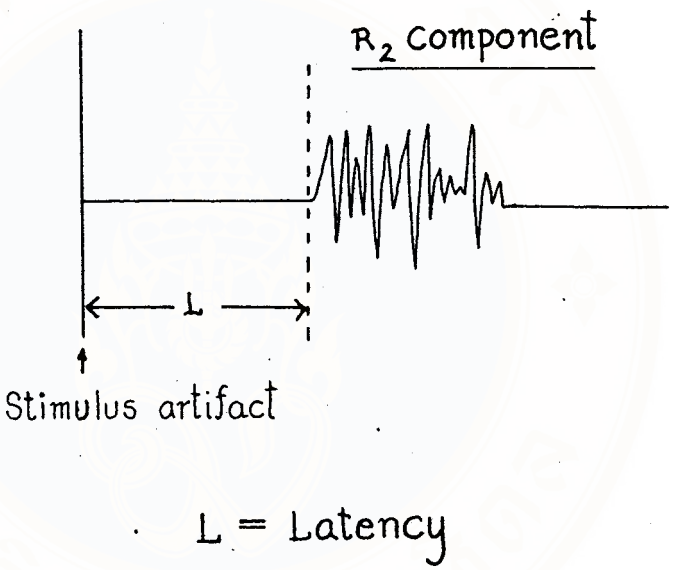


Figure 9. The measurement response in term of latency.

Statistical Analysis

The data were presented as mean with standard deviation of all data from both sample groups (normals and HFS patients). Statistical analysis was performed using student's t-test. Data with p values <0.05 were considered statistically significant.

Equipment

1. Dantec Neuromatic 2000C : the response recorder (Figure 10).

- The Dantec Neuromatic 2000C is a two-channel neuromyograph for clinical electromyography and evoked responses. It is a microcomputer-controlled instrument, comprising an active electrode box with patient isolated inputs, EMG amplifiers, microcomputer averages, monitor, loudspeaker and chart recorder.

2. Grass stimulator (model SD9) : the electrical stimuli generator (Figure 11).

- The SD9 is a solid-state stimulator, offering built-in stimulus isolation rather than remote stimulus isolation. It is designed for classical nerve and/or muscle stimulation by using single pulses, repetitive pulses and twin pulse pairs.

3. The delay time expansion module (Figure 12).

- This is an instrument module which is designed to

increase the time interval of twin pulse pairs from the Grass stimulator. It is composed of 3 selectable capacitors. By using the delay time expansion module, the SD9 has a variable delay function between 0.02 to 2,000 msec.

4. The connecting cables (Figure 13).

- They were used to join the delay time expansion module with the Grass stimulator, and the Grass stimulator with the Dantec Neuromatic 2000C, in the experimental hook up as shown in Figure 17.

5. The recording electrode (DISA 13L22) (Figure 14).

6. The patient ground (Figure 15).

7. The stimulating electrode (Figure 16).

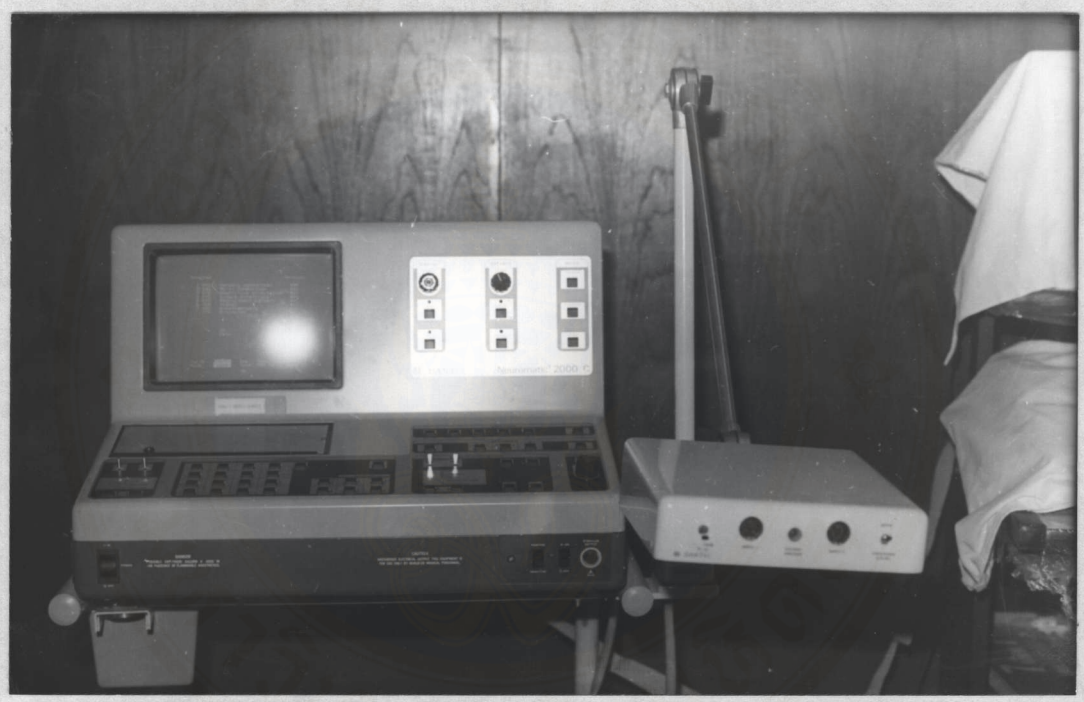


Figure 10. Dantec Neuromatic 2000C.

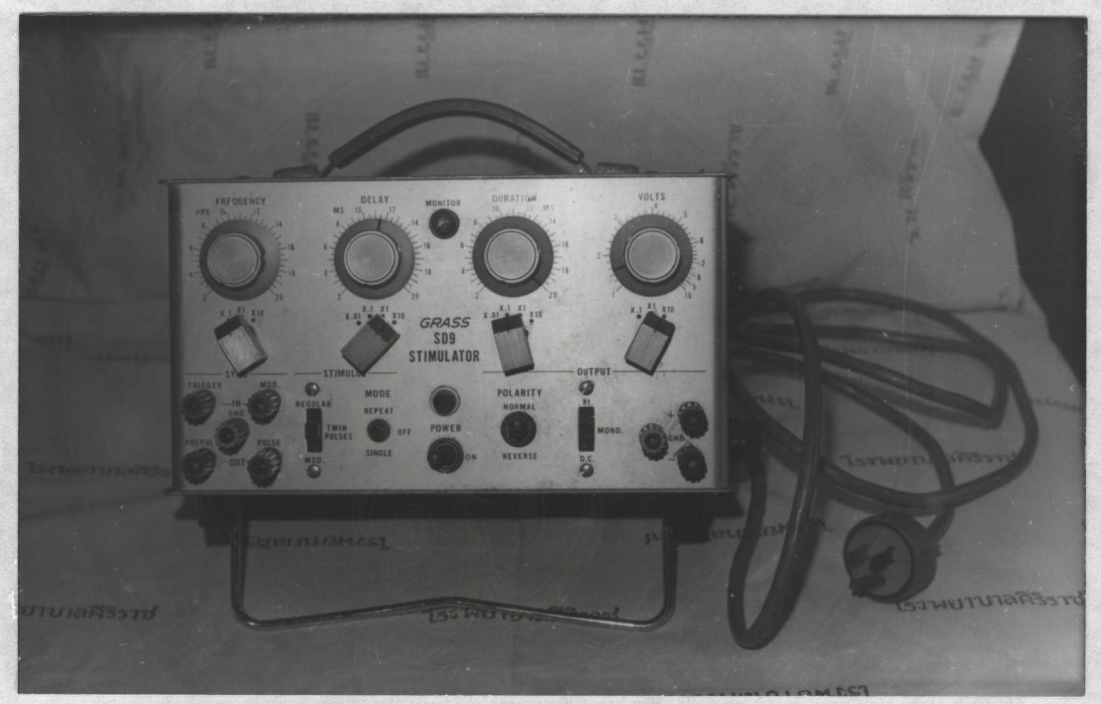


Figure 11. Grass stimulator (model SD9).

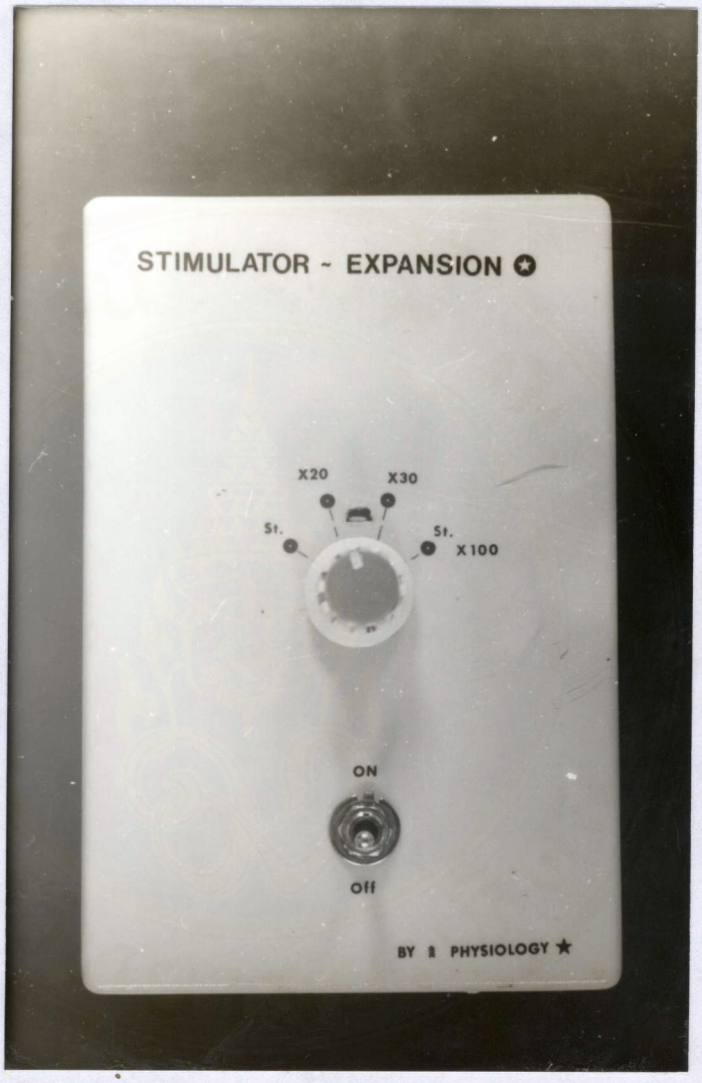


Figure 12. Delay time expansion module.

Figure 13. Connecting cables.

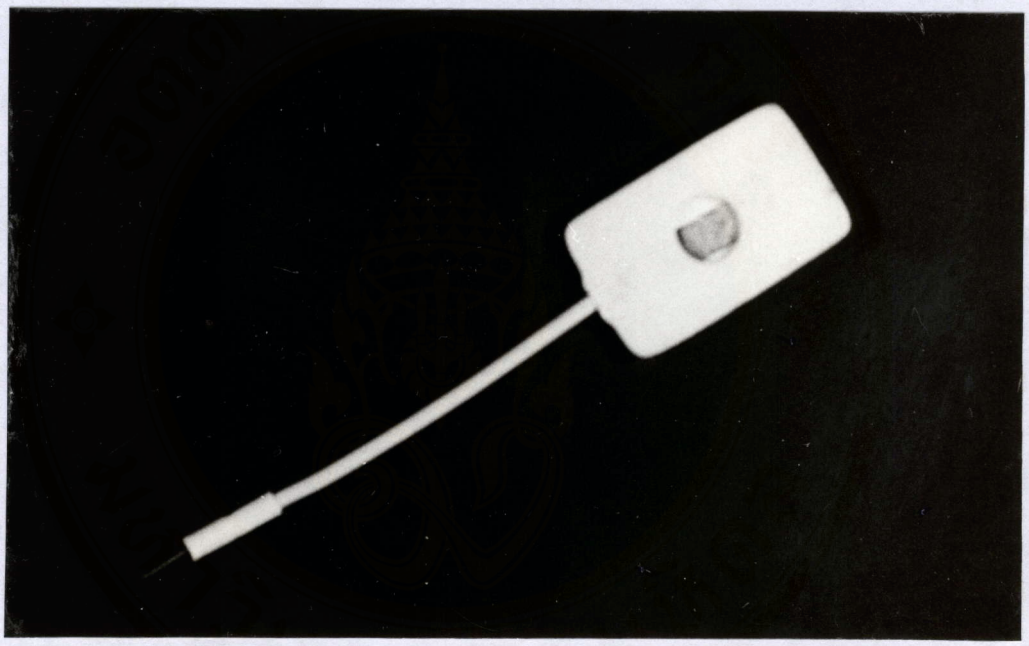


Figure 14. Recording electrode.

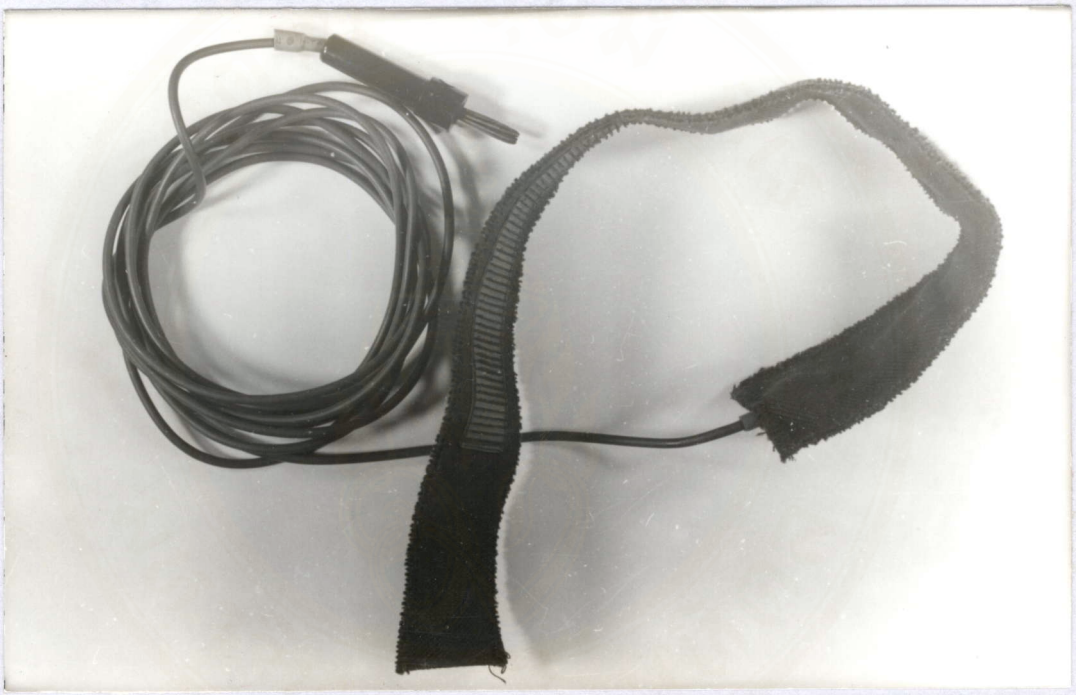


Figure 15. Patient ground.

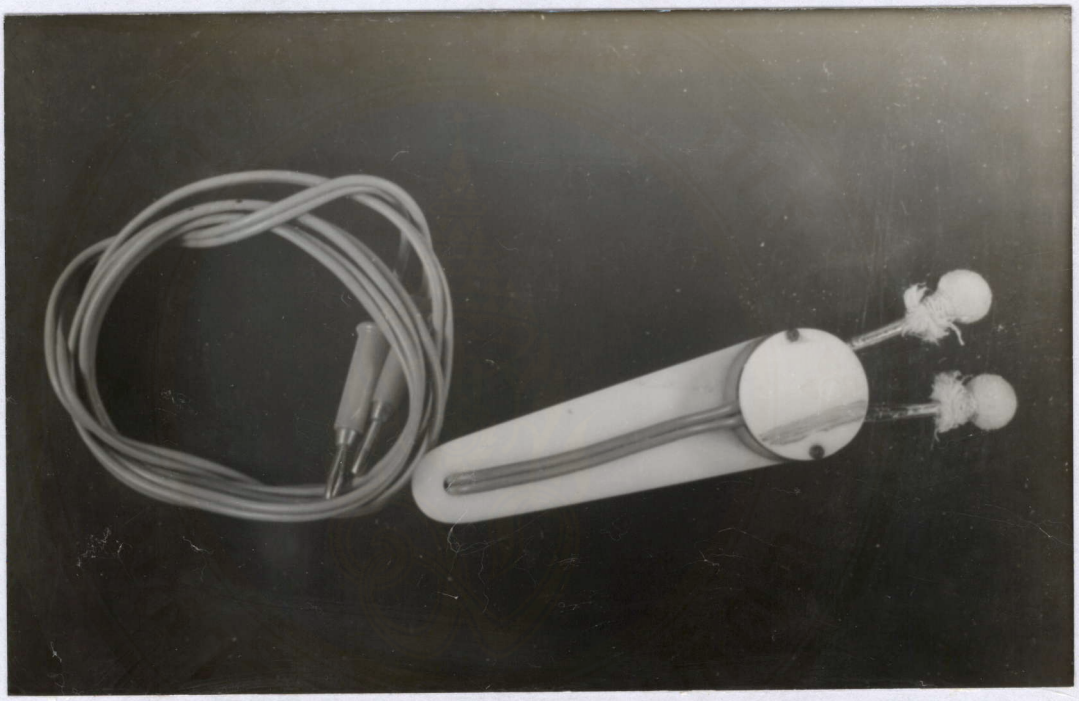


Figure 16. Stimulating electrode.

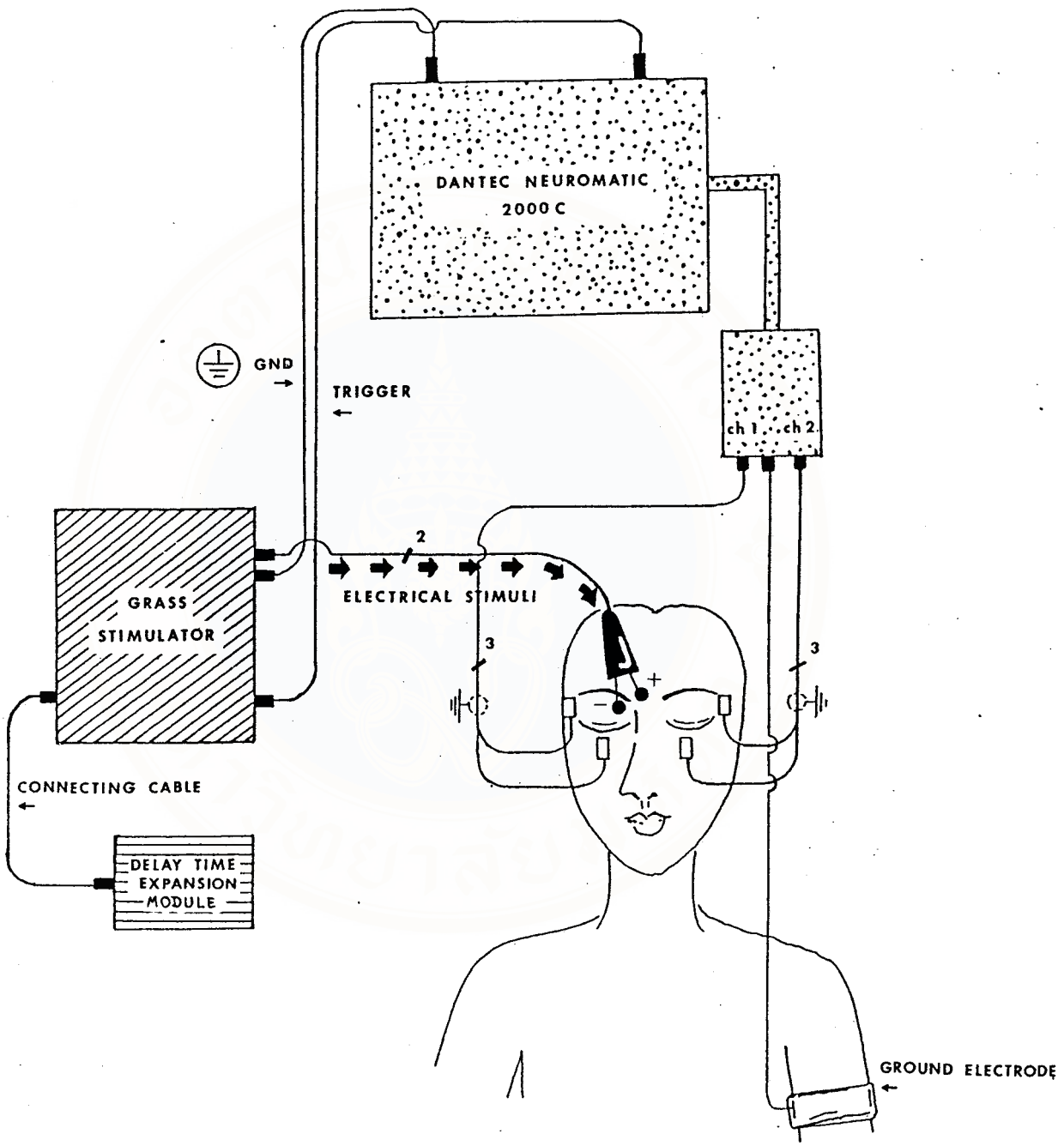


Figure 17. Diagrammatic representation of the apparatus used for paired shock technique to elicit blink reflex.

CHAPTER III

RESULTS

All subjects tolerated the test procedure very well, with no complaints of pain, headache or other sickness during the study procedure. In the control group, there were 12 males and 9 females. The mean age of normal subjects was 49.14 yrs (SD=5.28). In the patient group, there were 5 males and 15 females. Nine patients had right HFS and 11 patients had left HFS. Duration of symptoms ranged from 1 to 13 years. The mean age of patients with hemifacial spasm was 51.75 yrs (SD=9.51). No significant differences in age were found between two groups. The physical characteristics of the control and patient groups are shown in Table 2.

Table 2. Physical characteristics of the control and patient groups.

Group	N	Age (x ± SD) (yrs)	Sex		Duration of symptom (yrs)	Affected side	
			M	F		Right	Left
HFS	20	51.75 ± 9.51	5	15	1-13	9	11
Control	21	49.14 ± 5.28	12	9	-	-	-

For both controls and HFS patients, the mean latency of R_2 responses elicited by paired stimuli are shown in Table 3.

Table 3. The latency of R_2 response (mean ± SD)

Group	Latency of R_2 response	
	Cond. stimuli	Test stimuli
Control	28.95 ± 4.10	33.50 ± 4.76
HFS	29.92 ± 3.60	34.82 ± 4.63

The percentage of subjects related with the shortest interstimulus interval to elicit R_2 test responses and the mean

values of the shortest interstimulus interval are tabulated in Table 4 and 5. In normal subjects, the shortest interstimulus interval to elicit R_2 test responses was found to be 200 msec in 47.62%, 300 msec in 54.4% and 400 msec in 9.5%, with a mean and standard deviation at 271.42 and 64.36 msec respectively. In HFS patients, the shortest interstimulus interval to elicit R_2 test responses was found to be 100 msec in 40% and 200 msec in 60%, with a mean and standard deviation at 160 and 50.26 msec respectively. The shortest interstimulus interval for HFS patients was significant shorter ($p<0.05$) than that for normal subjects. Figure 18 represents the shortest interstimulus interval to elicit R_2 test responses related with the percentage of subjects in both groups and mean of those in Figure 19.

Table 4. The percentage of subjects related with the shortest interstimulus interval.

The shortest interstimulus interval (msec)	Percentage of subjects	
	Normal (N=21)	HFS (N=20)
100	-	40%
200	38.1%	60%
300	52.4%	-
400	9.5%	-

Table 5. The shortest interstimulus interval (mean ± SD).

Group	Stim.side/Rec.side	The shortest interstimulus interval
Normal	RR RL LR LL	271.42 ± 64.36
HFS	II IC CI CC	160 ± 50.26 *

* significant difference with p value<0.05 when compared between groups.

when RR, RL, LR, LL, II, IC, CI and CC represent :

RR = stimulated and recorded response on right side.

RL = stimulated right side and recorded response on left side.

LR = stimulated left side and recorded response on right side.

LL = stimulated and recorded response on left side.

II = ipsilateral responses following stimulation of the involved side.

IC = contralateral responses following stimulation of the involved side.

CI = contralateral responses following stimulation of the uninvolved side.

CC = ipsilateral responses following stimulation of the uninvolved side.

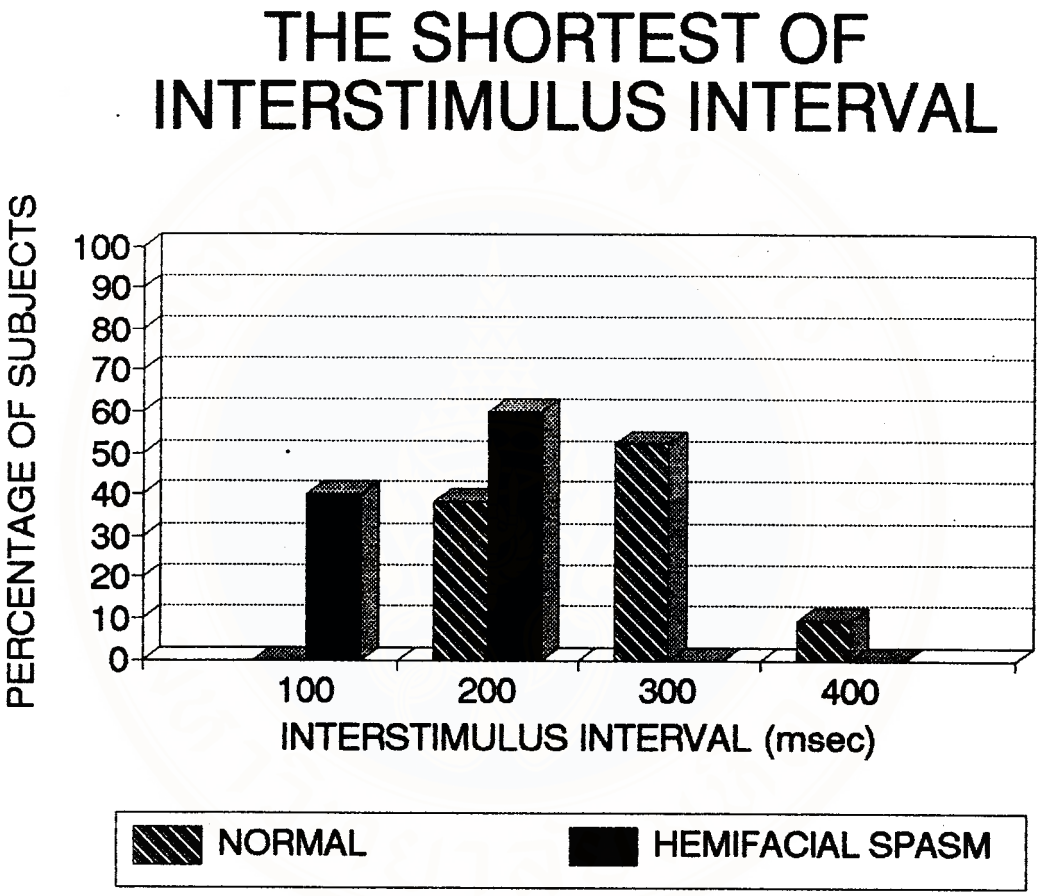
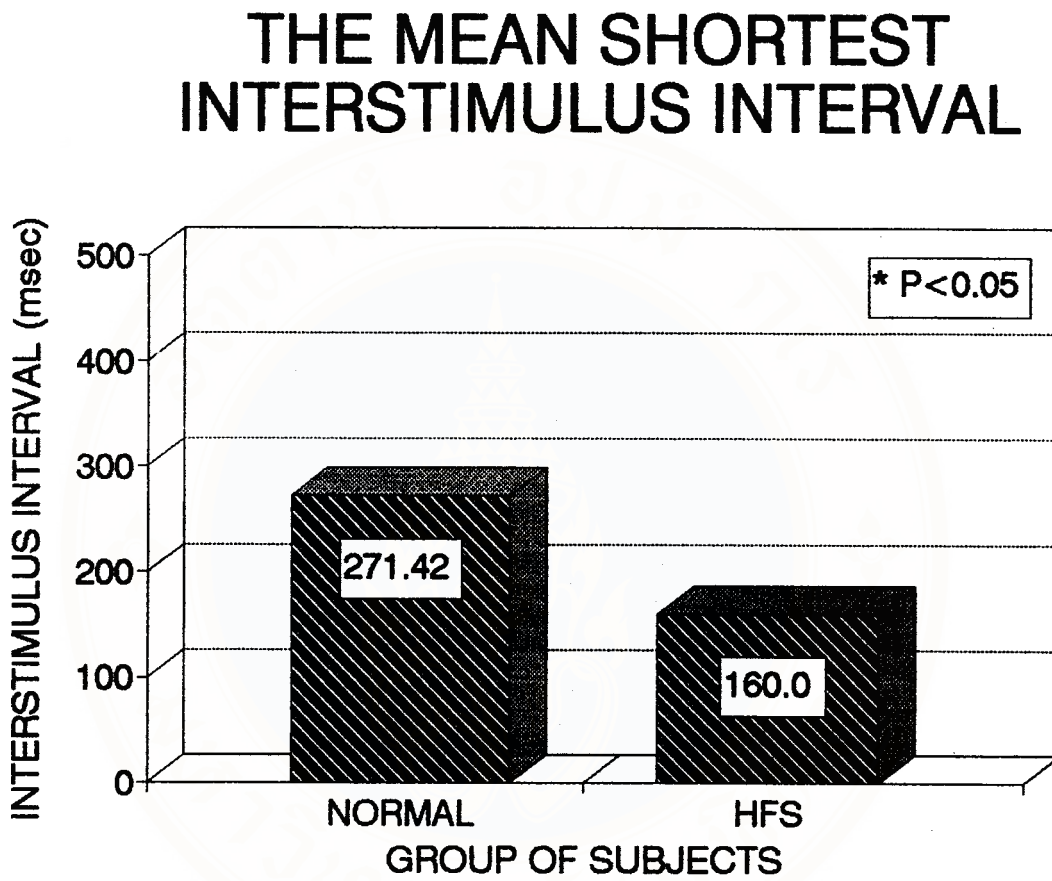


Figure 18. The shortest interstimulus interval to elicit R_2 test response.



* significant difference with p value <0.05 when compared between groups.

Figure 19. The mean shortest interstimulus interval.

The R_2 conditioning and test responses following paired-shock technique at the shortest interstimulus interval of typical normal subject and HFS patient were depicted in Figures 20 and 21. In normal subjects the recovery of R_2 test responses was obtained at an interstimulus interval of 300 msec. In HFS patients the recovery of R_2 test responses were obtained earlier i.e, at a 100 msec interval.

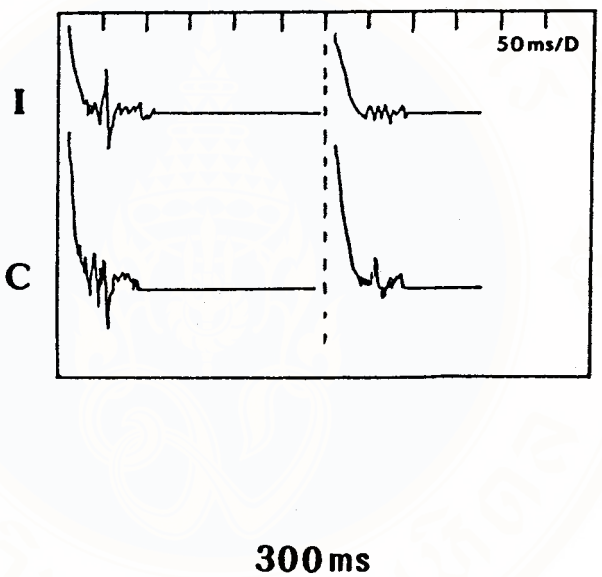


Figure 20. Recording tracing of R_2 responses in typical subject from normal subjects.

I = ipsilateral responses of stimulated side.

C = contralateral responses of stimulated side.

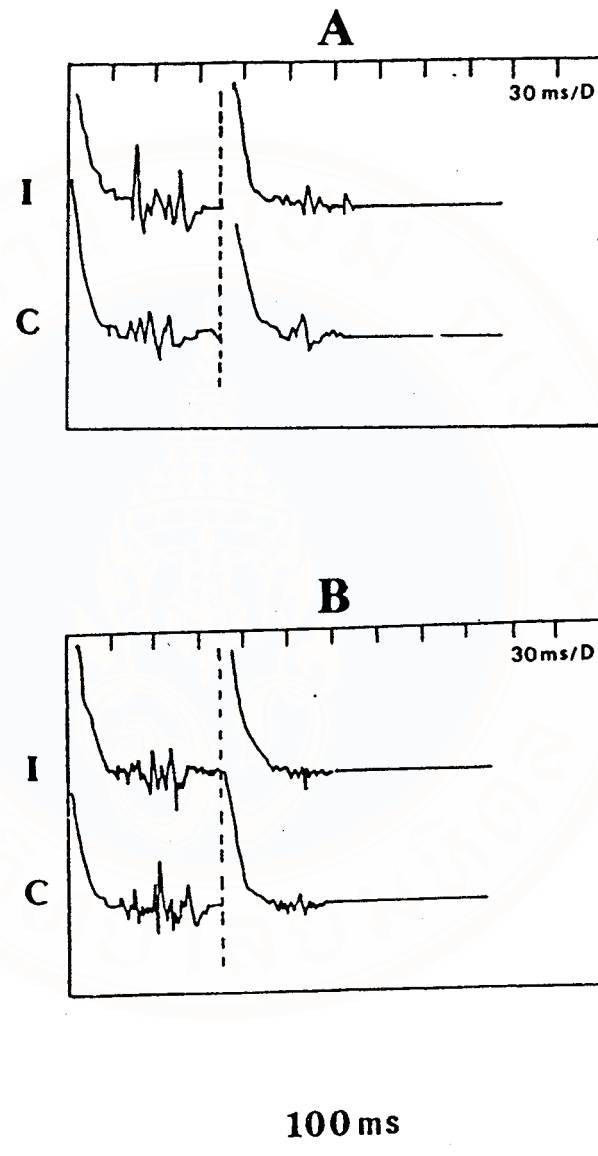


Figure 21. Recording tracing of R_2 responses in typical subject from patients with hemifacial spasm.

A = stimulating the involved side.

B = stimulating the uninvolved side.

I = ipsilateral responses.

C = contralateral responses.

CHAPTER IV

DISCUSSION

The current view on the etiology of HFS (3, 9, 12, 14, 15) is that a vascular structure compresses the facial nerve near its entry zone at the level of the pons. This hypothesis has been strongly supported by the satisfactory results obtained after surgery on that region (9, 12, 27). Electrophysiological studies to try to explain the mechanism of muscle spasm were performed several years ago, but they were contradictory. Abnormal prolonged response (after-activity) and late-activity as well as synkinesis, in which voluntary activation of one muscle is accompanied by involuntary coactivation of other facial muscles, were all observed. These observations led to ectopic excitation and/or ephaptic transmission as the underlying causes for HFS (10, 11, 17, 18). However, the ephaptic transmission theory cannot explain spontaneous tonic/clonic spasm or the lateral spreading of early (R_1) blink reflex on the contralateral unaffected side (8, 28), and neither theory explains why similar motor phenomena do not occur in areas supplied by other cranial or somatic nerves (8). So, after-activity and late-activity, as well as synkinesias, may represent either facial motoneuron hyperexcitability or unstable interneuron pools.

In intraoperative studies of facial nerve stimulation, it was reported that latency of the orbicularis oculi response to mandibular nerve stimulation was longer than the sum of conduction times from the same mandibular nerve stimulation to the facial root entry zone and from facial root entry zone to the orbicularis oculi muscle (14, 15, 16). The time differences obtained would be due to the time elapsed in reverberant activity of facial motonucleus prior to firing along facial nerve. In addition, the R_1 component of the blink reflex can be elicited from the affected side in HFS patients who were undergoing microvascular decompression operations under inhalation anesthesia, but not on the unaffected side (9, 29). That supports the hypothesis that the blood vessel pressing upon the facial nerve changes the function of the facial motor nucleus.

Ferguson, in his extensive review of anatomical, physiological and clinical studies, has proposed that the nucleus reaction following proximal facial nerve injury and reorganization of facial motoneuron pools should be the mechanism underlying muscle spasm in HFS patients (8). This was supported by an animal study showing that normal function of the facial mimetic muscle is dependent on this somatotopy. After peripheral nerve transection, regenerating axons frequently fail to find their way back to their original innervation territory. Consequently, alterations in the central localization of motor neurons projecting to different peripheral nerve branches might

be expected (32). All of this precludes ephaptic transmission as the underlying mechanism of muscle spasm in HFS patients.

It is the purpose of this research study to prove the hypothesis that hyperexcitability of facial motoneurons and brainstem interneurons is the underlying mechanism of HFS-type muscle spasm.

There are several techniques to test neuronal excitability. For example, one is the strength-duration curve (31, 32, 33) (Figure 22). The threshold intensity, just capable of exciting the axons, varies according to the duration of the current, in that the shorter the duration, the greater the intensity to achieve the same degree of depolarization. The strength-duration curve plots this relationship with motor point stimulation that elicits a constant muscle response. The excitability characteristics expressed by this curve can therefore differentiate a normally innervated muscle from a partially or totally denervated one. For the formulation of numeric indices of excitability, rheobase is defined as the minimal current strength below which no response occurs, even if the current lasts 300 msec or longer. Chronaxic is the minimal duraton of a current required to excite the cell at twice the rheobase strength. Although of historical interest, neither rheobase nor chronaxic has proven satisfactory as a test in clinical practice, and the strength duration curve itself has

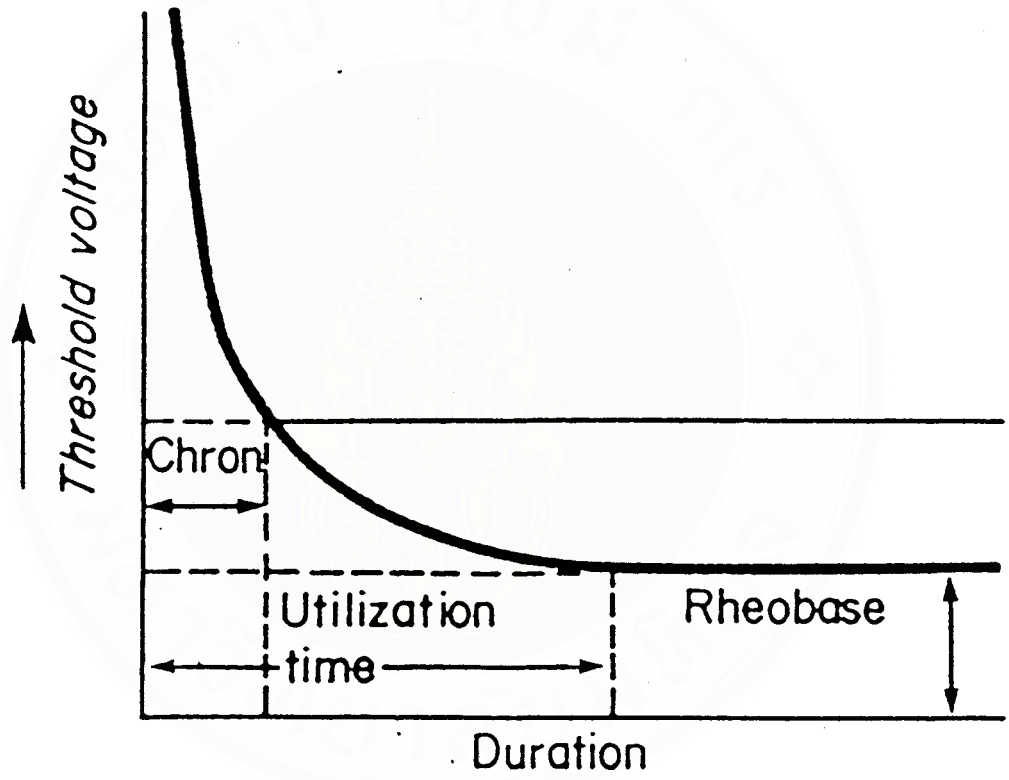


Figure 22. The strength-duration curve.

fallen into disrepute because of the excessive time required for its determination and the complexity of its interpretation.

Paired-shock is another technique to test excitability. It is based on the principle that a second shock delivered at a varying time interval after the first reveals excitability changes induced by the preceding impulse. This technique is a quantitative, accurate, non-painful test. Excitability, as tested by this technique, is not modified by the effect of treatment with botulinum toxin (34). For these reasons it is therefore superior to nerve conduction and electromyographic study (35). Application of paired shock technique to the blink reflex should assess the motor excitability of facial motoneurons in primary HFS.

According to the results for both normals and HFS patients in this study, the mean latency of R_2 responses evoked by the conditioning and test were similar to those obtained from previous research (23, 25). It was further verified that the measured components were really R_2 responses. The latencies of R_2 responses elicited by test stimuli were longer than the latencies of R_2 responses elicited by conditioning stimuli in both groups, according to explanation about the relative refractory period, the test response shown increased latency (25).

The shortest interstimulus interval to elicit R_2 test responses represents the absolute refractory period of the blink reflex R_2 responses. In the normal control group, data from the majority of subjects revealed this absolute refractory period to be 200 msec, with a minority of subjects showing a prolongation to 300-400 msec. The average absolute refractory period was 271.42 ± 64.36 msec on both sides of the face, irrespective side of stimulation. HFS patient data showed the absolute refractory period to be 100 msec in the minority, with a lot of patients at 200 msec, the mean absolute refractory period being 160 ± 50.26 msec on both sides of the face, irrespective side of stimulation. It is concluded that the absolute refractory period of HFS patients is significant shorter ($p<0.05$) than the absolute refractory period of normal control subjects similar to a report by Valls - Sole et al (21).

When the shortest interstimulus interval related with the percentage of subjects was considered. The majority of subjects from both normal and HFS patient groups revealed the absolute refractory period to be 200 msec. Then the judgement excitability should considers the value of the blink reflex excitability curve too.

In this research we had not studied the blink reflex excitability curve to represents the relative refractory period of reflex. This can be obtained from those response to paired

shock by measuring the percentage action potential area of the R_2, and of the R_{2c} components, of the test response, compared to the values obtained on the response from the conditioning stimuli (arbitrarily considered to be 100%) in each interstimulus interval. The equipment in our experiment was unable to calculate the action potential area of those responses. So the neuronal excitability was demonstrated only by the mean absolute refractory period. However the excitability curve is suggested to be performed in the future study to confirm our study.

The ealry onset of R_2 recovery from both affected and unaffected sides obtained in this research revealed hyperexcitability of the blink reflex bilaterally in primary HFS. Since there were no sensory symptoms viz, paresthesia or pain, and the R_2 latencies in blink reflexes in this research as well as facial nerve distal motor latencies were with in normal limits in previous studies (23, 25, 28), both afferent and efferent pathways were excluded as being the pathological sites of lesions. The R_2 hyperexcitability would be the result of hyperexcitability of facial motoneurons and those brainstem interneurons mediating the blink reflex. The bilateral hyperexcitability observed was similar to other upper motoneuron lesions in stroke and Parkinson's diseases (34). The former, a unilateral impairment, may be directly related to the development of spasms originating either at the proposed site of a vascular compression (10, 17, 27), or at the facial nucleus itself, after being antidromically

excited (8, 15). The latter, a bilateral impairment, may be a secondary effect of the disease, as is inferred from the fact that patients with a longer duration of the disorder showed more striking abnormalities. Several factors that extent in this study (e.g., non-maching age between normal control and HFS groups, the duration of symptom and the severity of disease in HFS patients) may be responsible for the bilateral hyperexcitability. Out of these, from animal experiments (30), Thomander suggested that changes of the supranuclear control of facial motoneurons may be necessary to maintain normal bilaterally coordinated movements of facial expression in the presence of unilaterally impaired motor function. Evidence from this research lends strong support to Ferguson's theory of nuclear reorganization with hyperexcitability in facial motoneurons as being the underlying mechanism of HFS.

Others have used the paired shock technique, applied to the blink reflex, to study neuronal excitability on patients with various extrapyramidal lesions (34, 35), and, in most instances, the findings were similar to what was found in patients with HFS (21). The pattern of lack of R_2 inhibition with a normal R_1 recovery curve in previous report is thought to be an expression of the altered suprasegmentary inhibition of brainstem interneurons (36), where the polysynaptic pathway of R_2 is more exposed to influences by the changes of local excitability than the oligosynaptic R_1. This research cannot determine to what

extent such a pattern in HFS patients can be attributed to alteration in cellular excitability proximal to the facial nucleus, i.e., at the brainstem interneuronal pool, or to an increase of motoneuron excitability, as discussed above. However, the present findings suggest that enhanced facial motoneuron and brainstem interneuron excitability is responsible for the altered excitability curve of the blink reflex R_2 response on both sides of the face.

CHAPTER V

CONCLUSION

This research was attempted in order to prove the underlying mechanism of muscle spasm in HFS patients. The paired-shock technique was applied to elicit the blink reflex, as a test of facial motoneuron and brainstem interneuron excitability.

In studying 21 normal control subjects and 20 HFS patients, the conclusions of this study are as follow :

1. In normal subjects, the absolute refractory period of the blink reflex R_2 response is found to be between 200-400 msec (mean $\pm$ SD = 271.42 $\pm$ 64.36) on both sides of the face, irrespective of the side of stimulation.

2. In HFS patients, the absolute refractory period of the blink reflex R_2 response is found to be between 100-200 msec (mean $\pm$ SD = 160 $\pm$ 50.26) on both the affected and the unaffected sides, irrespective of the side of stimulation.

3. The absolute refractory period obtained from both the affected and the unaffected sides of HFS patient group show significant shorter ($p<0.05$) than those obtained from the normal group.

"The above data supports the hypothesis that hyperexcitability of the facial motoneuron and brainstem interneurons is the underlying mechanism of muscle spasm in patients with HFS."

BIBLIOGRAPHY

1. Tortora JG, Anagnostakos PN. Principle of Anatomy and Physiology. 6th ed. New York: Harper & Row Publishers, 1990: 267-9.

2. Anderson EJ. Grant's Atlas of Anatomy. 8th ed. Baltimore: Williams & Wilkins Company, 1983: section 7.

3. Digre K, Corbett JJ. Hemifacial spasm: Differential diagnosis, mechanism and treatment. In: Advances in Neurology, vol 49. Edited by Jankovic J, Tolosa E. New York: Raven Press, 1988: 151-76.

4. Wilkins HR. Hemifacial Spasm: A Review. Surg Neurol 1991; 36: 251-77.

5. Kapoor R. Hemifacial spasm. Br J Hos Med 1991; 45: 306-7.

6. Montagna P, Imbriaco A, Zucconi M, Liguori R, Cirignotta F, Lugaresi E. Hemifacial spasm in sleep. Neurology 1986; 36: 270-3.

7. Tolosa E, Marti MJ, Kulisevsky J. Botulinum toxin injection. In: Advances in Neurology, vol 49. Edited by Jankovic J, Tolosa E. New York: Raven Press, 1988: 39-61.

8. Ferguson HJ. Hemifacial spasm and the facial nucleus. Ann Neurol 1978; 4: 97-103.

9. Moller RA, Jannetta JP. Blink reflex in patients with hemifacial spasm observations during microvascular decompression operations. J Neuro Sci 1986; 72: 171-82.

BIBLIOGRAPHY

10. Nielsen KV. Electrophysiology of the facial nerve in hemifacial spasm: ectopic/ephaptic excitation. Muscle Nerve 1985; 8: 545-55.

11. Sadjadpour K. Postfacial palsy phenomena: faulty nerve regeneration or ephaptic transmission?. Brain Res 1975; 95: 403-6.

12. Haines JS, Torres F. Intraoperative monitoring of the facial nerve during decompressive surgery for hemifacial spasm. J Neurosurg 1991; 74: 254-7.

13. Code EJ, Wirtschafter DJ, Haines JS, Heros CR, Perrone T. Familial hemifacial spasm associated with arterial compression of the facial nerve. J Neurosurg 1991; 74: 290-6.

14. Moller RA, Jannetta JP. Hemifacial spasm: Results of electrophysiologic recording during microvascular decompression operations. Neurology 1985; 35: 969-74.

15. Moller RA, Jannetta JP. On the origin of synkinesis in hemifacial spasm: results of interacranial recordings. J Neurosurg 1984; 61: 569-76.

16. Moller RA, Jannetta JP. Synkinesis in hemifacial spasm: results of recording intracranially from the facial nerve. Experientia 1985; 41: 415-7.

BIBLIOGRAPHY

17. Nielsen KV. Pathophysiology of hemifacial spasm: I. Ephaptic transmission and ectopic excitation. Neurology 1984; 34: 418-26.

18. Nielsen KV. Pathophysiology of hemifacial spasm: II. Lateral spread of the supraorital nerve reflex. Neurology 1984; 34: 427-31.

19. Esteban A, Molina-Negro P. Primary hemifacial spasm: a neurophysiological study. J Neurol Neurosurg Psychiatry 1986; 49: 58-63.

20. Elmqvist D, Toremalm GN, Elner A, Mercke U. Hemifacial spasm: electrophysiological findings and the therapeutic effect of facial nerve block. Muscle Nerve 1982; 5: s89-s94.

21. Valls-Sole J, Tolosa SE. Blink reflex excitability cycle in hemifacial spasm. Neurology 1989; 39: 1061-6.

22. Shahani B. The human blink reflex. J Neurol Neurosurg Phychiatry 1970; 33: 792-800.

23. Shahani TB. The Blink, H and Tonic vibration reflexes. In: Electrodiagnosis of neuromuscular disease. Edited by Goodgold J, Eberstein A. 3rd ed. London: Williams & Wilkins, 1983: 258-81.

BIBLIOGRAPHY

24. Molina P, Hardy J, Bertrand AR. Contribution of trigeminal and facial reflexes to the localization of Vth, VIIth cranial nerve dysfunction. Appl Neurophysiol 1978; 41: 157-68.

25. Kimura J. Blink reflex. In: Electrodiagnosis in diseases of nerve and muscle: principles and practice. Edited by Kimura J. 2nd ed. Philadelphia: F.A Davis company, 1989: 307-31.

26. Kimura J. Facts, fallacies, and fancies of nerve stimulation technique. In: Electrodiagnosis in diseases of nerve and muscle: principles and practice. Edited by Kimura J. 2nd ed. Philadelphia: F.A Davis company, 1989: 157-8.

27. Nielsen KV, Jannetta JP. Pathophysiology of hemifacial spasm: III. Effects of facial nerve decompression. Neurology 1984; 34: 891-7.

28. Horowitz HS. Hemifacial spasm and facial myokymia: electrophysiological findings. Muscle Nerve 1987; 10: 422-7.

29. Moller RA. Interaction between the blink reflex and the abnormal muscle response in patients with hemifacial spasm: results of intraoperative recordings. J Neurol Sci 1991; 101: 114-23.

BIBLIOGRAPHY

30. Schwartz LI, Siegel JG. Excitation, conduction, and transmission of the nerve impulse. In : Best and Taylor's Physiological Basis of Medical Practice. Edited by West BJ. 11th ed. London : Williams & Wilkins Baltimore, 1985: 28-57.

31. Guyton CA. Textbook of Medical Physiology. 7th ed. Igaku-Shoin: Saunders, 1981: 116-7.

32. Thomander L. Reorganization of the facial motor nucleus after peripheral nerve regeneration. Acta Otolaryngol 1984; 97: 619-26.

33. Valls-Sole J, Tolosa SE, Ribera G. Neurophysiological observations on the effects of botulinum toxin treatment in patients with blepharospasm. J Neurol Neurosurg Psychiatry 1991; 54: 310-3.

34. Kimura J. Disorder of interneurons in parkinsonism: the orbicularis oculi reflex to paired stimuli. Brain 1973; 96: 87-96.

35. Geller DB, Hallett M, Ravits J. Botulinum toxin therapy in hemifacial spasm: clinical and electrophysiologic studies. Muscle Nerve 1989; 12: 716-22.

RAW DATA OF NORMAL SUBJECTS

NO	THE SHORTEST INTERSTIMULUS INTERVAL (msec)			
	RR	RL	LR	LL
1	300	300	300	300
2	200	200	200	200
3	300	300	300	300
4	200	200	200	200
5	200	200	200	200
6	200	200	200	200
7	200	200	200	200
8	300	300	300	300
9	300	300	300	300
10	300	300	300	300
11	200	200	200	200
12	300	300	300	300
13	300	300	300	300
14	300	300	300	300
15	400	400	400	400
16	200	200	200	200
17	300	300	300	300
18	200	200	200	200
19	300	300	300	300
20	300	300	300	300
21	400	400	400	400

when RR, RL, LR and LL represent:

RR = stimulated and recorded responses on right side.

RL = stimulated right side and recorded responses on left side.

LR = stimulated left side and recorded responses on right side.

LL = stimulated and recorded responses on left side.

RAW DATA OF HFS PATIENTS

NO	THE SHORTEST INTERSTIMULUS INTERVAL (msec)			
	II	IC	CI	CC
1	100	100	100	100
2	200	200	200	200
3	200	200	200	200
4	100	100	100	100
5	200	200	200	200
6	200	200	200	200
7	200	200	200	200
8	100	100	100	100
9	200	200	200	200
10	200	200	200	200
11	200	200	200	200
12	200	200	200	200
13	200	200	200	200
14	200	200	200	200
15	100	100	100	100
16	100	100	100	100
17	100	100	100	100
18	200	200	200	200
19	100	100	100	100
20	100	100	100	100

when II, IC, CI and CC represent:

II = ipsilateral responses following stimulation of the involved side.

IC = contralateral responses following stimulation of the involved side.

CI = contralateral responses following stimulation of the uninvolved side.

CC = ipsilateral responses following stimulation of the uninvolved side.