Postactivation depression changes after robotic-assisted gait training in hemiplegic stroke patients

Carlo Trompetto [1], Lucio Marinelli [1], Laura Mori [1], Elena Cossu [2], Roberto Zilioli [2], Marina Simonini [2], Giovanni Abbruzzese [1], Luigi Baratto [2]

1 Institute of Neurology, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Largo Daneo 3, 16132 Genova, Italy

2 Rehabilitation Service, Hospital "La Colletta", 16011 Arenzano, Italy

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Corresponding author: Lucio Marinelli, Institute of Neurology, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Largo Daneo 3, 16132 Genova, Italy. Telephone: +39 0103537040, FAX: +39 0103538631, E-mail: lumarinelli@yahoo.it

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Abstract

Postactivation depression is decreased in patients with spasticity and partially restored by physical exercise in spinal cord injured patients. Up until now, the possibility to modulate postactivation depression with motor training has never been explored in subjects with spasticity following brain lesions. Postactivation depression, assessed as frequency related depression of soleus H-reflex, was investigated before and after robotic-assisted gait training in a group of 7 subjects with spastic hemiparesis following hemispheric stroke. Patients received 3 sessions per week of robotic-assisted gait training for a period of 4 weeks (12 sessions in total). Postactivation depression was measured before the treatment (T0), after the first session (T1) and after the last session (T2). Postactivation depression was quantified as the ratio between H-reflex amplitude at 1Hz and at 0.1Hz. The greater the 1Hz/0.1Hz ratio, the smaller the postactivation depression. Following robotic-assisted gait training, the 1Hz/0.1Hz ratio decreased from 0.79±0.26 at T0 to 0.56±0.18 at T1 and 0.58±0.13 at T2. Post-hoc analysis showed a significant difference between T0 and T1 and between T0 and T2, stating an increase of postactivation depression. No significant differences were found between T1 and T2.

This study provides the first demonstration that physical exercise can determine a partial normalisation of postactivation depression in hemiparetic patients with spasticity following unilateral hemispheric stroke.

Introduction

Postactivation depression is a presynaptic mechanism regulating the excitability of the stretch reflex [1]. It refers to the inhibition of the test reflex response (either H reflex or stretch reflex), elicited in a given muscle at rest, induced by a preceding conditioning stimulus able to activate the afferents mediating the test response (e.g. vibration, tendon tap, voluntary contraction, electrical nerve stimulation). For instance, postactivation depression of soleus H-reflex can be obtained using a tap or a vibration to the Achilles tendon, a dorsi-flexion or a plantar-flexion of the foot or an electrical stimulus eliciting another soleus H-reflex. When the test response is elicited, the conditioning stimulus is already terminated; hence the term of postactivation depression [1,2].

In comparison to healthy controls, postactivation depression has been found to be lower in spastic patients with spinal cord injury [3-6], amyotrophic lateral sclerosis [7], multiple sclerosis [3,8], stroke [9-11] and cerebral palsy [12]. A positive correlation has been reported between the diminished postactivation depression and the severity of spasticity following stroke [10] and cerebral palsy [12]. Moreover, in subjects with spinal cord injury postactivation depression is normal in the acute phase and becomes depressed only just before the development of spasticity [6]. Altogether these studies state that postactivation depression is one of the mechanisms underlying spasticity.

In spinal rats, postactivation depression can be transiently restored by passive cycling [13]. As the normalisation of postactivation depression is not seen in spinal rats with an additional damage of the large sensory peripheral fibers, it is thought that repeated activation of afferent pathways is likely to be involved in the normalisation of postactivation depression [14].

Also in humans, postactivation depression increases after physical exercise. In healthy subjects, postactivation depression increases after motor training [5,15] and decreases after immobilization [16]. In chronic patients with spinal cord injury, both cycling [5,17] and treadmill walking [18] can increase postactivation depression.

Up until now, the possibility to modulate postactivation depression with motor training has never been explored in subjects with spasticity following brain lesions. In the present study, we investigated postactivation depression changes induced by robotic-assisted gait training in seven hemiparetic subjects, who developed spasticity after unilateral hemispheric stroke. To assess postactivation depression we used the frequency-related depression of the soleus H reflex [2,19].

Materials and methods

Subjects

The investigation was carried out in 7 hemiparetic subjects with spasticity following unilateral hemispheric stroke occurring in the middle cerebral artery territory, aged 41-73 years (mean and SD: 59±11 years) and in 7 normal subjects aged 40-73 years (mean and SD: 56±14 years). Patients' criteria for inclusion were: 1) mono-hemispheric stroke resulting in a contralateral dense hemiparesis or hemiplegia; 2) spasticity of the ankle extensor muscles (*triceps surae*); 3) the need of a cane to walk independently and a 6-minute walking test < 120 meters; 4) a stable clinical picture in the last 4 months.

The interval between stroke and investigation ranged from 14 months to 52 months. Details of the 7 patients are reported in Table 1 and Table 3.

The study has been approved by the local ethical committee. All subjects gave informed consent according to the Declaration of Helsinki.

Clinical evaluation

Muscle tone of the ankle extensors was rated with the Modified Ashworth Scale (MAS) [20]. The Medical Research Council (MRC) score was used to evaluate the strength in the ankle extensor muscles. The passive range of motion (ROM) of the ankle was evaluated with a manual goniometer. Walking endurance was assessed by means of the 6-minute walking test [21].

Electro-physiological assessment (H-reflex recruitment curve and postactivation depression)

Subjects were tested while lying in a bed relaxed in a prone position with their feet over the edge of a table. Special care was taken to assure that muscles acting on the ankle joint were at complete rest.

The posterior tibial nerve was stimulated by a surface bipolar electrode placed in the popliteal fossa. Rectangular pulses of 2ms duration were administered by means of a constant-current stimulator (model DS7A, Digitimer, UK).

EMG was recorded through bipolar surface preamplified electrodes (TSD150B, Biopac Systems Inc, USA) positioned over the soleus muscle, 3cm below the insertion of the gastrocnemii. EMG signals were amplified (×3000), band-pass filtered (10Hz–1kHz, -6dB/octave), analog-to-digital converted at a 2kHz frequency. Each recorded epoch lasted 200 ms, of which the first 100 ms were the pre-stimulus background EMG activity. M-wave and H-reflex peak-to-peak amplitudes were evaluated by means of the Acqknowledge software (Biopac Systems Inc, USA).

At the beginning, for each subject, a soleus H–M recruitment curve was built up using a stimulation frequency of 0.1Hz. The electrical stimulation intensities producing H-max (the H-reflex with the maximal amplitude) and M-max (the M-wave elicited by a supramaximal stimulus) was defined and the H-max/M-max ratio was calculated.

Postactivation depression was evaluated by frequency-related changes of soleus H-reflex. Twenty soleus H-reflexes were evoked with an inter-stimulus interval of 10 s (0.1Hz). Stimulus strength was set to produce H-reflexes (obtained on the ascending limb of the input-output curve) with an amplitude ranging from 30% to 50% of H-max and preceded by a small M-wave. After this, twenty soleus H-reflexes were elicited with the same intensity, but using an inter-stimulus interval of 1s (1Hz). Since the first H-reflex evoked at 1Hz was not influenced by postactivation depression, it was excluded and the remaining 19 responses were measured. Postactivation depression was quantified as the ratio: mean amplitude of the 19 H-reflexes obtained at 1Hz / mean amplitude of the 20 H-reflexes obtained at 0.1Hz. This is referred to as the 1Hz/0.1Hz ratio; the greater the 1Hz/0.1Hz ratio, the smaller the postactivation depression. Trials showing EMG activity in the pre-stimulus period were rejected. Furthermore, to ensure that there was no displacement of stimulation or recording electrodes during the experiment, just after the assessment of postactivation depression

we checked that M-waves recorded at 0.1Hz had the same amplitudes of those recorded at 1Hz. Otherwise, after repositioning the electrodes the assessment was repeated.

In each subject, the amplitude of the 20 H-reflexes obtained at 0.1Hz (0.1Hz H-reflex) were normalized to both the corresponding M-max value (0.1Hz H-reflex/M-max ratio) and H-max value (0.1Hz H-reflex/H-max ratio).

As the sensitivity of the H-reflex to inhibition can vary with the size of the test reflex [22], when postactivation depression was compared in patients *versus* healthy subjects and when postactivation depression was compared in patients before and after robotic-assisted gait training, great attention was paid to the amplitude of the H-reflex elicited at the frequency of 0.1Hz (see statistical analysis).

All values have been reported as mean ± standard deviation, unless otherwise specified.

Robotic-assisted gait training

The gait training was performed using the 'Lokomat®' (Hocoma AG, Zurich, Switzerland). This device consisted of two robotic legs, a bodyweight unloading system and a treadmill [23]. Thigh and leg straps secured the Lokomat exoskeleton to the patients; motors on each robotic leg induced movement of the hip and knee joints, while the ankle joints were passively moved. For the first session, walking speed of 1.65±0.19Km/h, walking distance of 550.5±172.67m and a guidance force of 100% were provided. In the following sessions, train intensity was progressively increased by increasing walking distance (last session: 704.83±2.14m) and walking speed (last session: 1.8±0.15Km/h) and decreasing guidance force (last session: 84.33±27.37%) (values are reported as mean ± standard deviation). Body weight support was adjusted for each subject individually.

General design and statistical analysis

Patients received 3 sessions per week of robotic-assisted gait training for a period of 4 weeks (12 sessions in total). No other rehabilitative treatments have been administered during the period.

Both clinical evaluation and electro-physiological assessment were performed before the first session (T0), after the first session (T1) and after the twelfth (last) session (T2).

To assess the effect of robotic-assisted gait training, one-way repeated measures ANOVA was used to compare, between the 3 sessions (T0, T1, T2), the following parameters: 1) H-max/M-max ratio; 2) 1Hz/0.1Hz ratio (postactivation depression); 3) 0.1Hz H-reflex amplitude; 4) 0.1Hz H-reflex/H-max ratio; 5) 0.1Hz H-reflex/M-max ratio; 6) ankle passive range of movement (ROM); 7) 6-minute walking test (expressed as meters). Bonferroni post-hoc analysis was performed on significant comparisons.

The electro-physiological study was carried out also in healthy subjects, in a single recording session. An unpaired t-test was used to compare parameters 1-5 between control subjects and patients (at T0, T1 and T2).

Results

Electro-physiological assessment in patients: effect of robotic-assisted gait training (Table 2)

Following robotic-assisted gait training, the ratio 1Hz/0.1Hz decreased from 0.79±0.26 at T0 to 0.56±0.18 at T1 and 0.58±0.13 at T2 ($F[2,30]=4.6$; $p=0.02$). Post-hoc analysis showed a significant difference between T0 and T1 ($p=0.012$) and between T0 and T2 ($p=0.015$), stating an increase of postactivation depression (Figure 1). No significant differences were found between T1 and T2 ($p=0.94$).

No significant changes were found among sessions in the other parameters: H-max/M-max ratio ($F[2,30]=2.08$, $p=0.14$), 0.1Hz H-reflex amplitude ($F[2,10]=0.68$, $p=0.53$), 0.1Hz H-reflex/H-max ratio ($F[2,12]=1.39$, $p=0.29$) and 0.1Hz H-reflex/M-max ratio ($F[2,10]=0.7$, $p=0.52$).

Electro-physiological assessment: comparison between patients and healthy controls (Table 2)

In Figure 2, mean values of H-max/M-max ratio and 1Hz/0.1Hz ratio are compared between patients and normal controls.

The H-max/M-max ratio in patients at T0 was greater than that found in the control subjects ($p=0.038$), while no differences were found between the control subjects and patients at T1 ($p=0.085$) and T2 ($p=0.097$).

Compared to healthy subjects, the 1Hz/0.1Hz ratio in patients was significantly increased at T0 ($P=0.002$), T1 ($p=0.04$) and T2 ($p=0.005$), indicating a decrease of postactivation depression in patients.

Clinical assessment (Table 3)

Compared to baseline value at T0, the MAS score at T1 was reduced of 1 point in subjects 5 and 7. At T2, patient 7 remained stable, while patient 5 showed a further reduction of 1 point. Moreover, at T2 a third subject (patient 1) presented with a reduction of 1 point in the MAS score compared to baseline value.

MRC scores did not change after training.

The passive range of movement marginally increased across sessions ($F[2,12]=3.94$; $p=0.049$); however, post-hoc analysis was unable to disclose significant differences ($p>0.0167$).

The 6-minute walking test increased across sessions ($F[2,12]=37.5$; $p=0.008$); post-hoc analysis showed a significant difference (on average 16.3m) only between T0 and T2 ($p=0.003$).

Discussion

The aim of the present study was to investigate postactivation depression, assessed as frequency related depression of soleus H-reflex, before and after robotic-assisted gait training in a group of 7 subjects with spastic hemiparesis following hemispheric stroke.

Before gait training, we found that postactivation depression was lower in patients with respect to age-matched healthy controls. Postactivation depression was significantly enhanced after the first session of treatment (T1), although it remained low in comparison to healthy controls. The effects at T1 were maintained at T2 and no further increase of inhibition was observed.

The present results should be discussed in the light of what is already known about the physiological mechanisms underlying postactivation depression.

Physiological mechanisms of postactivation depression

Firstly, postactivation depression is a presynaptic phenomenon acting on the Ia terminals. In fact, during postactivation depression of the soleus H-reflex, both voluntary contraction [24] and motor

potentials evoked by transcranial magnetic stimulation [1] are not reduced in the soleus muscle, ruling out a long-lasting excitability decrease of the motoneurons as the cause of H-reflex inhibition.

Secondly, postactivation depression is different from the "classical" presynaptic inhibition, which consists of a GABA-mediated depolarization of the Ia terminals (primary afferent depolarization, PAD) [25]. This GABA-ergic presynaptic inhibition lasts only 300-400 ms and is widely distributed among the afferent fibres of the stimulated limb [26]. On the contrary, postactivation depression lasts several seconds (usually up to 10 s) and it is confined to the afferents stimulated by the conditioning stimulus [1,27].

On the basis of these characteristics, it is now largely accepted that postactivation depression corresponds to the homosynaptic depression described in animals [1,16], which is viewed as an intrinsic neuronal property associated with a decreased probability of transmitter release from the repetitively activated afferents [28,29]. However, the molecular mechanisms responsible for homosynaptic depression are still an open issue [27].

Summing up, postactivation depression reflects the reduced efficacy of the synapses between the Ia fibres and motoneurons when they are evaluated after a previous activation; this reduction of efficacy is due to some intrinsic neural properties of the Ia terminals.

Decreased postactivation depression before robotic-assisted gait training

Before gait training, we found that postactivation depression was lower in stroke patients with respect to age-matched healthy controls. This result confirms previous observations [9-11].

As largely expected, soleus H-max/M-max ratio was higher in patients, when evaluated at T0, *versus* healthy controls. The reduction of postactivation depression did not play a role in this finding, since the ratio was investigated using a frequency of 0.1Hz, at which postactivation depression is considered to be absent or minimal [2,8].

In patients with stroke or spinal cord injury, it has been shown that the decrease of postactivation depression is not an immediate consequence of the lesion, but instead a gradual phenomenon induced by plastic changes [6]. Since postactivation depression decreases after immobilization in healthy subjects [16], it is conceivable that also in patients with upper motor neuron syndrome immobilization may play a role in the plastic changes involved in the decrease of postactivation depression. It has been suggested that the disuse of Ia afferents and motoneurons, induced by immobilization, could be responsible for the reduction of postactivation depression in patients with spasticity [30].

The patients in the present study were all suffering from a severe loss of strength in the calf muscles with important limitation in walking, possible only with support. At the time of our assessment, this clinical picture persisted for at least 14 months in all the patients. Therefore, from a theoretical point of view, it is possible that in these 7 subjects loss of movement may have caused the plastic changes which led to the decrease of postactivation depression.

It must be stressed that the present data do not allow us to exclude that the reduction of postactivation depression was due to the disruption of some descending pathways able to control the spinal mechanisms underlying postactivation depression. However, there is so far no evidence in mammals for such a descending control.

Postactivation depression after robotic-assisted gait training

The novel finding of our study is that postactivation depression in hemiparetic stroke subjects can be increased by gait training. While soleus H-max/M-max ratio did not change after motor training, an increase of postactivation depression was found after the first session of treatment (T1) and remained stable after the last session (T2). Notwithstanding this increase, postactivation depression remained significantly lower in patients in comparison to healthy subjects.

The possibility to increase postactivation depression in patients with spasticity after a single session of motor training confirms previous findings in subjects with incomplete spinal cord injury [5]. The partial recovery of postactivation depression in the present research may be related to the chronic condition of the investigated subjects. In fact, in patients with complete spinal cord injury, it has been recently demonstrated that the recovery of postactivation depression is complete only when the treatment is applied in the acute phase, before the development of spasticity [31].

In spinal injured rats, activity in proprioceptive pathways has been found to be critical for normalization of postactivation depression after motor training [14]. We suggest that activity in proprioceptive pathways may be also involved with its intrinsic limitations in our subjects, as robotic-assisted gait training induced repetitive stretching of the soleus muscle. Sensory inputs from soleus spindles may have led to reorganization of spinal neural circuits by strengthening existing and previous inactive connections [32], according to the view that the decrease of postactivation depression in spastic subjects could be due to the disuse of Ia fibers and motoneurons [30].

Clinical results

Robotic-assisted gait training induced a significant improvement of walking endurance, evaluated with 6-minute walking test after the last session. Muscle strength did not vary and muscle tone, assessed with MAS, decreased in less than half of patients. However it must be underlined that MAS provides only semi-quantitative assessment and is prone to subjective evaluation. These results are in line with those previously obtained in chronic stroke patients using treadmill training with partial body weight support [33]. Considering that gait training is a treatment with effects at multiple levels and taking into account the complex pathophysiology of both spasticity and gait disturbances, it seems that any attempt to correlate these clinical and neurophysiological data, obtained in only 7 patients, would be unfeasible. Such correlation was beyond the aims of the present study and the clinical assessment was performed just to verify the treatment efficacy.

Moreover, the improvement in the 6-minutes walking test, although significant, was very small and much lower than the minimal detectable change of 29m [34].

Relevance of the present findings and conclusions

This study provides the first demonstration that robotic assisted gait training can lead to a partial normalisation of postactivation depression in hemiparetic patients with spasticity following unilateral hemispheric stroke. The importance of this finding, fitting with the results obtained in spinal cord injured patients [18], lies in the connection between spasticity and reduced postactivation depression, which has been recently demonstrated [10,12]. Further studies are needed to determine if the manipulation of postactivation depression in patients with brain lesions might play a considerable role in the recovery from spasticity in order to design specific training protocols.

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Figure 1. Postactivation depression in the patients before and after robotic-assisted gait training.

The figure illustrates mean (± standard error) postactivation depression of the 7 stroke patients before robotic-assisted gait training (T0), after the first session of treatment (T1) and after the last session of treatment (T2). At each session in the abscissa (T0, T1 and T2), the ordinate shows the average amplitude of the soleus H-reflex elicited at 1Hz normalised to the amplitude of the H-reflex obtained at 0.1Hz (1Hz/0.1Hz ratio). The asterisk (*) indicates a significant difference ($p<0.0167$) in comparison to the pre-treatment (T0) value.

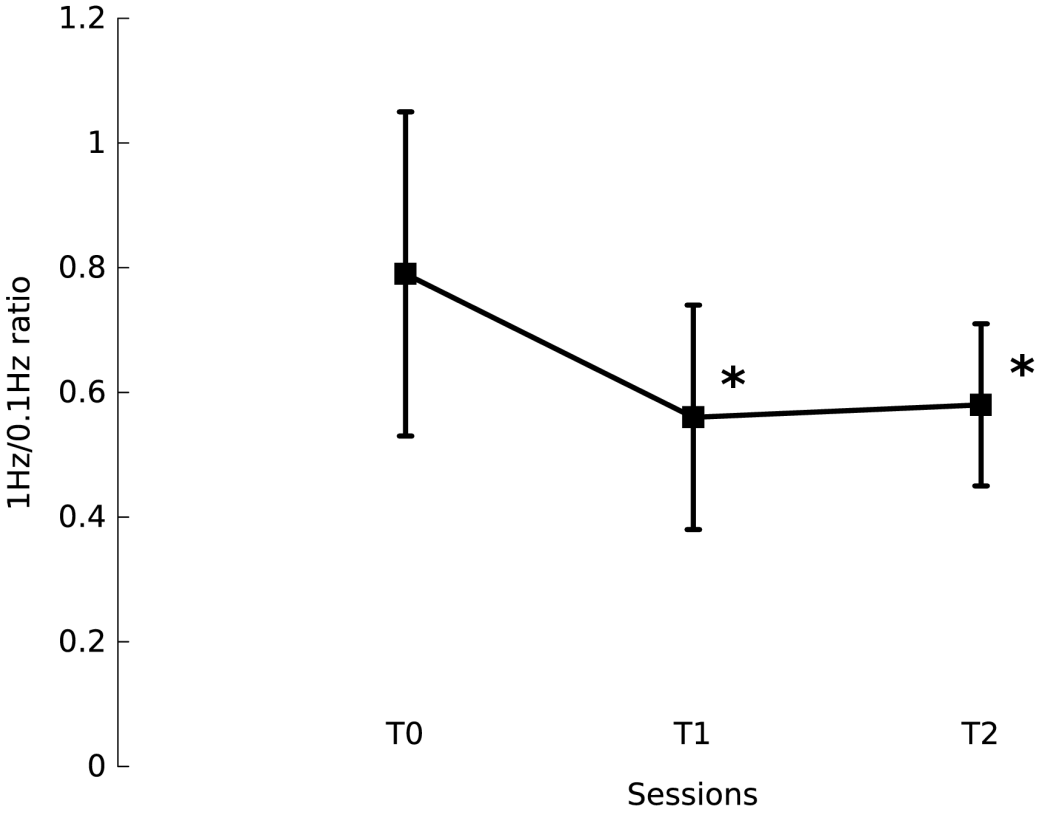

Figure 2. H-max/M-max ratios and postactivation depression (1Hz/0.1Hz ratios) in healthy subjects and in the patients.

The figure illustrates H-max/M-max ratios (left part) and 1Hz/0.1Hz ratios (right part) of the 7 healthy subjects (HS) (white bars) and of the 7 stroke patients before robotic-assisted gait training (T0) (black bars), after the first session of treatment (T1) (vertical lines bars) and after the last session of treatment (T2) (horizontal lines bars). Standard error is shown. The asterisk (*) indicates a significant difference ($p<0.05$) in comparison to healthy controls (white bars).

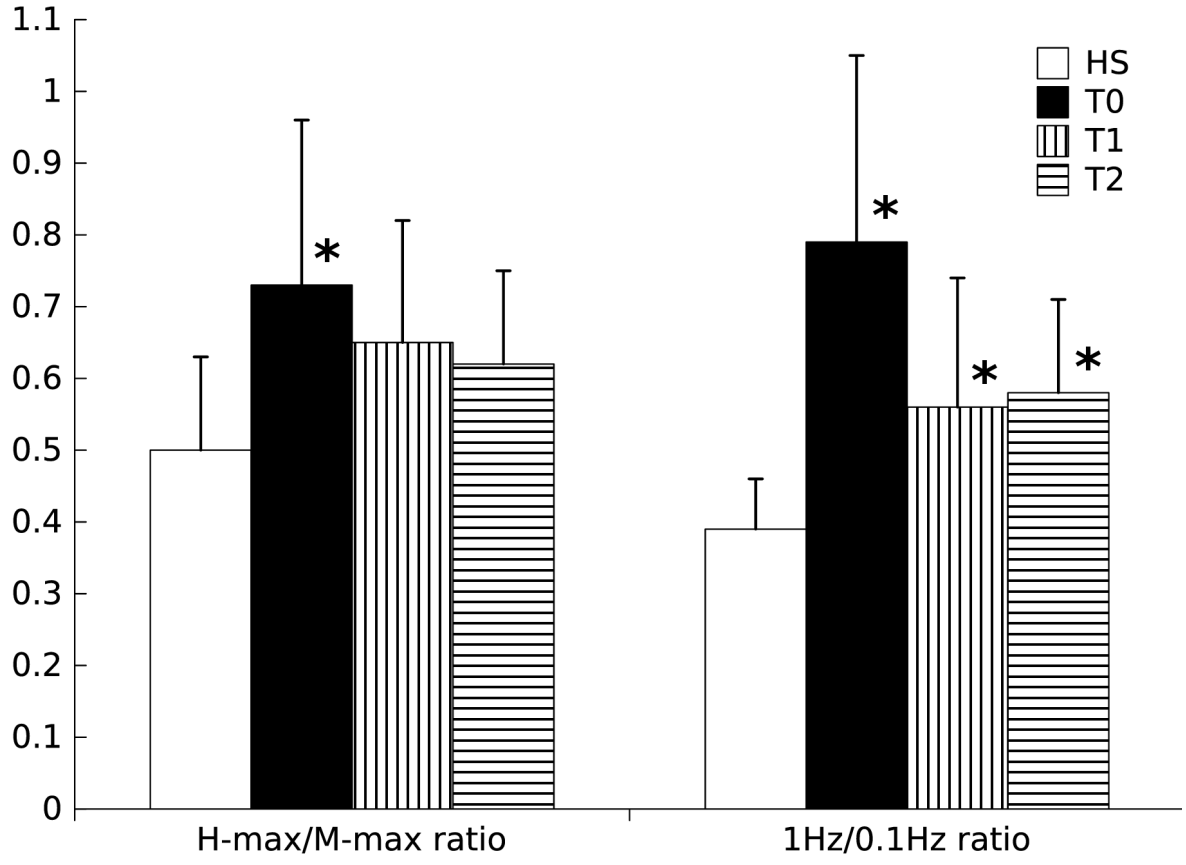

Table 1. Demographic and clinical features of patients.

Delay means the number of months between the acute event and the time of our first assessment (T0).

Demographic and clinical features of patients

Patient	Sex	Age	Hemiplegic side	Mechanism	Delay (months)
1	F	61	right	ischaemia	27
2	M	51	left	ischaemia	23
3	M	73	left	ischaemia	14
4	M	68	right	haemorrhage	52
5	F	65	left	ischaemia	14
6	F	41	left	haemorrhage	34
7	M	54	left	ischaemia	33

Table 2. H-reflex parameters in patients and healthy subjects

Each value refers to the grand mean among patients (rows 1-3) or healthy subjects (HS) ± standard deviations. Significant values in patients compared to healthy controls are shown in bold ($p<0.05$).

H-reflex parameters in patients and healthy subjects

	H-max/M-max ratio	0.1 Hz H-reflex (mV)	0.1Hz H-reflex/H-max ratio	0.1Hz H-reflex/M-max ratio	1Hz/0.1Hz ratio
T0	**0.73 ± 0.23**	2.15 ± 0.92	0.45 ± 0.09	0.32 ± 0.10	**0.79 ± 0.26**
T1	0.65 ± 0.17	1.98 ± 0.67	0.44 ± 0.08	0.29 ± 0.09	**0.56 ± 0.18**
T2	0.62 ± 0.13	2.37 ± 1.34	0.48 ± 0.09	0.28 ± 0.06	**0.58 ± 0.13**
HS	0.53 ± 0.15	1.71 ± 0.48	0.54 ± 0.17	0.26 ± 0.07	0.39 ± 0.07

Table 3. Clinical parameters

The degree of spasticity of ankle extensor muscles (*triceps surae*) was estimated using the Modified Ashworth Scale (MAS). The force of ankle extensor muscles was tested using the Medical Research Council (MRC) scale (0-5). The passive range of movement (ROM) of ankle joint was measured with a manual goniometer. The 6-minutes walking test is measured in meters.

Clinical parameters

Patient	MAS			MRC			ROM			6-minute walking test		
	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2
1	4	4	3	1	1	1	13	30	33	70	70	90
2	3	3	3	2	2	2	17	17	23	85	80	110
3	4	4	4	0	0	0	17	17	20	110	130	130
4	2	2	2	3	3	3	37	30	30	70	75	78
5	4	3	2	2	2	2	17	30	30	90	90	86
6	3	3	3	1	1	1	30	43	37	86	100	105
7	3	2	2	1	1	1	17	20	27	22	20	48