Ghost spasticity in multiple sclerosis

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Abstract

Spasticity is the velocity-dependent hypertonia frequently encountered in patients affected by Upper Motor Neuron Syndrome. It is due to a tonic stretch reflex, which is evoked in patients at rest. The aim of this study, performed using surface electromyography (EMG), was to investigate stretch reflex excitability in the hamstrings muscles of patients affected by progressive Multiple Sclerosis (MS) and to correlate EMG results with clinical findings. Thirty patients and 20 age-matched healthy controls were investigated. EMG activity was recorded from biceps femoris muscle with the patient at rest. To stretch hamstrings muscles, the patient's leg was manually moved from maximal flexion to maximal extension at 3 different velocities to investigate both phasic and tonic stretch reflex. Only 7 patients were affected by hypertonia of the hamstrings; 4 of them showed muscle contracture. A tonic stretch reflex was present in the vast majority of the recruited patients, whether they presented hypertonia of the hamstrings or not. Tonic stretch reflex is often present in the hamstrings muscles of progressive MS patients without producing increased muscle tone. This "ghost spasticity" is likely to be, for its intrinsic features, an important risk factor for the development of contractures in the hamstrings muscles.

Introduction

Hyperexcitability of the stretch reflex is a common finding in subjects affected by Upper Motor Neuron Syndrome (UMNS) (Lance, 1980; Trompetto et al., 2014).

The stretch reflex has both phasic and tonic components. Phasic stretch reflexes are produced by rapid stretches, such as the sharp blows to the tendon used to elicit tendon jerks. Tonic stretch reflexes are produced by muscle stretches of slower velocity, such as those commonly used in the clinic to test muscle tone (Sheean, 1998a).

In fully relaxed healthy subjects, phasic stretch reflexes can be evoked. On the contrary, it is largely accepted that tonic stretch reflexes cannot be elicited (Sheean, 1998a, 2002; Thilmann et al., 1991; Yeo et al., 1998). These findings led to the view that muscle tone in fully relaxed healthy subjects is only determined by the mechanical properties of the limb (Rothwell, 1994).

In UMNS subjects attempting to relax their muscles, tendon jerks (i.e. phasic stretch reflexes) are often exaggerated and may cause clonus. Furthermore, tonic stretch reflexes are often present, thus leading to velocity-dependent hypertonia (i.e. greater resistance is felt with faster stretches) (Trompetto et al., 2014). Among muscles showing velocity-dependent hypertonia, some are actually relaxed before muscle stretch. This hypertonia is best referred to as spasticity. Others are tonically activated before passive muscle stretch, notwithstanding the attempt of the subject to relax. This hypertonia is best referred to as spastic dystonia (Marinelli et al., 2017a; Trompetto et al., 2019a, 2019b). In both spasticity and spastic dystonia, muscle hypertonia is "reflex" in nature, since it is produced by the tonic stretch reflex.

It must be stressed that soft tissue changes in the muscles, tendons and joints can increase muscle tone. This form of hypertonia, usually referred to as intrinsic hypertonia, is considered not velocity-dependent (Sheean, 1998b). The most severe form of intrinsic hypertonia is represented by muscle contractures, which cause shortening of muscles and the ensuing reduction of range of movement (Gracies, 2005a). The main cause of contracture is immobilization of the muscle in a shortened position. Both spasticity and spastic dystonia, by resisting muscle stretch and lengthening, may constrain the muscle in a shortened position for prolonged periods, possibly resulting in intrinsic hypertonia (Gracies, 2005b).

Therefore, hypertonia may have a reflex component and an intrinsic component. Very often both components are present in the same muscle (Sheean, 1998b). Although only reflex hypertonia is reported to be velocity-dependent, in a clinical setting it can be difficult to distinguish between the two forms (Malhotra et al., 2008; O'Dwyer and Ada, 1996).

Hyperexcitability of the quadriceps stretch reflex is frequently revealed by clinical examination of UMNS subjects. Patellar reflexes are often increased stating the hyperexcitability of the phasic component of the stretch reflex. Moreover, during passive flexion of the knee performed to evaluate muscle tone, the resistance appreciated by the examiner commonly melts away as the passive movement continues, giving rise to the clasp-knife phenomenon (Burke et al., 1970; Marinelli et al., 2017a). This clinical sign is due to the inhibition of the quadriceps tonic stretch reflex produced by the action of the secondary spindle endings from the quadriceps, thus clearly indicating a reflex mechanism underlying spasticity (Burke et al., 1970; Lance, 1980) or spastic dystonia (Marinelli et al., 2017a).

On the contrary, hyperexcitability of the hamstrings stretch reflex is not frequently reported at the clinical examination. However, it must be said that tendon jerks of the hamstrings are not evaluated, at least during the standard clinical examination. Moreover, in the hamstrings the clasp-knife phenomenon is absent (Burke et al., 1971), while intrinsic hypertonia and muscle contractures are very common (Mayer and Esquenazi, 2003). In this context, it can be difficult to distinguish clinically between reflex hypertonia and intrinsic hypertonia.

Therefore, the question arises whether stretch reflex hyperexcitability can be properly assessed in the hamstrings by clinical examination. This issue could be particularly relevant in patients affected by progressive multiple sclerosis (MS), in whom intrinsic hypertonia and muscle contractures of the hamstrings are very common (Hoang et al., 2014), especially in those with severe disability, thus challenging the capability to clinically detect stretch reflex hyperexcitability in hypertonic muscles.

The present study has been designed to investigate, using surface electromyography (EMG), stretch reflex excitability of the hamstrings in a cohort of subjects affected by progressive MS and to correlate EMG results with the clinical findings. A population of healthy controls was also investigated.

To our knowledge, this is the first study specifically designed to investigate stretch reflex excitability in the hamstrings of MS subjects.

Materials and methods

Subjects

MS patients were consecutively enrolled according to the following inclusion criteria:

- age $\geq$ 18 years
- secondary progressive (SP) MS or primary progressive (PP) MS diagnosed according to the 2010 revision of the McDonald criteria (Polman et al., 2011)
- Expanded Disability Status Scale (EDSS) > 3.0 (Kurtzke, 2008), not acquired within the 12 months before enrollment
- cognitive functioning to give informed consent and to understand instructions (specifically to remain relaxed during evaluation), identified by a Mini-Mental Status Examination (MMSE) score $\geq$ 24/30 (Folstein et al., 1975)

Exclusion criteria were:

- neurological conditions in addition to MS that may affect motor function and other medical conditions likely to interfere with the study protocol
- use of intrathecal baclofen
- treatment with botulinum toxin in the lower limbs in the last 8 months

A population of age-matched healthy volunteers was also enrolled.

All subjects provided their written informed consent to participate in the study, which was approved by the local ethical committee.

Clinical assessment

Tone and strength of knee flexor muscles (hamstrings) and knee extensor muscles (quadriceps femoris) were respectively rated according to the Modified Ashworth Scale (MAS) (Bohannon and Smith, 1987) and the Medical Research Council (MRC) scale. Patellar jerks were graded as follows: 0 = no response; 1 = a slight but definitely present response; 2 = a brisk response; 3 = a very brisk response; 4 = a tap elicits a repeated reflex.

EMG and kinematic recordings

In the enrolled MS patients and healthy controls, a surface preamplified electrode with fixed inter-electrode distance (TSD150B, Biopac Systems Inc, USA) was placed over the muscle belly of Biceps Femoris (BF) following SENIAM (Surface Electromyography for Non-Invasive Assessment of Muscles) guidelines (Hermens, 1999). The excursion of the knee joint was recorded by a twin-axis electronic goniometer placed across the joint (TSD130B, Biopac Systems Inc, USA). All signals were acquired by an MP150 unit (Biopac Systems Inc, USA) with a 2 KHz sampling rate and underwent a Blackman -61 dB 10-350 Hz band-pass filter for offline processing (AcqKnowledge 3.8.1 software by Biopac Systems Inc, USA).

Experimental protocol

Subjects were examined when lying prone (Figure 1). For the entire duration of the recording session, subjects were instructed to stay completely relaxed and in silence. They were examined through the following 3 phases:

- *Phase 1: looking for the presence of spontaneous EMG activity at rest, with the leg passively held in maximal flexion (hamstrings shortened).*
  After placing the electrode and the goniometer, the leg was positioned in the maximal flexion. Then, the EMG signal was recorded for 60s. In the case of tonic EMG activity, subjects were urged to stay relaxed every 10s.
- *Phase 2: dynamic stretch of hamstrings.*
  The examiner (CT, medical doctor) grasped the subject's ankle and moved the leg from the position of phase 1 to maximal extension.
- *Phase 3: static stretch of hamstrings.*
  After the dynamic phase of the stretch, the subject's leg was passively held in maximal extension for 60s.

These three phases constitute a trial. In each subject 3 trials were performed, the first with a duration of dynamic stretch (phase 2) of 4s (4s-trial), the second with a duration of 1s (1s-trial) and the last with a duration of 0.5s (0.5s-trial). To control the duration of the passive displacement, a method developed in our laboratory was used (Marinelli et al., 2013).

Analysis of data

The angle values detected by the electronic goniometer were used to calculate onset and termination times of the dynamic phase of the stretch (phase 2). Onset and termination times were visually detected on the goniometer trace displayed on the computer screen, using a display gain of 20°/cm and a temporal window of 340ms/cm (Marinelli et al., 2017a).

Single-subject analysis. Each trial was examined separately. Visual examination of the unrectified EMG signal was carried out to look for muscle activity at phase 1, phase 2 and phase 3. Average Rectified Value of the EMG signal (ARV) (Hermens, 1999) at phase 1, phase 2 and phase 3 was measured only when muscle activity was detected in the corresponding phase by visual examination. For phase 2, the angle at which EMG activity started (EMG onset angle) was measured (Figure 1). Phase 3 were divided into 6 bins of 10s each (bin 1: 0-10s; bin 2: 10-20s; bin 3: 20-30s; bin 4: 30-40s; bin 5: 40-50s; bin 6: 50-60s). For each bin, ARV was calculated.

Analysis across subjects. To compare EMG activity detected in patients with MAS score in the hamstrings ≥ 1 (subjects with hypertonia) to EMG activity detected in patients with MAS score in the hamstrings = 0 (subjects without hypertonia), for each trial (0.5s-trial, 1s-trial, 4s-trial) we analyzed ARVs and EMG onset angles by means of a factorial ANOVA using HYPERTONIA as main factor; furthermore, we analyzed the six BINS by means of a repeated measure ANOVA using HYPERTONIA as main factor and BINS as within-subject factor.

To compare ARVs of phase 2 and EMG onset angles obtained at the 3 velocities (1s-trial; 4s-trial and 0.5s-trial), we used a factorial ANOVA with VELOCITY as main factor. For phase 3, to compare ARVs obtained in the 6 bins, a repeated measure ANOVA was performed with VELOCITY as main factor and the 6 BINS as within-subject factor.

In all the paper, data are reported as mean value ± standard deviation (SD).

Figure 1
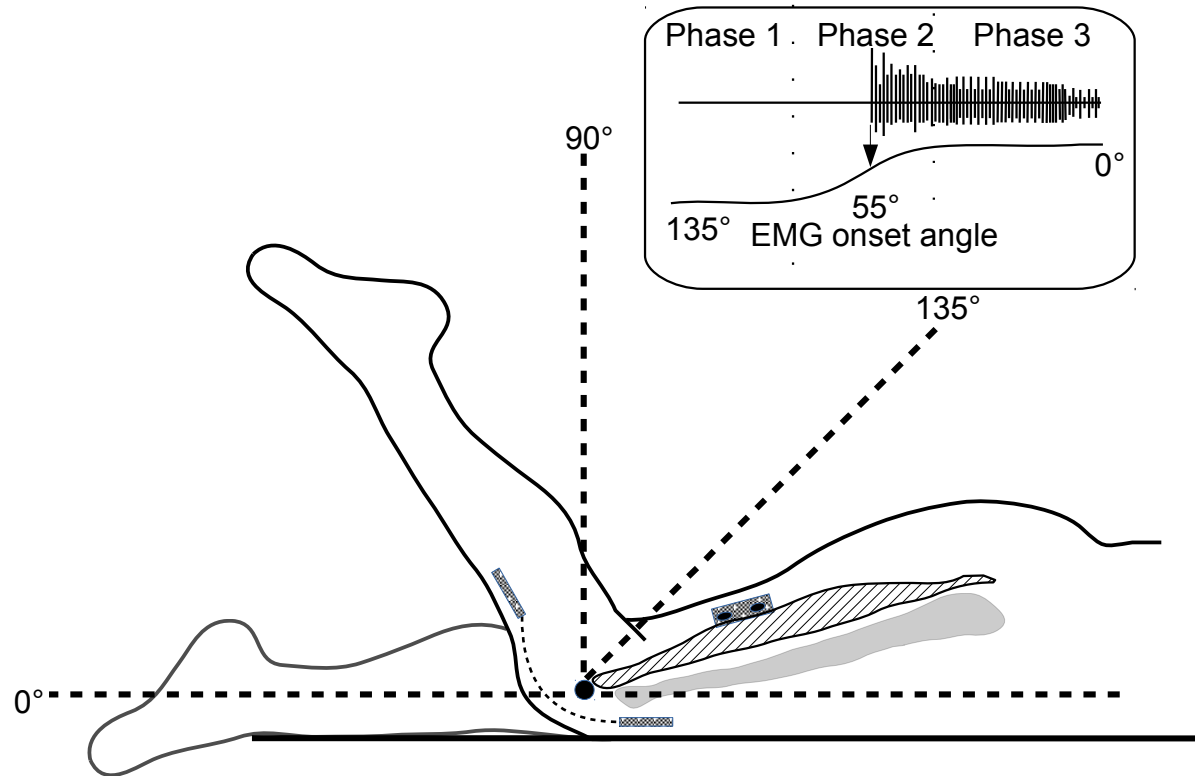
Figure 1. Representation of the experimental setup.
Maximum leg flexion depends on size of both leg and thigh. Here it is shown at a knee angle of 135°. Maximum leg extension always corresponds to a knee angle of 0°, unless the subject has a contracture of the hamstrings. In the rectangle, the two measured parameters are shown: EMG activity from *biceps femoris* and knee angle, measured with an electronic goniometer. In this stretch, the EMG activity began at 55°. The leg is depicted at this angle.

Results

According to the inclusion criteria, 30 consecutive patients (19 women; age 52 ± 11.5 years) were enrolled. Their demographic and disease-related variables are reported in Table 1. Twenty age-matched healthy subjects were also investigated (12 women; age 54.7 ± 14.1 years).

Clinical findings (Table 1)

In the hamstrings, MAS score was > 1 in 7 patients. Four of them (patients 1-2, 4-5) showed contracture in the hamstrings. In all the 7 patients with MAS > 1, the resistance to stretch progressively increased across the range of motion and was maximal when the muscles were fully stretched. Therefore, the clasp-knife phenomenon was not observed. In the remaining 23 patients, the muscle tone of the hamstrings was normal.

In the quadriceps, MAS score was ≥ 1 in 20 patients. All of them showed the clasp-knife phenomenon and patellar reflexes brisk or very brisk.

Table 1

Patient's number (evaluated side)	Age	Sex	Disease course	EDSS	Muscle strenght (MRC score)		Muscle tone (MAS score)		Patellar tendon reflex	Oral drugs for spastisity
					QF	HS	QF	HS		
1*(L)	75	M	SP	7	4	4	1.5	1.5	2	Baclofen
2*(L)	45	F	SP	8	0	0	3	3	2	\
3 (L)	71	F	SP	8	2	4	0	3	1	\
4*(R)	55	F	SP	8	2	0	3	2	2	Baclofen
5*(L)	53	F	SP	6.5	4	4	2	2	2	Gabapentin
6 (L)	52	F	PP	7	3	0	3	2	3	Baclofen
7 (R)	58	M	SP	6.5	4	4	0	3	1	Baclofen
8 (R)	52	F	PP	5	5	5	1.5	0	2	Baclofen
9 (R)	64	F	PP	6.5	5	2	0	0	1	\
10 (L)	48	M	PP	7.5	3	2	3	0	3	Baclofen
11 (R)	47	M	SP	6	5	2	3	0	2	\
12 (L)	32	F	PP	5.5	5	5	0	0	2	Nabiximols
13 (L)	52	F	SP	6.5	3	0	3	0	3	Baclofen
14 (R)	44	F	PP	6.5	5	3	3	0	3	Nabiximols-Tizanidine
15 (L)	31	F	SP	4.5	5	5	1.5	0	2	Baclofen
16 (L)	58	M	SP	4.5	5	4	0	0	1	\
17 (L)	34	F	SP	6	5	4	0	0	3	Tizanidine
18 (R)	71	F	SP	7.5	5	3	3	0	3	Baclofen
19 (R)	30	F	SP	3.5	5	5	0	0	2	\
20 (R)	57	M	SP	8	4	0	2	0	2	Nabiximols
21 (R)	50	F	PP	6.5	5	3	0	0	1	Baclofen
22 (L)	55	M	SP	5.5	5	4	1	0	2	Baclofen - Nabiximols
23 (R)	69	F	SP	3.5	5	4	0	0	3	Tizanidine
24 (L)	60	M	SP	8	3	0	1	0	3	\
25 (L)	59	M	SP	6	5	4	1	0	2	\
26 (R)	46	F	PP	7	5	5	1	0	3	Baclofen
27 (L)	51	F	SP	6	5	4	0	0	3	\
28 (R)	44	M	SP	6.5	4	4	3	0	3	Nabiximols
29 (L)	46	M	SP	4.5	5	4	1	0	3	\
30 (R)	51	F	SP	6	3	2	3	0	2	Gabapentin

Table 1. Patients' demographic and clinical features.
HS = Hamstrings muscles; QF = Quadriceps Femoris; * = patients showing contracture in the hamstrings; SP = secondary progressive; PP = primary progressive. MAS = modified Ashworth Scale: MRC = Medical Research Council.

EMG findings in MS patients (Table 2 and Table 3)

The velocity of passive displacement was 31.2°/s ± 3.1°/s for 4s-trial, 124.8°/s ± 12.4°/s for 1s-trial and 249.7°/s ± 24.7°/s for 0.5s-trial.

Among the 7 patients with hypertonia in the hamstrings (patients 1-7), in each one of the 3 trials, EMG activity was detected in 1 patient at phase 1 (patient 1), in all 7 patients at phase 2 and in 6 patients at phase 3 (patients 1-6). Figure 2 shows EMG activity from patient 6.

Among the 23 patients without hypertonia in the hamstrings (patients 8-30), at the lowest velocity of leg displacement (4s-trial), EMG activity was found in 2 patients at phase 1 (patients 9-10), in 15 patients at phase 2 (patients 8-22) and in 15 patients at phase 3 (patients 8-22). At the intermediate velocity 1s-trial, EMG activity was found in 2 patients at phase 1 (patients 9-10), in 19 patients at phase 2 (patients 8-23, 25-27) and in 16 patients at phase 3 (patients 8-23). Finally, at the highest velocity of passive leg displacement (0.5s-trial), EMG activity was found in 2 patients at phase 1 (patients 9-10), in all 23 patients at phase 2 and in 17 patients at phase 3 (patients 8-24). Figure 3 shows EMG activity from patient 8.

In both patients with and without hypertonia in the hamstrings, EMG activity of phase 1 showed a tonic pattern and persisted for the entire duration of the phase. EMG onset angle was 38.3° ± 16.1° at 4s-trial, 58.8° ± 18.9° at 1s-trial and 80.0° ± 15.5° at 0.5s-trial. From its beginning (EMG onset angle), EMG activity of phase 2 persisted until the end of the phase in all the subjects. In its initial part, EMG activity of phase 2 was usually low in amplitude. Then, it increased as muscle length increased, to reach the greatest amplitude towards the end of the passive movement (Figure 2). In some patients, EMG activity appeared only at the end of passive movement (Figure 3). EMG activity of phase 3 showed a tonic pattern and persisted for the entire duration of the phase (all six bins) (Figure 2 and Figure 3).

Comparing EMG activity of the patients with hypertonia vs. those without hypertonia within each trial, statistical analysis showed no difference of EMG onset angle (4s-trial: $F[1,20]=0.4$, $p=0.55$; 1s-trial: $F[1,24]=0.1$, $p=0.8$; 0.5s-trial: $F[1,28]=0.02$, $p=0.9$), ARV of phase 2 (4s-trial: $F[1,20]=0.07$, $p=0.8$; 1s-trial: $F[1,24]=1.1$, $p=0.3$; 0.5s-trial: ($F[1,28]=1.5$, $p=0.2$) and ARVs of the six BINS of phase 3 (4s-trial: $F[1,19]=1.2$, $p=0.3$; 1s-trial: $F[1,20]=1.9$, $p=0.2$; 0.5-trial: $F[1,21]=1.2$, $p=0.3$).

Comparing EMG activity obtained in all the subjects across the trials, factorial ANOVA for ARV of phase 2 showed a significant effect of velocity ($F[2,75]=5.9$, $p=0.0043$). Post-hoc analysis confirmed that ARV at the fastest velocity (0.5s-trial) was significantly higher compared to the

ARV at the lowest velocity (4s-trial) (p=0.001). The same effect of velocity was detectable when taking into account the EMG onset angle. With faster velocities EMG activity appeared at higher angles (F [2,75]=39.3, p<0.0001), with a significant difference among the 3 tested velocities (0.5s-trial and 1s-trial: p<0.0001; 1s-trial and 4s-trial: p<0.0001; 0.5s-trial and 4s-trial: p<0.0001) (Figure 4). Furthermore, repeated measure ANOVA showed a significant decrement of ARV across the 6 bins of phase 3 (F[5,310]=38.3, p<0.0001). We found no significant difference between ARVs obtained in the 6 bins at the three velocities, as confirmed by post-hoc analysis. However, a significant interaction VELOCITY X BINS was found (F[10,310]=2.8, p=0.0029), suggesting that ARV decrement was steeper when the muscle was stretched at high than low velocity (Figure 5).

Figure 2

A

100 µV

10s

B

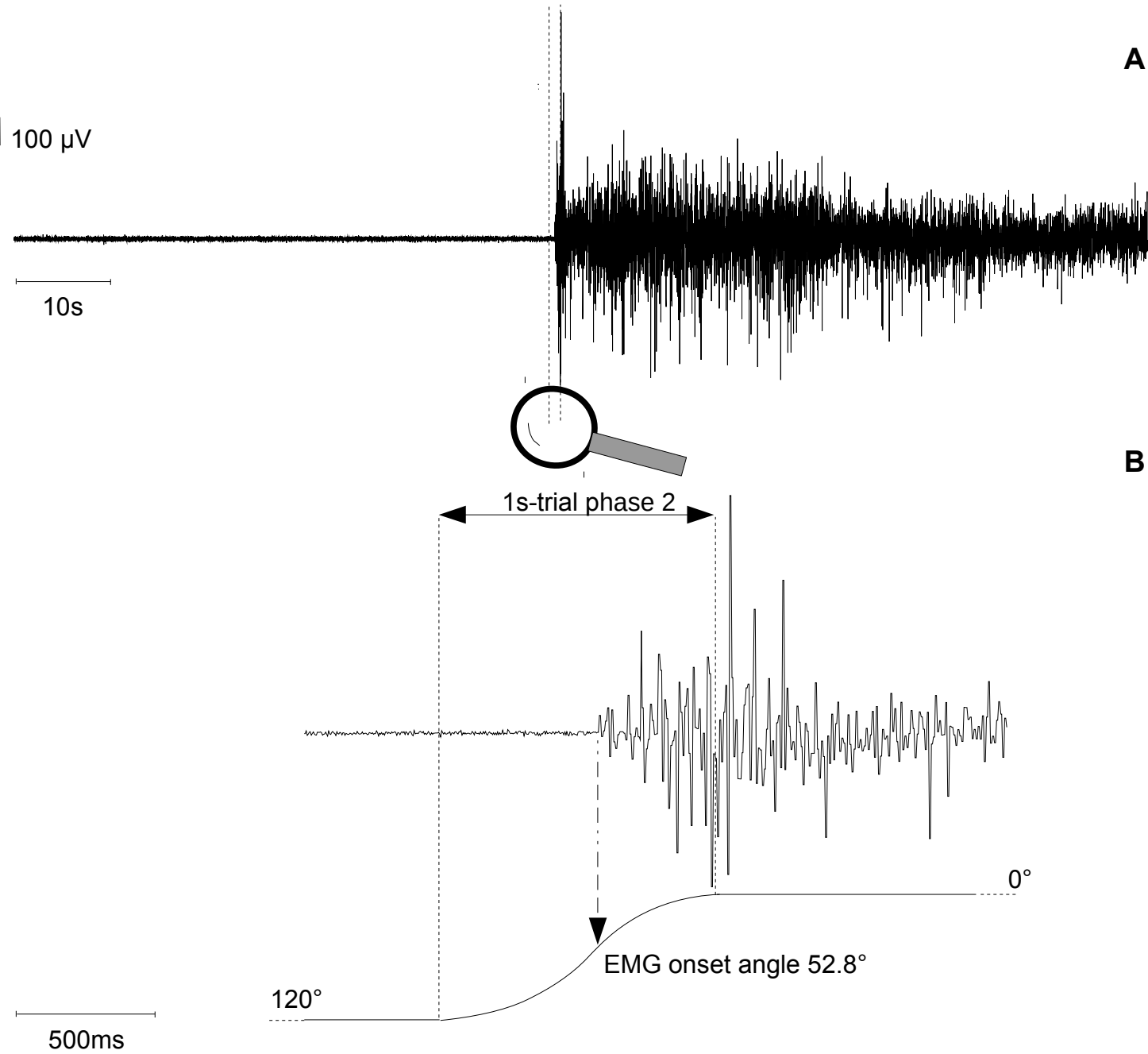1s-trial phase 2

0°

EMG onset angle 52.8°

120°

500ms

Figure 2. EMG activity of the Biceps Femoris produced by passive stretching in a patient with increased muscle tone in fully paralyzed hamtrings (patient 6).
A shows surface electromyogram (EMG) of the whole 1s-trial. First vertical dotted line indicates the start of passive linear stretch, while second vertical dotted line indicates the end of passive linear stretch (phase 2 is between vertical dotted lines). To the left of first vertical dotted line, the muscle is kept in a shortened position (phase 1), while to the right of the second vertical dotted line, muscle is kept in an elongated position (phase 3). EMG activity starts in the second part of phase 2. After the end of passive movement, the muscle still keeps contracting for the whole duration of phase 3.
B is a focus on phase 2 (passive linear movement) reported in A. First trace shows EMG activity, while second trace shows knee angle recorded using an electronic goniometer. EMG activity starts in the second part of passive linear movement and reaches its maximum amplitude at the end of passive movement.
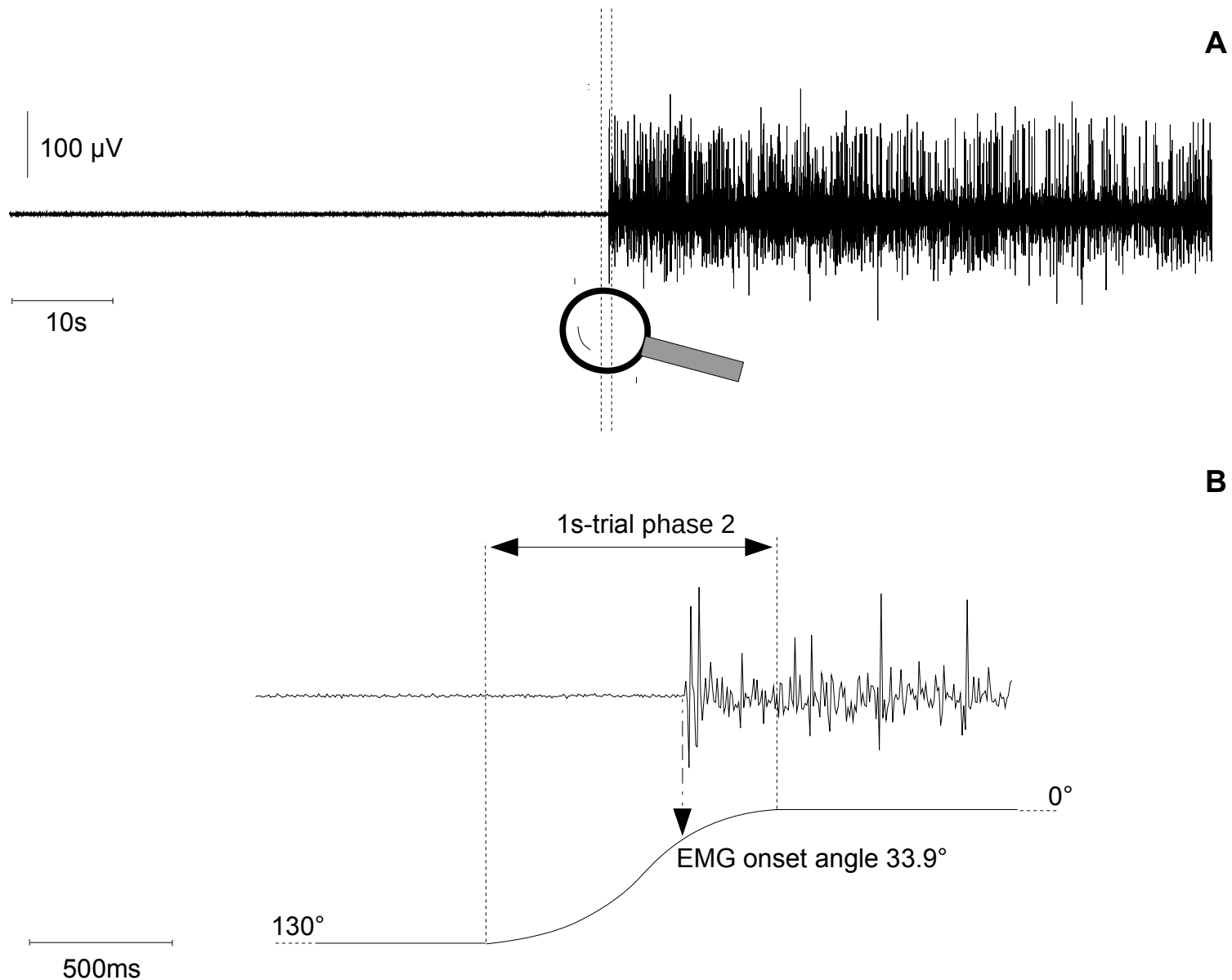
Figure 3

Figure 3. EMG activity of the Biceps Femoris produced by passive stretching in a patient with normal muscle tone in the hamtrings (patient 8).
Paradigm as in Figure 2. EMG activity appears only at the end of passive movement. After the end of passive movement, the muscle still keeps contracting for the whole duration of phase 3.

Figure 4
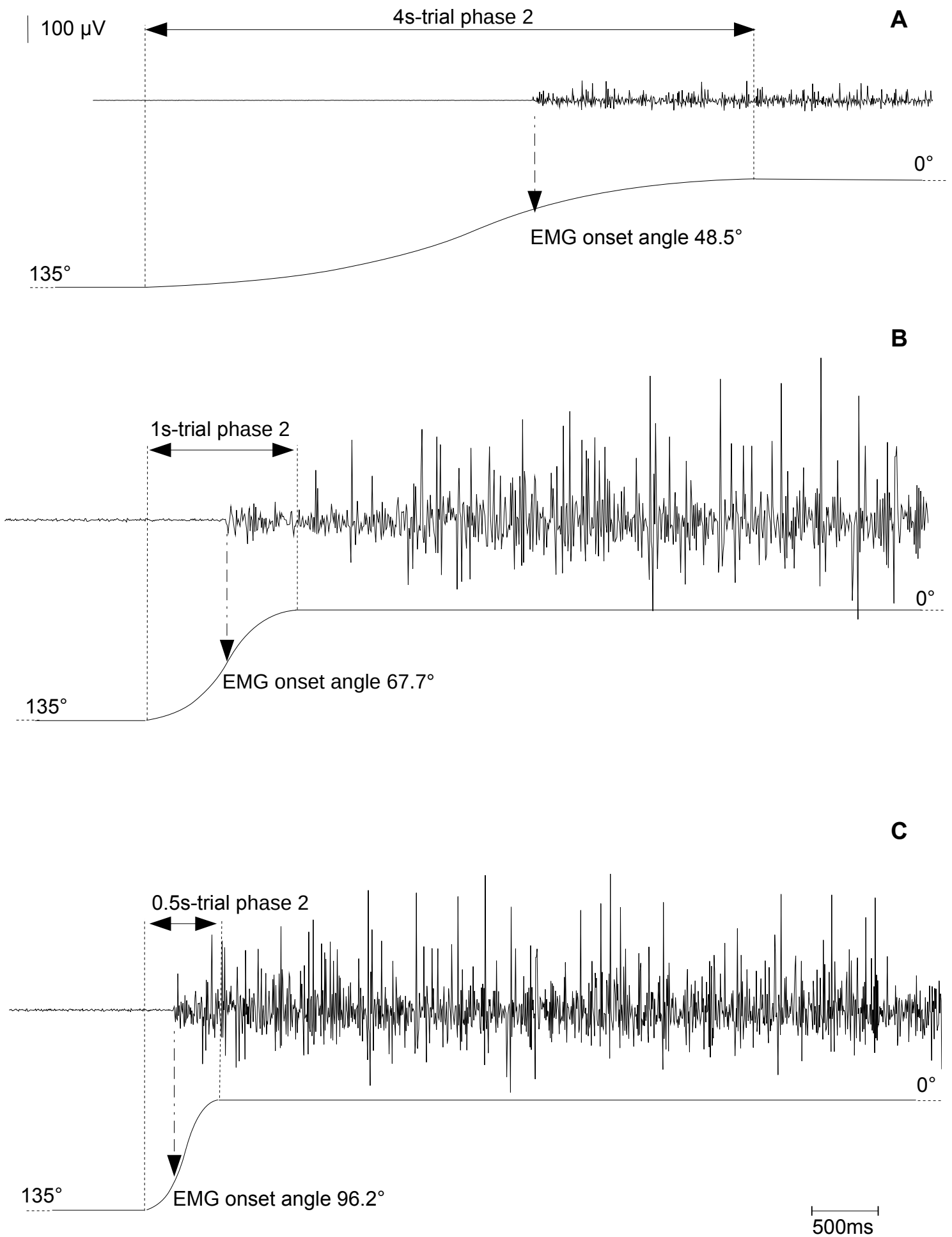
Figure 4. Velocity sensitivity of EMG activity in a patient (patient 12).
A shows 4s-trial, B shows 1s-trial and C shows 0.5s-trial. In A, B and C: first trace shows surface electromyogram (EMG) of the Biceps Femoris, second trace shows knee angle recorded using an electronic goniometer; first vertical dotted line indicates the start of passive linear stretch, while second vertical dotted line indicates the end of passive linear stretch (phase 2 is between vertical dotted lines); to the left of first dotted vertical line, the muscle is kept in a shortened position (phase 1, only partially shown), while to the right of second dotted line, muscle is kept in an elongated position (phase 3, only partially shown). With increasing velocity of linear passive stretch (from A to B and C), both EMG amplitude and EMG onset angle increase.

Table 2

Patient	ROM maximal flexion/ maximal extension (degrees)	4s-trial Phase 2 Starting angle	ARV (µV)	Phase 3 ARV (µV) Bin 1	Bin 2	Bin 3	Bin 4	Bin 5	Bin 6	1s-trial Phase 2 Starting angle	ARV (µV)	Phase 3 ARV (µV) Bin 1	Bin 2	Bin 3	Bin 4	Bin 5	Bin 6	0.5s-trial Phase 2 Starting angle	ARV (µV)	Phase 3 ARV (µV) Bin 1	Bin 2	Bin 3	Bin 4	Bin 5	Bin 6
1*	130/30	42.4	3.1	3.0	3.8	3.3	3.3	3.3	3.0	55.6	14.2	19.8	18.4	17.7	16.1	12.8	13.1	75.5	17.9	17.1	17.3	16.2	16.3	14.0	13.9
2	120/40	46.5	4.5	5.1	4.8	3.7	4.5	4.9	4.4	56.7	7.0	6.1	4.4	4.0	4.7	4.3	3.7	79.9	9.1	9.0	8.8	8.1	7.7	7.3	6.5
3	130/0	39.1	3.3	2.8	2.6	1.9	1.8	1.9	1.4	46.6	6.2	4.2	3.4	3.4	2.3	2.2	2.0	52.2	11.3	7.6	7.4	6.4	4.3	4.6	5.1
4	125/20	37.0	2.2	2.6	2.6	2.5	2.4	2.4	2.2	54.0	3.5	2.0	2.9	2.2	2.1	2.2	2.1	87.7	11.4	3.8	3.3	3.3	2.3	2.3	3.0
5	130/25	43.5	15.2	19.3	18.2	20.5	18.5	17.0	16.5	77.3	20.2	20.8	19.2	20	20.2	21.0	20.9	91.6	23.0	23.5	23.5	23.2	20.9	19.0	18.5
6	120/0	27.0	7.6	18.3	18.3	18.3	17.9	17.0	16.4	52.8	21.3	20.5	20.4	19.7	17.7	16.2	15.1	68.2	23.0	23.7	23.4	22.2	22.2	21.5	21.1
7	130/0	54.1	3.5	/	/	/	/	/	/	78.4	10.0	/	/	/	/	/	/	110.1	13.5	/	/	/	/	/	/
8	130/0	10.8	2.5	4.6	5.8	5.4	5.1	5.1	4.9	33.9	3.6	3.9	4.6	3.6	3.9	4.0	3.6	66.1	5.5	5.9	6.0	4.5	4.7	4.1	3.8
9*	135/0	65.2	1.1	1.0	1.0	1.0	1.0	1.0	1.0	86.8	3.9	1.8	1.7	1.1	1.1	1.1	1.0	95.5	6.0	5.5	5.4	5.3	5.3	4.9	4.0
10*	125/0	48.6	16.2	13.2	13.1	13.1	13.9	14.3	14.5	71.2	23.2	20.5	17.1	16.4	15.2	16.3	16.7	97.7	25.1	22.0	21.3	19.7	19.1	19.0	18.7
11	125/0	49.1	11.1	11.5	10.7	9.9	7.0	6.7	6.1	53.1	11.9	5.1	2.8	2.5	2.1	2.2	1.9	67.5	21.0	19.0	18.7	17.0	17.3	16.5	16.5
12	135/0	48.5	5.6	5.1	4.7	6.2	6.3	6.0	6.1	67.7	8.2	11.4	9.7	5.5	5.5	5.0	5.1	96.2	13.4	15.2	12.1	10.0	9.9	9.8	9.9
13	125/0	41.0	4.5	5.0	5.5	4.9	5.5	4.8	4.5	87.5	14.1	9.7	7.7	7.9	6.9	6.2	6.0	99.5	17.1	17.0	16.5	16.1	15.7	15.6	13.2
14	130/0	67.5	8.1	7.8	6.6	7.0	6.5	6.8	6.4	83.2	12.2	10.0	9.9	9.3	9.3	8.3	8.2	91.2	13.7	11.9	11.1	11.0	9.9	9.7	9.6
15	130/0	15.5	3.2	2.4	2.1	3.0	2.9	2.6	2.0	48.3	5.3	5.4	4.8	4.2	4.2	4.4	3.9	61.5	7.1	7.0	6.6	6.1	5.9	5.9	4.7
16	130/0	29.2	2.5	2.6	2.4	2.4	2.3	2.2	2.2	35.2	4.5	4.4	4.2	4.1	3.9	3.9	3.2	77.3	7.1	3.2	3.2	3.1	2.8	2.9	2.3
17	130/0	34.0	1.2	1.6	1.4	1.4	1.3	1.4	1.2	38.2	2.3	1.7	1.6	1.4	1.3	1.3	1.2	78.3	2.8	1.8	1.8	1.7	1.4	1.4	1.3
18	125/0	17.4	25.0	16.8	15.7	15.0	14.3	14.0	13.7	88.1	23.7	24.1	23.9	23.3	22.0	22.2	21.2	95.3	26.5	24.0	23.3	23.1	22.2	21.2	20.0
19	130/0	43.7	5.2	4.6	4.0	3.4	3.4	3.4	3.4	66.1	8.5	6.6	7.6	7.4	7.5	7.5	7.5	95.5	13.4	9.0	8.7	8.6	8.5	8.5	8.4
20	125/0	43.9	2.8	2.7	2.8	1.9	1.4	1.4	1.2	67.7	9.4	7.5	7.1	7.1	5.7	5.5	5.3	99.9	14.3	14.0	13.7	13.1	13.0	12.7	11.9
21	135/0	27.0	2.4	2.5	2.5	2.6	2.5	2.5	2.5	48.9	4.2	4.5	4.5	4.4	4.5	4.3	4.5	55.5	5.7	5.9	5.8	5.8	5.7	5.7	5.7
22	130/0	7.5	4.1	2.4	2.4	2.4	2.4	2.4	2.4	15.5	2.2	2.7	2.6	2.6	2.7	2.7	2.6	49.3	11.4	2.6	2.4	2.4	2.4	2.4	2.4
23	130/0	/	/	/	/	/	/	/	/	31.3	2.1	1.8	1.5	1.3	1.3	1.2	1.2	80.2	2.5	2.5	2.3	2.3	2.2	2.1	2.0
24	130/0	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	74.4	16.5	6.1	7.1	5.5	7.1	3.0	3.6
25	130/0	/	/	/	/	/	/	/	/	61.9	5.9	/	/	/	/	/	/	68.8	21.2	/	/	/	/	/	/
26	135/0	/	/	/	/	/	/	/	/	54.6	2.8	/	/	/	/	/	/	86.5	4.5	/	/	/	/	/	/
27	135/0	/	/	/	/	/	/	/	/	67.5	15.3	/	/	/	/	/	/	72.4	23.0	/	/	/	/	/	/
28	120/0	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	81.1	3.6	/	/	/	/	/	/
29	135/0	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	65.3	5.8	/	/	/	/	/	/
30	120/0	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	79.9	3.1	/	/	/	/	/	/
Mean	**129/4**	**38.3**	**6.1**	**6.4**	**6.2**	**6.2**	**5.9**	**5.8**	**5.5**	**58.8**	**9.5**	**8.8**	**8.2**	**7.7**	**7.3**	**7.0**	**6.8**	**80**	**12.7**	**11.1**	**10.9**	**10.2**	**9.9**	**9.3**	**9.0**
SD	**5/10**	**16.1**	**5.9**	**5.8**	**5.5**	**5.8**	**5.5**	**5.2**	**5.1**	**18.9**	**6.8**	**7.4**	**7.0**	**7.0**	**6.5**	**6.4**	**6.4**	**15.5**	**7.4**	**7.4**	**7.4**	**7.2**	**7.0**	**6.7**	**6.5**

Table 2. EMG findings in patients.

ARV = Average Rectified Value of the EMG signal; bin 1: 0-10s; bin 2: 10-20s; bin 3: 20-30s; bin 4: 30-40s; bin 5: 40-50s; bin 6: 50-60s; * = patients showing EMG activity at phase 1.

Table 3

	Patients with hamstrings MAS score > 1			Patients with hamstrings MAS score = 0		
	4s-trial	*1s-trial*	*0.5s-trial*	*4s-trial*	*1s-trial*	*0.5s-trial*
Starting angle (°)	41.4 ± 8.4	60.2 ± 12.5	80.7 ± 18.4	36.8 ± 18.7	58.3 ± 21.1	79.8 ± 14.9
ARV phase 2 (µV)	5.6 ± 4.6	11.8 ± 7.0	15.6 ± 5.7	6.4 ± 6.6	8.6 ± 6.7	11.8 ± 7.7
ARV phase 3 bin 1 (µV)	8.5 ± 8.0	12.2 ± 9.0	14.1 ± 8.5	5.6 ± 4.7	7.6 ± 6.5	10.0 ± 7.0
ARV phase 3 bin 2 (µV)	8.4 ± 7.7	11.5 ± 8.7	14.0 ± 8.7	5.4 ± 4.5	7.0 ± 6.1	9.8 ± 6.8
ARV phase 3 bin 3 (µV)	8.4 ± 8.6	11.2 ± 8.8	13.2 ± 8.5	5.3 ± 4.3	6.4 ± 5.9	9.1 ± 6.6
ARV phase 3 bin 4 (µV)	8.1 ± 7.9	10.5 ± 8.4	12.3 ± 8.6	5.1 ± 4.2	6.1 ± 5.6	9.0 ± 6.4
ARV phase 3 bin 5 (µV)	7.8 ± 7.2	9.8 ± 8.0	11.5 ± 7.9	5.0 ± 4.2	6.0 ± 5.7	8.6 ± 6.3
ARV phase 3 bin 6 (µV)	7.3 ± 7.1	9.5 ± 8.0	11.4 ± 7.6	4.8 ± 4.2	5.8 ± 5.6	8.1 ± 6.1

Table 3. EMG findings in patients with and without increased muscle tone in the hamstrings.
ARV = Average Rectified Value of the EMG signal; bin 1: 0-10s; bin 2: 10-20s; bin 3: 20-30s; bin 4: 30-40s; bin 5: 40-50s; bin 6: 50-60s.
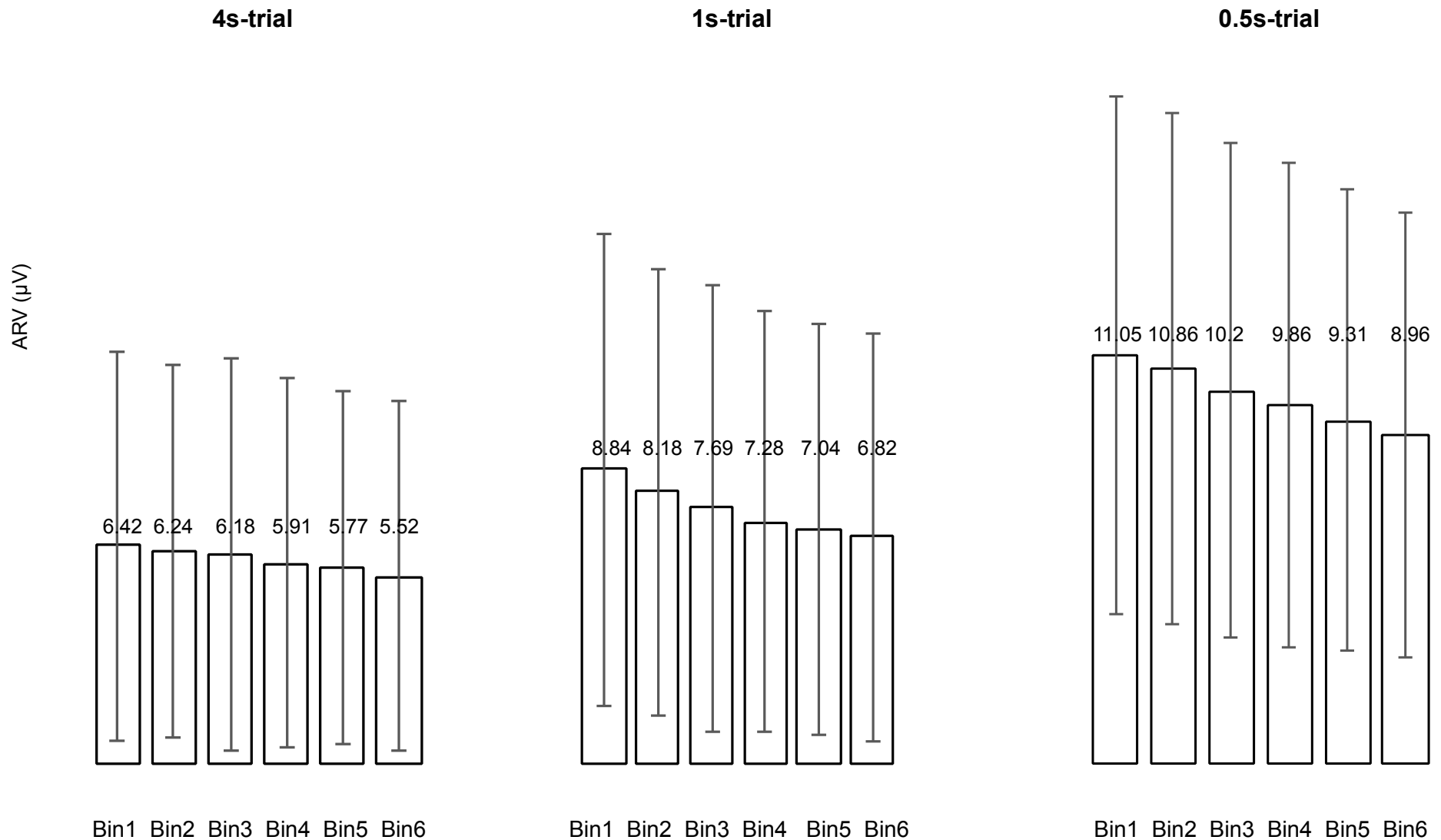
Figure 5. Mean data (±SD) of the average rectified value of the EMG signal (ARV) obtained in the patients during phase 3 (static phase of the stretch).
Data of the 21 patients in whom the static phase was detected in all 3 trials (4s-trial, 1s-trial, 0.5 trial) are shown. Bin 1: 0-10s; bin 2: 10-20s; bin 3: 20-30s; bin 4: 30-40s; bin 5: 40-50s; bin 6: 50-60s. Average Rectified Value (ARV) significantly decreases over time (p<0.0001).

EMG findings in healthy subjects (Table 4)

The velocity of passive displacement was 35.0°/s ± 6.1°/s for 4s-trial, 130.7°/s ± 11.5°/s for 1s-trial and 260.3°/s ± 23.5°/s for 0.5s-trial.

EMG activity was detected only during the dynamic phase of muscle stretch (phase 2).

At 0.5s-trial, EMG activity was detected in 12 subjects (1-12).

At 4s-trial and at 1s-trial, EMG activity was detected in 3 subjects (1-3). At 1s-trial, EMG onset angle was in the first half of stretching movement in all the 3 subjects. In the 3 subjects in whom EMG activity was detected during tonic stretch (4s-trial and 1s-trial), the examiner (CT) was able to appreciate that hamstrings muscles were not relaxed during passive stretch. Figure 6 shows EMG activity from subject 1.
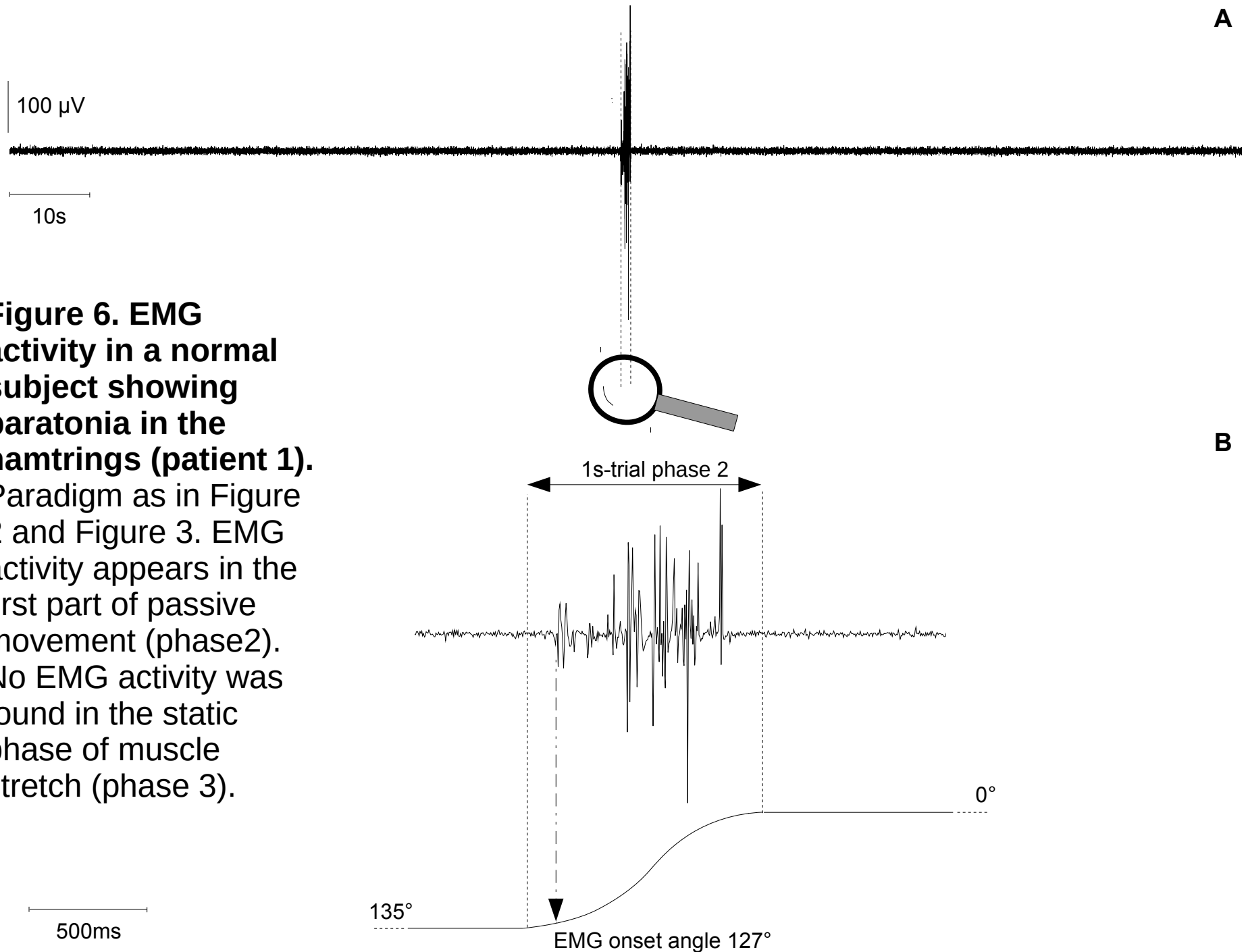
Table 4

Subject	ROM maximal flexion/ maximal extension (degrees)	4s-trial Phase 2		1s-trial Phase 2		0.5s-trial Phase 2	
		Starting angle	ARV (µV)	Starting angle	ARV (µV)	Starting angle	ARV (µV)
1	135/0	35.2	20.8	127.0	23.3	75.0	28.6
2	135/0	80.9	53.0	110.0	40.7	111.6	23.6
3	130/0	119.8	14.0	125.0	13.0	128.2	14.7
4	130/0	\	\	\	\	126.5	18.6
5	135/0	\	\	\	\	96.0	35.6
6	130/0	\	\	\	\	124	11.2
7	130/0	\	\	\	\	87.7	5.9
8	130/0	\	\	\	\	62.0	2.6
9	135/0	\	\	\	\	121.5	9.3
10	130/0	\	\	\	\	75.5	11.5
11	130/0	\	\	\	\	36.1	8.6
12	135/0	\	\	\	\	126.6	12.9
Mean	132/0	78.6	29.3	120.7	25.7	97.6	15.3
SD	2.5	42.4	20.8	9.3	14.0	30.5	9.7

Table 4. EMG findings in healthy controls.
ARV = Average Rectified Value of the EMG signal. Subjects 13-20 are not reported since no stretch reflex was recorded.

Figure 6

A

100 µV

10s

Figure 6. EMG activity in a normal subject showing paratonia in the hamtrings (patient 1). Paradigm as in Figure 2 and Figure 3. EMG activity appears in the first part of passive movement (phase2). No EMG activity was found in the static phase of muscle stretch (phase 3).

B

1s-trial phase 2

0°

135°

EMG onset angle 127°

500ms

Discussion

Clinical findings

According to the inclusion criteria, we recruited a population of 30 consecutive patients affected by progressive MS. Clinical examination revealed that 20 patients (67%) were affected by velocity-dependent hypertonia of the quadriceps muscle with exaggerated patellar reflexes.

In the clinical practice, the association of velocity-dependent hypertonia with increased tendon jerks leads the clinician to the diagnosis of "spasticity" and makes him/her aware of the fact that the corresponding stretch reflex is hyperexcitable. This is in line with the "official" definition of spasticity as "a motor disorder characterised by velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motoneuron syndrome" (Lance, 1980). Several works stressed that spastic muscles are quiescent at rest, prior to muscle stretch (Burke, 1975; Thilmann et al., 1991), showing that spasticity is a disorder of spinal proprioceptive reflexes (Burke, 1988).

Recently, we published a couple of works that highlight how the situation is a little more complicated than the one envisaged by Lance's definition (Marinelli et al., 2017a; Trompetto et al., 2019a). In fact, using surface EMG in patients affected by velocity-dependent hypertonia, we were able to evoke a tonic stretch reflex in all of them. However, only a proportion of patients were able to relax their muscle prior to stretch. This proportion represented patients actually affected by spasticity. The remaining were patients having muscles tonically activated prior to muscle stretch. They were affected by spastic dystonia, which is another positive phenomenon frequently encountered in the UMNS (Trompetto et al., 2014). The basic feature that differentiates these two forms of velocity-dependent hypertonia is the role played by the afferent input, which acts as a trigger for motor neuron activation in the case of spasticity (disordered spinal proprioceptive reflex) and as a modulator of motor neuron activity in the case of spastic dystonia. As far as the present results are concerned, the relevant aspect is that hyperexcitability of the stretch reflex is present in both spasticity and spastic dystonia (Marinelli et al., 2017a; Trompetto et al., 2014, 2019a, 2019b).

In the present study, besides *velocity-dependent hypertonia of the quadriceps associated with increased patellar jerks*, a further element proving the reflex nature of increased muscle tone was the clasp-knife phenomenon, which was found in all the 20 patients with hypertonia of the quadriceps. This phenomenon refers to the sudden disappearance of muscle resistance as stretch

increases. In contrast, intrinsic hypertonia worsens at increasing muscle length, and in the more severe cases, it produces a fixed shortening of the muscle and a reduced range of movement (muscle contracture).

Our clinical examination revealed that only 7 patients (23%) exhibited hypertonia in the hamstrings muscles. In these patients, the resistance to passive movement was maximal as the hamstrings became fully stretched, so that no clasp-knife phenomenon was noted. Furthermore, 4 patients showed contracture of the hamstrings, stating the role of intrinsic hypertonia and limiting our capability to appreciate velocity-dependent hypertonia.

Therefore, based on the clinical findings of the present study, 67% of our patients definitely had a hyperexcitable stretch reflex in the quadriceps muscle, while only 23% possibly had hyperexcitability of spinal reflexes controlling the hamstrings muscles. These findings fit in well with the common notion that in the lower limbs, spasticity is much more common in the extensor than in flexor muscles.

EMG findings

The surface EMG protocol used in the present study has been designed to investigate EMG activity in the biceps femoris evoked by both phasic stretch and tonic stretch of the hamstrings. According to the literature, in normal subjects no EMG activity is seen until the stretch velocity is greater than 200°/s. A short burst of EMG activity at these velocities (greater than 200°/s) has been considered analogous to the tendon jerk (phasic stretch reflex). In subjects with velocity-dependent hypertonia, EMG responses are seen also at stretch velocities lower than 200°/s (tonic stretch reflex) (Rothwell, 1994; Sheean, 1998a; Thilmann et al., 1991).

In the present study, using a stretch velocity of 31.2°/s ± 3.1°/s (4s-trial), a tonic stretch reflex was found in 22 patients. Using a stretch velocity of 124.8°/s ± 12.4°/s (1s-trial), a tonic stretch reflex was found in 26 patients. Finally, using a stretch velocity of 249.7°/s ± 24.7°/s (0.5s-trial), a phasic stretch reflex was found in all 30 patients. The amplitude of EMG activity increased with increasing velocity of stretch with ARV at the fastest velocity (0.5s-trial) significantly higher compared to the ARV at the lowest velocity (4s-trial). Moreover, we found that with faster velocities EMG activity appeared earlier, with a significant difference among the 3 tested velocities. From its onset, the stretch reflex persisted for the entire duration of muscle stretch, confirming the lack of clasp-knife phenomenon. Tonic stretch reflex tended to appear only in the second half of stretching movement (Figure 2, Figure 3 and Figure 4). In its initial phase, the reflex was low in amplitude. As muscle

length increased, the reflex gradually increased, reaching the greatest amplitude towards the end of the passive movement (Figure 2) or just after the end of passive movement (Figure 4).

These findings, fully consistent with previous reports of the hamstrings stretch reflex in UMNS patients (Burke et al., 1971; Wu et al., 2006), showed that stretch reflex is velocity-dependent, a feature due to the velocity sensitivity of the primary spindle endings and shared by the stretch reflexes elicited in every muscle (Trompetto et al., 2014). Furthermore, they showed that stretch reflex in the hamstrings is not only velocity-dependent, but also length-dependent, being more sensitive at longer muscle lengths. Quadriceps stretch reflex is also known to be length-dependent, but this dependence has an opposite sign in comparison to that in the hamstrings, the reflex being more sensitive at shorter muscle lengths due to the presence of the clasp-knife phenomenon (Burke et al., 1970). Both the primary and secondary spindle endings are sensitive to length. Activation of the primary spindle endings produces autogenetic facilitation in both the hamstrings and quadriceps. On the contrary, while activation of the secondary spindle endings produces autogenetic facilitation in the hamstrings, it produces autogenetic inhibition in the quadriceps, causing the clasp-knife phenomenon. This different reflex effect produced by secondary endings of hamstrings and quadriceps, explains the opposing dependence on muscle length of the stretch reflexes elicited in the two antagonist muscle groups (Burke et al., 1971; Hunt, 1952).

In the overwhelming majority of the patients, EMG activity was maintained after cessation of passive movement (phase 3) (Figure 2, Figure 3 and Figure 4). This activity during the static phase of the stretch (detected in 21 patients at 4s-trial, in 22 patients at 1s-trial and in 23 patients at 0.5s-trial) persisted for all the time of observation (1 minute) (Figure 2 and Figure 3), declining in amplitude over time (Figure 5).

In the wrist flexors of stroke patients, we recently showed that muscle activation during the static phase of the stretch co-occurred with spastic dystonia. We discussed that this prolonged activity could be a static component of the stretch reflex. As a second mechanism, we suggested that it could reflect the inability to stop the reflex EMG activity evoked by passive muscle stretch (Trompetto et al., 2019a). This inability could be connected to the prolonged firing of α-motoneurons, a well-documented phenomenon in patients with UMNS, which is likely to play a role in spastic dystonia (Trompetto et al., 2014). In the present study, on the contrary, the muscle was fully relaxed prior to muscle stretch in the majority of the subjects in whom such static activity was found, making unlikely the hypothesis of an involvement of spastic dystonia. Reasonably, this activity reflects the static component of the stretch reflex due to the discharge of both the primary and secondary spindle endings (Burke et al., 1971; Hunt, 1952). However, in an attempt to interpret

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this static phase, it must also be discussed that in 2006, Wu and collaborators described in the hamstrings a velocity-dependent stretch reflex elicited by passive knee extension, which was consistent with the dynamic phase of the stretch reflex reported in our study (Wu et al., 2006). In addition, they also observed a concomitant flexion of the hip and ankle, which was interpreted as a flexion reflex. Since the magnitude of the ankle dorsiflexion torque responses correlated to the stretch reflex torque at the knee, the Authors concluded that "stretch reflex" (in the hamstrings) "initiate a muscle contraction that then can contribute to a flexor reflex response, possibly through muscle group III/IV afferent pathways" (Wu et al., 2006). Based on these previous findings, we cannot exclude that the static phase of the stretch reflex in the present study may have been contaminated, at least in its initial part, by a flexor reflex triggered by passive knee extension.

In the heterogeneous group of 16 patients studied by Burke and co-workers (8 patients with spinal cord trauma, 1 patient with spinal cord angioma, 2 patients suffering from familial spastic paraplegia and 5 MS patients), a sustained reflex response to maintained stretch was found only in 3 patients. Interestingly, 2 of them were affected by MS (Burke et al., 1971). We suggest that a static phase of the stretch reflex in the hamstrings could be rather specific for MS patients. This point deserves further investigations.

Our results in MS patients must be interpreted also in light of the results obtained in healthy subjects. At the clinical assessment of muscle tone, we appreciated that 17 healthy subjects were relaxed, while in the remaining 3 subjects a certain degree of resistance could be perceived. The latter finding did not surprise us as any experienced clinician knows that normal subjects may have difficulty relaxing their muscles during tone assessment. These healthy people are affected by oppositional paratonia (Dupré, 1910), a frequently encountered phenomenon not only in patients with cognitive impairment (Beversdorf and Heilman, 1998; Marinelli et al., 2017b), but also in healthy subjects (Damasceno et al., 2005; Manfredi, 1994). Tonic muscle stretch produced no EMG activity in the 17 healthy subjects who were fully relaxed at the clinical examination. These findings are in line with the results of previous studies showing that tonic stretch reflexes cannot be elicited in the relaxed muscles of healthy subjects (Thilmann et al., 1991; Yeo et al., 1998). In contrast, in the 3 healthy paratonic subjects, EMG activity was found during tonic muscle stretch. In line with our recent findings in paratonic patients with cognitive impairment (Marinelli et al., 2017b), such EMG activity tended to start in the first half of the stretching movement (Figure 6).

Undoubtedly, the fact that EMG activity can be evoked during tonic stretch in paratonic healthy subjects implies that the presence of a tonic stretch reflex does not necessarily endorses spasticity or spastic dystonia. This important issue, not adequately focused in previous works, needs to be investigated in further studies. However, as far as the present results are concerned, the tonic stretch reflex in MS patients was easily distinguishable from the EMG activity in healthy paratonic subjects for the static phase, which was found only in the patients.

A phasic stretch reflex was evoked in 12 subjects, including the 3 subjects with paratonia, confirming previous results in healthy subjects (Thilmann et al., 1991).

Conclusions

A tonic stretch reflex in the biceps femoris was present in the vast majority of recruited patients, whether they presented or not hypertonia of the hamstrings. It is reasonable that the marked dependence on muscle length of the stretch reflex that we described in the biceps femoris may have played a pivotal role in ensuring that in many patients the reflex was present without producing hypertonia. The tonic reflex tended to appear only in the second half of the passive movement, often in its final part. The amplitude of the first part of reflex activity was very low. Usually, it progressively augmented with the increase of muscle length, reaching the maximum value at the end of the passive movement or after the movement itself, in the static phase of the reflex. These features, due to the synergistic effects of the primary and secondary spindle endings, could explain why the reflex appears also in normotonic muscle. In this regard, it must be said that during the assessment of muscle tone the examiner tends not to reach the maximum degree of joint extension to avoid potential joint damage caused by the kinetic energy imposed by the examiner on the patient's leg (Marinelli et al., 2013). At the same time, this dependence on muscle length could confer a pernicious character to the tonic stretch reflex in the hamstrings muscles of MS patients. The reflex contraction appeared whenever the muscle reached a certain degree of muscle length. Based on our data, it is possible to suppose that this reflex contraction can continue for a long time when the muscle is stretched, for example when the patient is in bed. This prolonged contraction could silently prevent the muscle from reaching its maximum length, progressively leading to muscle contracture. The finding of a tonic stretch reflex in muscles with normal tone, which inspired the title of the present study, is not in line with previous observations made on the upper limb, where the reflex was reported only in muscles showing velocity-dependent hypertonia at the clinical examination (Thilmann et al., 1991).

In conclusion, our data state that a tonic stretch reflex is evoked in the overwhelming majority of progressive MS patients in the hamstrings muscles. The reflex is elicited also in patients without hypertonia of knee flexors, suggesting a marginal role for the reflex in determining hypertonia of hamstrings muscles. The latter is likely to be largely determined by secondary muscular changes of the hamstrings. However, it is very likely that tonic stretch reflex in the hamstrings muscles, due to its main dependence on muscle length, could be an important risk factor for the development of muscle contracture. Therefore, our data suggest that tonic stretch reflex in hamstrings muscles is a phenomenon to be searched for in patients with progressive MS and possibly treated not so much to alleviate muscle hypertonia as to prevent it. Longitudinal studies are needed to confirm this view.

Conflict of Interest Statement and funding

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