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CICLO XXXV

Miniaturized instrumented measurement of resistance to passive motion: the Smart Assessment of Spasticity (SAS) project

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Summary of the work

This work is the result of a three-year doctoral course, in which the final project had an industrial characterization, being part of the Innovative Doctorates by Italian Ministry of Universities and Research (PON Project – *Programma Operativo Nazionale Ricerca e Innovazione 2014-2020*).

The present dissertation is framed in three chapters, focusing on different aspects of the work:

- Chapter 1 provides an introduction to the main topic of spasticity, with a general overview of the major neurological conditions where it occurs, its pathophysiology and the main methods of assessment and management.
- Chapter 2 describes two experimental pilot *case-series* studies designed to characterise spasticity in multiple sclerosis (MS), in order to identify its neural and biomechanical manifestations and responses to prospective rehabilitation treatments aimed at counteracting hypertonia. Through the application of isokinetic dynamometry, the gold-standard in biomechanical evaluation of muscle performance and disorders, and surface electromyography, two different isokinetic resistance training programs were devised and carried out in a cohort of people with MS affected by muscle hypertonia. In Study 1, the effects of an isokinetic eccentric exercise protocol targeting the hypertonic elbow flexor muscles were tested, showing that lengthening contractions increased the active and passive range of motion, also reducing the patient-rated burden of spasticity. In Study 2, an isokinetic concentric training was administered to the spastic ankle plantarflexors. The exercise protocol proposed in this pilot case-series significantly reduced resistance to passive motion in the absence of changes in electromyographic activity from the hypertonic muscles, suggesting that this type of exercise may positively impact on muscle architecture with no modulation of hypertonia.

- Chapter 3 introduces the final project aimed at prototyping and developing a new quantitative device for measuring spasticity-related resistance to passive motion in a cohort of people with MS-related spastic hypertonia. The device, named “SAS - Smart Assessment of Spasticity”, is currently under consideration for patenting, thus this work will not include exact product specifications and details other than those strictly necessary for explaining its overall functions and purposes. Study 3 consisted of a two-phase validation of the SAS device: phase 1 dealt with the observational, test-retest validation of the –derived kinematic, dynamometric and electromyographic measurements; phase 2 aimed at testing the ability of the device to track changes induced by a single-session rehabilitative intervention, which is commonly employed in clinical practice to achieve short-term relief of hypertonia symptoms in MS.

  The main finding of this pilot study was that measurements of resistance to passive motion obtained by this newly introduced device are not only highly reliable and accurate but can also capture even subtle changes induced by acute, non-pharmacological interventions, thus proving a sensitive and responsive measuring system that can complement the subjective, clinical assessment of the motor manifestations of spasticity.

Chapter 1

Spasticity

Introduction

Among the most common consequences of a neurological injury, such as an upper motor neuron syndrome, insults to neural-muscular-skeletal structures involved in movement generation are regarded as those mostly contributing to disability [1]. As a consequence, this condition leads to immobilization and chronic disuse of the impaired body district, also manifesting in different ways [2]. Upper motor neuron syndrome has two distinctions in terms of signs and symptoms: the negative features detected as a loss of dexterity, weakness and fatiguability; and in contrast, the positive features, which are characterized by inappropriate muscle activity, such as abnormal reflex responses, spasms, clonus and, predominantly, spasticity [3]. Although both positive and negative features adversely impact the resulting functional loss in patients with UMNS, spasticity is the most troublesome hallmark [4].

Prevalence of spasticity is stated to be around 4% to 43% in stroke survivors [5], 65% in people injured by spinal cord lesions [6], and 60% in people with multiple sclerosis (PwMS) [7], raising to 75% in patients with longer disease duration [8]. The incidence of post-stroke spasticity is around 25%, with 39.5% of patients showing hypertonia after first-ever stroke [9]. Cross-sectional data from a pool of 21.000 PwMS (North American Research Committee on Multiple Sclerosis, NARCOMS) revealed that spasticity was minimal/mild, moderate or severe in 50, 17 and 17% of patients, respectively. Additionally, increasing severity was associated with spasticity and with a corresponding decrease in quality of life scale scores [10].

Among the most common symptoms associated with spasticity are muscle stiffness, spasms and mobility restrictions, followed by fatigue, pain and bladder dysfunction [11], which negatively impact mobility, daily living activities and pain [8].

Different descriptions of spasticity syndrome have been proposed and discussed over the past twenty years, and its scientific interest in mechanisms responsible for plastic changes is of utmost importance in relation to recovery following upper motor neuron syndrome.

Since the most cited and stated definitions by Lance in 1980 [12], who described the phenomenon as “a motor disorder characterized by a velocity-dependent increase in tonic stretch reflex (‘‘muscle tone‘‘) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex’, this statement has been frequently challenged. One of the first authors who elaborated on hypertonia and rigidity was Charles Scott Sherrington [13], who became the reference author in this field due to his series of experimental studies in animals and humans. In his body of work, the author ascribed the *decerebrate rigidity* effects to prolonged spasms some voluntary muscle groups, due to interruption of the pyramidal tract, accompanied by inhibition in the antagonist muscle group. Years later, Lance [14] clarified the difference between decerebrate rigidity and spasticity, where in the former the reflex resistance increases as the muscle fibres lengthen to the passive stretch whereas, in the latter, resistance to passive stretch reduces once the muscle stretch is enough to activate group II afferent fibres, which suppress the stretch reflex via a central mechanism, generating the so-called "clasp-knife" effect.

By being strict to the increased velocity-dependent feature and hyperactive tendon jerks, throughout the following decade spasticity definition was focused on the possible spinal mechanisms involved in its pathophysiology, according to other authors. Nevertheless, authors such as V. Dietz deemed also clinical and physical signs, defining hypertonia as “a resistance of passive muscle to stretch in a velocity-dependent fashion following activation of tonic stretch reflexes” [15]. In his 2005 review series, Gracies [2] ascribed how changes in increased muscle tone are also explained by changes in muscle properties and not only caused by alterations of central processing of sensory input in the spinal cord.

In this regard, from a clinical perspective, the distinction between the identification of increased hypertonia caused by passive muscular modifications and the stretch reflex-mediated changes arises the need to develop more valuable tools to evaluate spasticity [16].

In this chapter will be discussed the characteristics related to the pathophysiology of spasticity in neurologic populations, as well as the different assessment methods.

Pathophysiology of spasticity

As previously introduced, spasticity is commonly defined as a motor disorder characterised by a velocity-dependent increase in stretch reflexes[12], resulting from adaptive changes in transmission into spinal networks following lesions of supraspinal motor pathways [4]. As a result, patients clinically exhibit enhanced tendon jerks, increased muscle tone and other modifications of muscle tissue attributes, which constitute the broad aspects of phenomenon[4]. The causes of spasticity and the relative impairments with upper motor neuron lesions are diverse and vary in relation to their magnitude. Lesions in the central nervous system, both in the brain and spinal cord, may result from various sources and have various effects.

In this section will be overviewed the different mechanisms involved in the pathophysiology of spasticity, from the main alterations due to imbalanced control of spinal motor neurons to the intrinsic muscle mechanical properties.

Alterations in stretch reflex excitability due to upper motor neuron syndrome

The upper motor neuron pathways comprise descending motor tracts, which directly or indirectly influence the excitability of the lower motor neurons. Among such tracts is the corticospinal tract, which originates primarily from pyramidal cells located in the inferior part of cortical layer V in the primary motor cortex and sensory cortex, and, to a minor extent, from the supplementary motor area and the ventral and dorsal premotor cortices [17]. The corticospinal tract encloses multiple functions leading to the control of afferent inputs, spinal reflexes and motor neuron activity [18]. After leaving the neocortex, the corticospinal tract form bundles and run through the internal capsule and cerebral peduncles before reaching the

brainstem in a ventral position, forming the pyramids, and maintaining the ventral direction until the caudal part of the medulla. The vast majority of the corticospinal tract axons cross the midline and go from a ventral to a dorsal position, leading to the formation of pyramidal decussation, and then continuing their trajectory in the contralateral spinal cord [19]. The crossed corticospinal tract is mainly involved in fine movements of distal extremities; in contrast, the uncrossed tract leads to motor neurons innervating the proximal or axial musculature [20].

This pathway has direct excitatory input to the anterior horn cell. Over this, pathways originating in the brain stem with indirect influence are the excitatory medial reticulospinal tract, arising in the pontine and medullary areas of the reticular formation [21], and lateral vestibulospinal tract, while the dorsal reticulospinal tract has inhibitory input to anterior horn cell; the latter leads close to the lateral corticospinal tract, so when lesions occur both tracts are simultaneously involved [22].

Excitability of the spinal stretch reflex is maintained by a balanced control from inhibition by the dorsal reticulospinal tract and excitation by the medial reticulospinal tract, in association with the vestibulospinal tract [23]. Moreover, the dorsal reticulospinal tract acts as a suprabulbar inhibitory system by receiving facilitation from the motor cortex via the corticospinal tract (Figure 1) [24].

Since the velocity-dependent increase in muscle resistance and hyperreflexia have an important role in the pathophysiology of spasticity, analogue alterations in spinal reflex transmission could be responsible for the increased stretch reflex circuit activity [16].

Additionally, changes in muscle tone may reside from variations in the balance of inputs not only from a lesion on the corticospinal system - which isolated lesions in animal studies produce weakness, loss of dexterity, hypotonia and hyporeflexia [25], but particularly from

reticulospinal and other descending pathways to the motor and interneuronal circuits of the spinal cord [26].

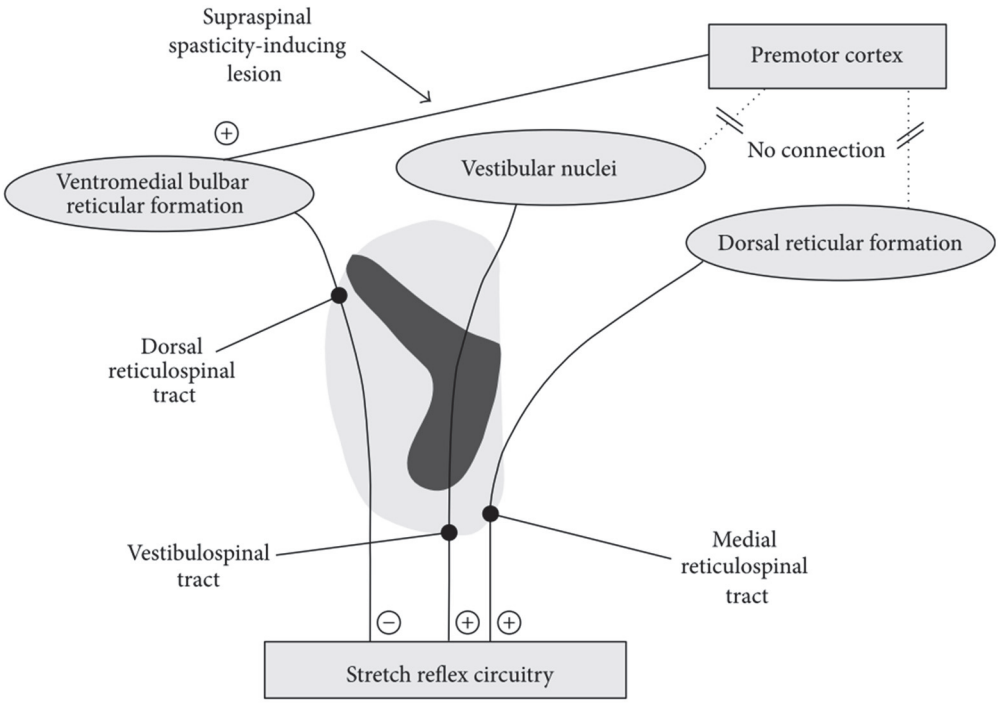


Figure 1 *Schematic representation of the descending pathways modulating the stretch reflex circuitry. From Trompetto et al., 2014 (modified).*

When a healthy muscle is passively stretched, the primary Ia afferent fibres, the largest and more rapidly conducting peripheral nerve fibres, are activated; this activation primes a monosynaptic excitation with the α motoneurons that supply the stretched muscle, resulting in contraction of the homologous and excitatory connections with α motoneuron that supplies synergistic muscles. Moreover, Ia afferent fibres have a monosynaptic connection with a spinal interneuron, which induces an inhibition of antagonist muscle, leading to reciprocal innervation [27].

The motor output to the muscle is delivered by α motoneurons, which receive monosynaptic excitatory inputs from Ia afferents, arising in the length-sensitive intrafusal muscle spindle, whereas the sensitivity of muscle spindles is regulated by the level of γ motoneuron activity. Following the discharge of Ia afferents, transmitter release is controlled by presynaptic

inhibition, which is conveyed by different groups of GABAergic interneurons in spinal cord, receiving inputs from both peripheral afferents and supraspinal control.

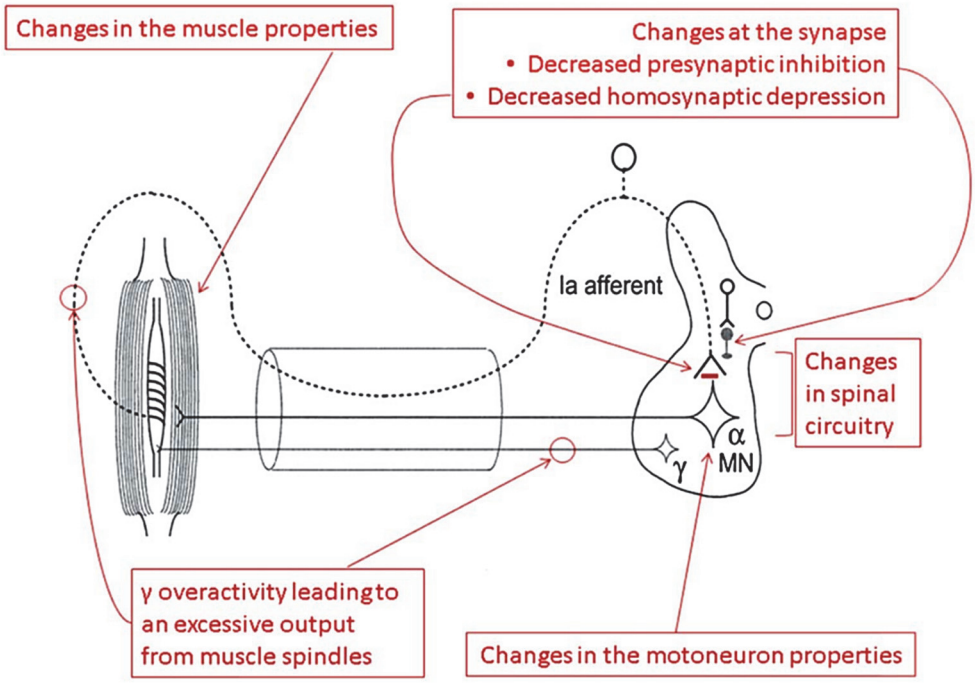


Figure 2 *Mechanisms of increased muscle tone in patients with hemiplegia. MN, motoneuron; Ia, group Ia afferents from primary spindle endings. From Burke et al., 2013 (modified).*

There are three main inhibitory control pathways involved in the excitability of spinal motoneurons (Figure 2) [28]: (1) *Reciprocal Ia inhibitory interneurons*: receiving input from Ia afferents and supraspinal centres, they lead to motoneurons on antagonist muscles to maintain low excitability of antagonist's motoneurons, concurrently with activation of agonist muscle; (2) *Ib inhibition interneurons*: inputs are controlled by Ib afferents, arising from Golgi tendon organs and supraspinal centres; they project both to agonist and synergistic motoneurons. (3) *Renshaw cells*: this type of interneuron receives input from spinal motoneuron collaterals and, in turn, conveys inhibit input back to motoneurons, as well as to IA inhibitory interneurons.

Following animal investigations, non-invasive electrophysiologic studies in healthy humans have confirmed comparable pathophysiologic mechanisms, as seen in the seminal works by

Crone and Nielsen in 1994 [29], Pierrot-Deseilligny in 1997 [30] and Katz and Pierrot-Deseilligny in 1999 [31]. In this regard, Nielsen showed that healthy subjects at rest have silent α motoneurons due to limited activity in corticospinal cells and Ia afferents with monosynaptic projections to motoneurons, as well as a tonic activity from descending and peripheral inhibitory pathways (Figure 3) [32].

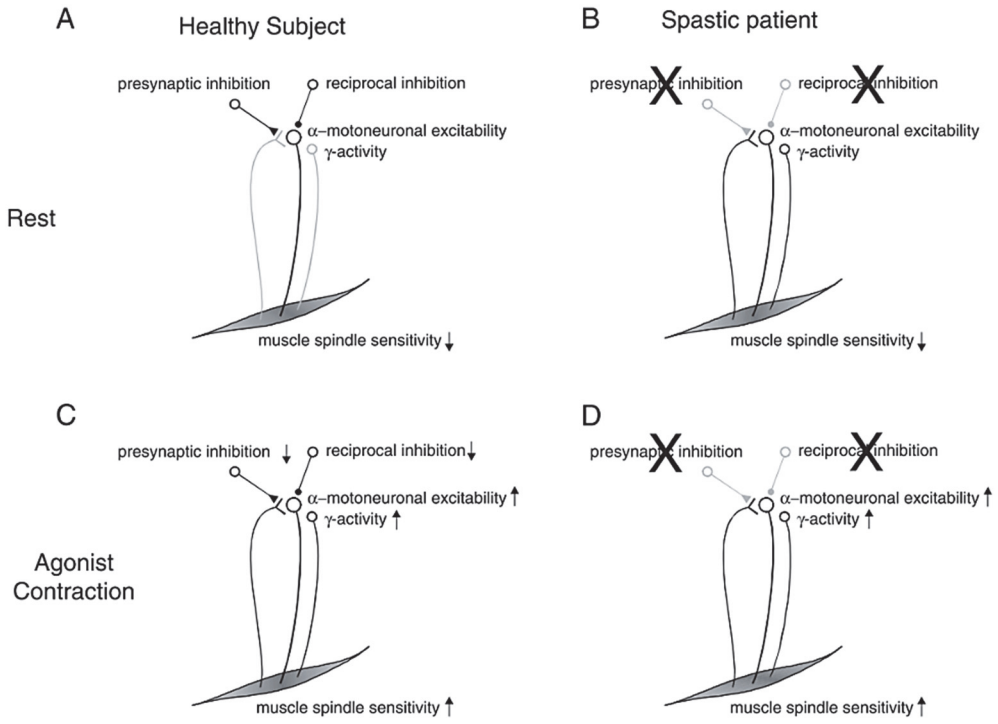


Figure 3 *Segmental motor control mechanisms in healthy subjects and spastic patients. The arrows designate whether the mechanism is decreased (arrow down) or increased (arrow up) during contraction in relation to rest. The crosses designate that the mechanism is affected in spasticity.*
From Nielsen et al., 2005 (modified).

Additionally, the activity of γ motoneurons and related sensitivity to muscle spindles are low. Moreover, presynaptic terminals of the muscle spindles Ia afferents make synapses with spinal interneurons and, through gamma-aminobutyric acid (GABA) release, transmitter releases from Ia afferents are suppressed. This presynaptic inhibition mechanism seems to be prominent in rest condition. During voluntary contraction of the healthy muscle, while presynaptic inhibition

presents lower activity, motoneuron excitability, muscle spindle sensitivity and Ia afferent discharge increase and, consequently, stretch reflex activity is high.

In contrast, spastic muscles reveal decreased level of presynaptic inhibition, Ib inhibition and Ia inhibition, followed by a stretch reflex activity already high at rest. This increased activity of stretch reflex does not differ also during contraction, or from stretch reflex activity in healthy subjects in the same condition.

In particular, Burke and colleagues in 2013 [28] outlined how the resulting changes in transmitter release from Ia afferents could contribute to the "habituation" of reflexes, which are elicited too rapidly. In this regard, a decrease in homosynaptic depression (also called post-activation depression) correlates with the degree of spasticity and is not seen on the uninvolved side. This could reside on the supraspinal control or may be indirectly conveyed by supraspinal drives.

Regarding spinal motoneurons, evidence demonstrated that intrinsic modifications of properties of motoneurons may support spinal spasticity and flexor spasms [33, 34], although evidence for hemiplegic spasticity still lacks. It has been hypothesized that disruption of inputs to the motoneuron pool could cause persistent activation of inward currents through dendritic L-type $Ca2^{+}$ channels and tetrodotoxin-sensitive persistent Na^{+} channels. These persistent inward currents may lead to the development of plateau potentials in motoneurons, increasing reflex gain and resulting in self-sustained firing, followed by an amplified motoneuron response that generates, in turn, a self-sustained discharge in response to a transient input [35]. These currents are managed by monoaminergic control, which are altered after acute spinal injury due to interruption of descending monoaminergic pathways.

Alterations in muscle tissue properties

Lieber and colleagues [36] reviewed the major structural and functional changes in spastic skeletal muscles in people affected by several conditions. Biopsy study results have attempted the variability of fibre Ia, IIa and IIb types. In healthy subjects, muscle biopsies exhibit firmly and well-distributed packed fibres forming a series of polygons next to the other, as shown in Figure 4A (mean coefficient of variations, CV=21.9%); in contrast, fibres from spastic muscle biopsies showed abnormalities and increased fibre size variability (mean CV=44.1%) evident as "rounded" fibres, or "moth-eaten" features, as well as increased extracellular space (Figure 4B). However, the mechanism based on this response is still debated.

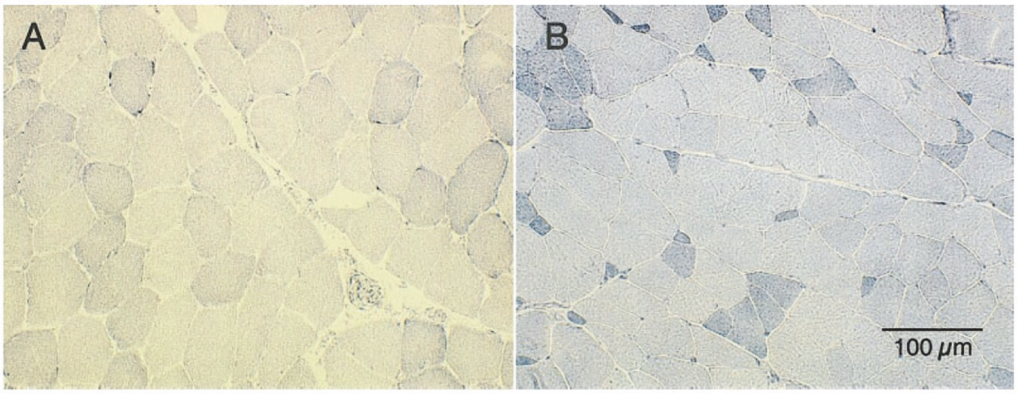


Figure 4 *Muscle fiber morphology is abnormal in spastic muscle. Light micrograph of a muscle obtained from a 19-year-old hemiplegic boy. A) Nonspastic extensor carpi radialis brevis muscle. Histochemical stain of the NADH oxidative enzyme that labels fiber type I and type IIA dark, and type IIB lighter. B) Spastic flexor carpi ulnaris muscle. Note the spastic muscle demonstrates greater fiber size variability. (Micrographs courtesy of Dr. Eva Pontén, Karolinska Institute, Stockholm, Sweden for Lieber et al., 2004). From Lieber et al., 2004 (modified).*

Changes in intrinsic components

As stated by Katz and Rymer [1], spastic hypertonia embraces both reflex and non-reflex changes, also called as "intrinsic component"; the former includes phasic and tonic reflex components, whereas the latter embraces dynamic component of viscosity (as "the ratio of the change of joint torque over that of joint velocity") and a static component of elastic stiffness (the spring property defined as "the ratio of the change of joint torque over the change of the joint position") [37]. The difference between these two elements lies in the resistance to passive

displacement in intrinsic hypertonia, which is not linked to the velocity of movement [24]. Reflex hypertonia, which corresponds to spasticity, and intrinsic hypertonia, due among the other to muscle contracture, often may be intimately connected [38].

The dynamic relation between joint position and the torque acting about it defines the mechanical behaviour of a joint [39]. This relation, called dynamic joint stiffness, characterizes the interactions of a joint with the associated limbs and the environment and is of value in the control of posture and movement. The overall dynamic stiffness, as well as possibly the relative contributions of the intrinsic and reflex components, may be modulated by the nervous system to determine the displacements induced by external forces, *i.e.*, during postural control and the forces required to conduct voluntary movements [39].

Due to the regulation of the stiffness of spastic muscle depending on active reflex mechanism and changes in stiffness, consequent modifications in passive properties of muscle could lead to contracture.

Contracture consists of a shortening of muscle length followed by a decrease in the number of sarcomeres in series along the myofibrils, accompanied by an increase in the resistance of passive stretch [40-42]. Morphometric investigations show adaptations in motor units and their contractile properties, possibly relying on the inherent nature of the innervating motoneurons and/or changes in the impulse along the motor axon leading to the muscle [43, 44].

In his review series, Gracies [2, 45] outlines the effects on muscle tissue and the possible mechanisms behind the structural changes in spastic paresis. After an injury, immobilization and shortened positions emerge, determining a significant reduction in longitudinal tension. Moreover, muscle unloading due to the deconditioning leads to other structural consequences, described as follows from the mentioned review:

Atrophy: the loss of muscle mass; caused by disuse in combination with induced paresis, atrophy rate negatively correlates with the length at which the limb is immobilized. Generally, disuse leads to reduced fibres' diameter and cross-sectional area as well as the reduced volume

of the whole muscle. In chronic hemiplegic patients, atrophy is more evident on the paretic limb compared to the non-paretic side.

Loss of sarcomeres: the forced shortened position heads to adaptation of the resting length losing sarcomeres, which tend to overlap optimally to enable development of maximal tension to the muscle at this length. The extent of these changes has been illustrated by the study of Tabary and colleagues in 1972 [46], where a period of four-week immobilization in shortened position produced around a 40% reduction in number of sarcomeres in cat soleus muscle.

Modifications in intramuscular connective tissue: stiffness (or reduced extensibility) of the immobilized muscle and diminished function are also likely to be attributed to quantitative and qualitative changes in the intramuscular connective tissue. In the aforesaid review, the Author reported immunohistochemical rat studies results, where a marked increase in the endomysial and perimysial connective tissue appear in immobilized rat muscles. Moreover, since a decrease in vascular density is followed by immobilization, its tensile strength is reduced.

Increased fat content: it has been stated that in chronic hemiplegic patients, impaired muscles show an increased amount of fat content, more in the paretic arm than in the spastic leg. Abnormalities in fat storage enclose altered and degenerated mechanoreceptors such as Ruffini and Pacini corpuscles, Golgi tendon organs and free nerve endings.

For what concern changes in contractile muscle properties, as what has been said so far, periods of imposed position and without weight bearing have relevant effects on skeletal muscle both for spastic hemiplegia and normal subjects, leading to characteristic adaptations as described here in this section.

While such features are shared by different neurological diseases including stroke, cerebral palsy and MS, spasticity in the latter condition is regarded as particularly challenging, given the concurrent evidence of brain and spinal cord lesions as well as the frequently progressive nature of MS [27]. Due to the peculiar clinical manifestations and pathophysiologic features of

spasticity in multiple sclerosis (MS), performing an in-depth overview and analysis of MS-related spasticity seems a worthy endeavour.

Introducing multiple sclerosis

MS is an immune-mediated, chronic idiopathic inflammatory and neurodegenerative disease of the central nervous system, characterised by inflammation, demyelination and primary or secondary axonal transection [47]. It is estimated that MS affects 2.5 million people around the world, with the highest prevalence occurring in Northern Europe and North America (over 100/100,000) [48] and with an incidence in Europe of 4.3 new cases per 100,000 individuals with approximately female:male ratio of 2:1 [49].

PwMS show several characteristics in terms of signs and symptoms, depending on progressive features and neuronal central nervous system damage, leading to progression of disease disability and impaired mobility [50]. MS typically begins between the ages of 20 and 50 years and can have variable prognoses. Relapsing-remitting MS is the more represented course, present in 80% of this special population; symptoms and signs have an oscillatory evolution, starting with a period of several days, followed by a stabilization and then often improvement, spontaneously or with corticosteroid therapy. Oftentimes, after a relapse, persistent signs of dysfunction in central nervous system could develop and disease may progress between relapses (to a secondary progressive MS). Twenty percent of people affected by MS have primary progressive course, which differs for gradually progressive clinical development [47].

The pathological hallmark of chronic multiple sclerosis is the demyelination plaque, consisting of a well-demarcated hypocellular area characterized by loss of myelin, relative preservation of axons, and the formation of scars on astrocytes. Lesions typically target optic nerves, periventricular white matter, brain stem, cerebellum, and spinal cord white matter. Inflammatory cells normally infiltrate the parenchyma, varying depending on the stage of demyelinating activity. Lymphocytes and macrophages are predominant, the latter in high

proportion. Axonal demyelination, which leads to slow or even stall conduction, may convey to the onset of first symptoms. Inflammatory cytokines may inhibit axonal function, which irreversible cases result from repeated episodes of disease activity and progressive loss of neurologic function. The pathogenesis of this early axonal injury is still debated [47].

Among the symptoms referred by PwMS, around 86% of them experience fatigue as the most current, but spasticity is present in 74% of patients, accompanied by stiffness and/or spasms; therefore, thus follows balance problems, muscle weakness, bladder or bowel problems, muscle stiffness and numbness, pain and muscle spasms [51].

Such an array of symptoms is a negative influence on the quality of life and daily living activities of patients.

Spasticity in multiple sclerosis

Spasticity is currently listed by PwMS among the three most frequently reported physical complaints, with 54% of them rating it as 'moderate' or 'severe'. Since MS occurs through both myelin and axonal degeneration, all symptoms as well as spasticity in MS undergo the same pathophysiological pathway. MS plaques may inhibit the supraspinal control of reflex activity, leading to impairment in movement generation and muscle function [50]. Progressive damage caused by MS leads to a loss of inhibition and altered the reflex arc mechanism; as a result, will include increased tone, muscle weakness, poor dexterity, fatigue, pain and resistance to passive movement, the latter often accompanied by abnormal posture and muscle spasm [27, 50]. In addition, a strong correlation has been found between degree of severity of MS spasticity and the level of disability, where patients with moderate-to-severe MS spasticity show higher disability level scores [10].

Spastic symptoms in MS, and other autoimmune diseases disabling central nervous system, suffer from highly dynamic neural changes and relate structural changes at the level of muscle tissue as well as metabolic alterations. Regarding inflammation-related changes, alterations in

the neural function equilibrium have been considered as a critical factor. Among the acute effects of inflammatory mechanisms reviewed by Patejdl [52] are increased energy demands due to demyelination, where decreased resistance of non-myelinated membrane areas allows larger passive current flows at rest and when action potentials are conducted. To maintain membrane potential stability, active transport through sodium-potassium-ATPase is increased, as well as an increase in ATP utilization, but inflammatory mediators, such as TNF-α, tackle this process; the course of inflammation interfere, among others, on mitochondrial function leading to the "energy failure" of axons caused demyelination [52].

In the spectrum of MS disease course, spasticity may occur in different expressions, as reported by Patejdl and Zettl [52], and could depend on individual disease history and lesion distribution, as well as its unpredictability. Such expressions reside on increased muscle tone during active movements and/or during passive stretching; transient, painful, paroxysmal muscle spasms. Data from the North American Research Committee on Multiple Sclerosis (NARCOMS) 2016 study reported occurrence of stiffness, spasms, pain and clonus in arms and legs, with severe stiffness of one or both arms reported by 3,2%, but 18,8% of the cohort referred severe stiffness of one or both legs.

Hoang and colleagues in 2014 [53] in their work explored the prevalence of contracture among PwMS with muscle weakness, since the severity of the latter tends to increase with the disease progression, as well as disability. Given the highly relevant manifestation of contracture in this special population (nearly 60% had at least one major joint affected), an important finding of the work belongs to the presence of contracture in PwMS at the level of the ankle, the most common site among the cohort examined (43.9%, 95% CI 36.9-50.9), of which 61% exhibited it in association with muscle weakness [53]. In addition, muscle contractures and intrinsic hypertonia of lower limbs are very common in patients affected by progressive MS, thus

hindering the clinical ability to detect hyperexcitability of stretchy reflexes in hypertonic muscles [53, 54].

Spasticity assessments

Clinical evaluations

The most common clinical assessment of spasticity is as a component of the standard neurological examination. Established clinical scales for estimating spasticity degree and burden are the Ashworth Scale and the Modified Ashworth Scale, the Tardieu Scale and Modified Tardieu Scales and the Spasm frequency scales.

The Ashworth Scale and the Modified Ashworth Scale are the most validated and used assessment scales among neurologists, physical therapists, and occupational therapists, as well as the most common assessment tools in research studies [55, 56] (Figure 5).

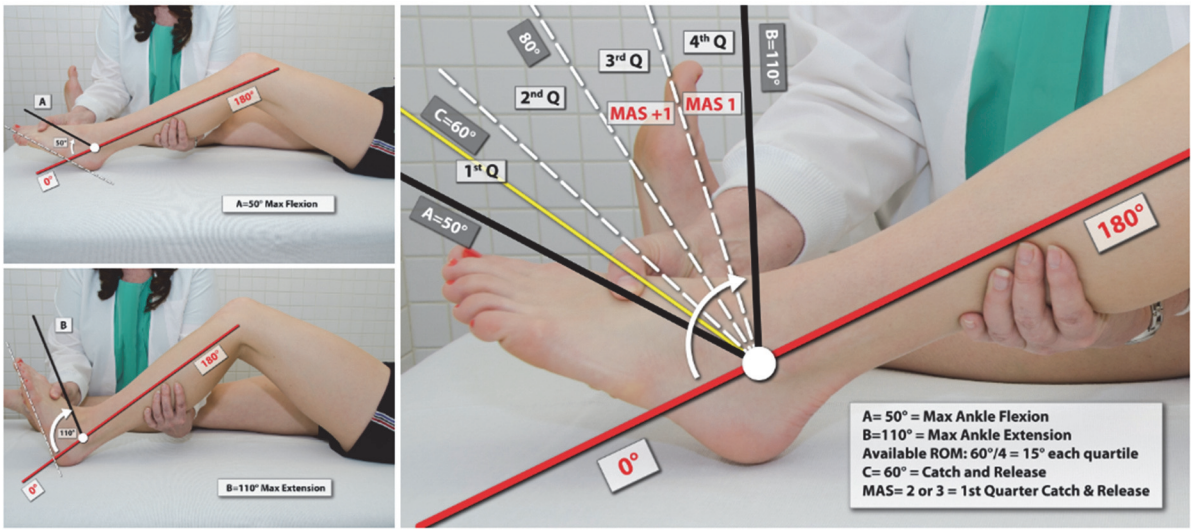


Figure 5 *Modified Ashworth Scale assessment of the ankle joint. As here portrayed, the scale measures the resistance to passive movements of a joint during a manoeuvre imposed by the operator. From assesschild.com/modified-ashworth-scale [57].*

The Ashworth Scale is a simple tool, easy and quick to administer, which estimates the amount of muscle tone by the examiner's perception during a brisk manoeuvre imposed on the spastic limb (Figure 5), resulting in a subjective score between 0 (no increase in tone) and 4 (limb rigid

in flexion or extension). Years later, Bohannon and Smith [56] modified the definitions of each score to allow a more discrete estimation of the symptom, due to the need for more accurate categorization of the lower end of the scale for those patients whose scores fluctuate between 1 and 2, adding an extra category (1+) (Table 1).

Table 1 The Ashworth and Modified Ashworth scales [55, 56]

Ashworth scale	*Score*	*Modified Ashworth scale*
No increase in tone	0	No increase in muscle tone
Slight increase in tone giving a 'catch' when the limb was moved in flexion or extension	1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end range of motion when the affected part(s) is moved in flexion or extension
-	1+ (2)	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
More marked increase in tone but limb easily flexed	2 (3)	More marked increase in muscle tone through most of the ROM, but the affected part(s) is easily moved
Considerable increase in tone – passive movement difficult	3 (4)	Considerable increase in muscle tone, passive movement is difficult
Limb rigid in flexion or extension	4 (5)	Affected part(s) rigid in flexion or extension

ROM, range of movement

The interrater and intra-rater reliability of the two tests has been tested in several studies [4]; although holding an acceptable interrater reliability for testing of upper limb spasticity, this finding was not confirmed in lower limb spasticity [58]. For instance, interrater reliability for spastic plantarflexors in traumatic brain injury was significantly lower than that reported for elbow flexor spasticity by Bohannon [59], in line with findings from Gregson and colleagues, where ankle data were associated with lower reliability compared to good to very good intra- and inter-rater reliability for elbow, wrist and knee [60]. Additionally, other concerns have been raised regarding the testing protocols used, as they can interfere with the evaluations. Among these, Modified Ashworth scale testing is highly dependent on the evaluator's background experience, since the mobilization imparted by the tester can vary in speed, range of motion and power, thus changing the test results [61]. In conclusion, as suggested by Pandyan and

colleagues, Ashworth Modified Ashworth scales can be used as '*an ordinal level measure of resistance to passive movement, but not spasticity*' [62].

Among the clinical tools evaluating hypertonic muscles, there are also the Tardieu and Modified Tardieu scales. The Tardieu scale [63] has been suggested as a more suitable alternative to the Ashworth scale, as it assesses and compares the response of the muscle to passive motion at both slow and fast speeds. Differentiation is achieved by comparing the angle of arrest during different stretching speeds, a slow one, under the stretch reflex threshold, and a fast speed above the threshold that would trigger the reflex.

In 1999, Boyd and Graham proposed an alternative version of the tool designed by Tardieu, the Modified Tardieu Scale adding angle position referent of the hypertonic reflex. The assessment scale is based on principles named R1and R2; the former is defined as the 'catch' resulting from the overactive stretch reflex seen in a fast range of motion at a particular angle, and the latter as an indication of muscle length recorded during slow passive joint range of movement. Moreover, the recent Modified Tardieu Scale version embedded a more accurate characterization of the velocities, described as follows: (1) The first stretch V1 is the slowest possible (lower than the natural rate of limb fall under gravity), which is used to evaluate the angle of muscle reaction at low speed; this represents the equivalent of the passive ROM; (2) The second stretch is at the same speed as the segment of the limb that falls according to gravity, defined as V2, or the fastest possible, V3 (greater than the natural rate of fall of the limb according to gravity); both speeds evaluate the angle of muscle reaction and the quality of muscle reaction at a high speed. Essentially, R1 is recorded when a fast stretch manoeuvre is applied, using either V2 or V3; R2 is recorded with the application of V1. The angle for R1 and R2 are measured with a goniometer. The semi-quantitative rating on a 6-level ordinal scale of muscle reactions is described (Table 2) as follows: 0) absence of muscle reaction; 1) weak resistance throughout the stretching movement, without clear catch; 2) A clear catch, followed

by release when the stretching force is maintained; 3) Fatiguing clonus, <10 seconds; 4) Non-fatiguing clonus, >10 seconds; 5) Joint immovable [64, 65].

Table 2 Tardieu Scale (adapted for stroke) (Tardieu et al., 1954; Held and Pierrot-Deseilligny, 1969; J.M. Gracies) [65].

Velocity of stretch: once velocity is chosen for a muscle, it remains the same for all tests			
V1	As slow as possible (slower than the natural drop of the limb segment under gravity)		
V2	Speed of the limb segment falling under gravity		
V3	As fast as possible (faster than the rate of the natural drop of the limb segment under gravity)		
Quality of muscle reaction (X)			
0	No resistance throughout the course of the passive movement		
1	Slight resistance throughout the course of passive movement, no clear 'catch' at a precise angle		
2	Clear catch at a precise angle, interrupting the passive movement, followed by release		
3	Fatiguable clonus (<10s when maintaining the pressure) appearing at a precise angle		
4	Unfatiguable clonus (>10s when maintaining the pressure) appearing at a precise angle		
5	Joint immovable		
Angle of muscle reaction (Y)			
Measured relative to the position of minimal stretch of the muscle (corresponding to angle zero) for all joints except hip where it is relative to the resting anatomical position			
Lower limb: to be tested in a supine position, at the recommended joint positions and velocities			
Hip	Extensors (knee extended, V3)	X Y	(degrees)
	Adductors (hip flexed/knee flexed, V3)		
	External rotators (knee flexed by 90°, V3)		
	Internal rotators (knee flexed by 90°, V3)		
Knee	Extensors (hip flexed by 90°, V2)		
	Flexors (hip flexed, V3)		
Ankle	Plantarflexors (knee flexed/extended by 90°, V3)		

Grading is always done at the same time of day, using a constant position of the body for a given limb. Other joints, particularly the neck, must remain in a constant position throughout the assessment and from one test to another. For each muscle group, reaction to stretch is rated at a specified stretch velocity with two parameters (X, Y).

Generally, several studies examined reliability and validity of the Modified Tardieu Scale in adult populations. As Morris and Williams [64] reported in the cited review, several studies investigated on reliability of MTS, stating poor reliability coefficients [66, 67].

Another clinical scale that is routinely employed in spasticity evaluation is the Spasm Frequency Scale by Penn [68], mostly used in combination with the Ashworth Scale to evaluate spasm frequency, which underwent some modifications years later by the work of Priebe and colleagues [69]. The scale, in its most recent version, embeds two components: the first is a 5-

point scale assessing the frequency with which spasms occur ranging from "0 = No spasms" to "4 = Spontaneous spasms occurring more than ten times per hour"; the second component is a 3-point scale assessing the severity of spasms ranging from "1 = Mild" to "3 = Severe". The second component is not answered if the person indicates no presence of spasms in part 1 [68] (Table 3).

Table 3 Penn Spasm frequency scale [68].

First component: frequency of spasms		**Second component: degree of spasm's frequency**
Description	*Score*	*Description*
No spasm	0	No spasm
No spontaneous spasm/mild stimulation-induced spasms	1	One or a few spasms per day
Spontaneous, strong but sporadic spasms occurring less than once per hour / can be easily induced	2	Between 1 and 5 spasms per day
Spasms occurring more than once per hour	3	5 to less than 10 spasms per day
Spasms occurring more than 10 times per hour	4	10 or more spasms per day, or continuous contraction

Regarding its reliability, a lack of evidence has been found in the pertinent literature; a study by Mills and colleagues, 2017 [70] showed intra-rater and inter-rater reliability weighted-kappa statistics as 'substantial' for both conditions analyzed in people suffering from chronic traumatic SCI, questioning about the Spasm Frequency outcome measure to assess self-reported spasticity after.

Biomechanical assessments

In addition to existing clinical, subjective and semi-quantitative score scales, biomechanical methods offer an objective quantifiable separation of passive and active contributions of muscle stiffness during the examination, leading to the development of more efficient tools [71].

In laboratory settings, parameters such as velocity of motion, measurements of reflex onset, resistance opposed by passive mobilization can be controlled, along with measures like torque and surface electromyographic activation (sEMG), which provide a reliable, and objective distinction between passive and active contributions to muscle stiffness [71-74]. Among the

objective methods to assess hypertonic muscles and relative resistance to passive mobilization, dynamometers have a prominent role in applied research studies, particularly when coupled with electrophysiological measurements when attempting to quantify resistance to passive motion from hypertonic muscle groups [71, 72, 75-77] (Figure 6). Hand-held dynamometers have been introduced over the past twenty years, which offer the possibility to measure the resistance against passive motion, showing variable intra- and inter-rater variability and appear generally to provide reliable measures of muscle stiffness [74].

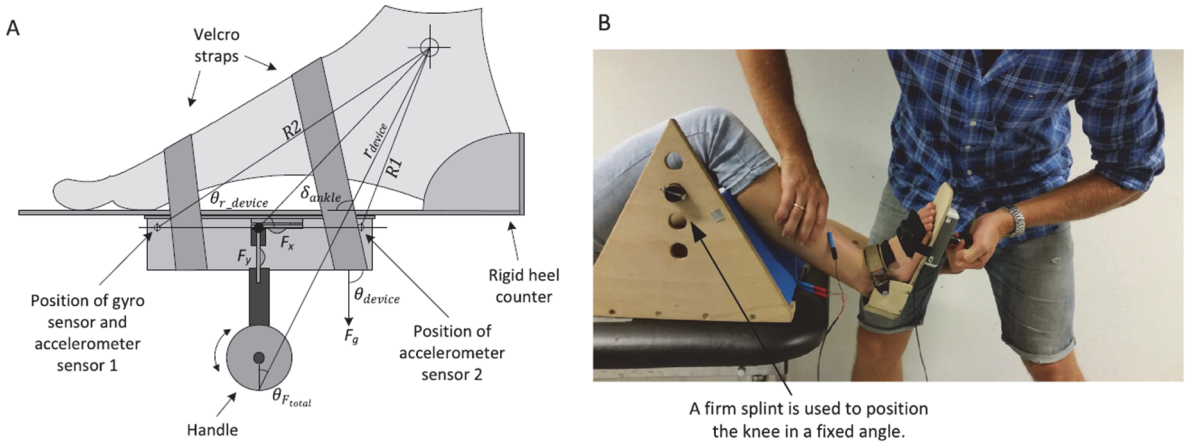


Figure 6 *(A) Illustration of the hand-held dynamometer, which integrates measurement of force, joint movement and reflex-mediated muscle activity. Ftotal is the resulting force measured through two load cells Fx and Fy. The length of the lever arm of the applied force (r-device) and the angle between the force vector and the arm (h-Ftotal) was calculated from R1 and R2 through two distinct points on the apparatus to the lateral malleolus. Accelerometers measured the position of the device relative to gravity (h-device) and the angular displacement of the device passive dorsiflexion of the ankle joint (d-ankle). (B) Illustration of the experimental setup. From Yamaguchi et al., 2018 (modified).*

Despite the ease and portability offered by hand-held dynamometers, adequate standardization of the muscle stretches imparted is crucial, especially for the amplitude and velocity of the movement, requiring more advanced devices that control the displacement imparted to the patient' limb. Among those, isokinetic dynamometers stand as the reference, gold-standard method. The main advantages offered by the isokinetic relate to the accurate determination of velocity-dependent characterization, intrinsic contributions and stretch-evoked muscle resistance, often accompanied by sEMG techniques [78].

Reliability and validity of isokinetic dynamometers have been tested in several studies, as reported by Biering-Sørensen and colleagues in their review [4], reporting a high reproducibility for resistive force values at low as well as high angular velocities, both in healthy humans and people with neurological impairments. The main disadvantage is that such methodology demands considerable technical expertise, time commitment, and the use of stationary equipment, which comes at high purchase and maintenance costs [74].

As in the manual method, while tonic stretch reflexes are elicited, angle characteristics can be measured along with torque and EMG responses; resulting signals, such as slope of the torque-velocity curve, allow to discern spasticity and hypertonia.

More recently, several attempts have been made to develop miniaturized, wearable and low-cost devices for assessing hypertonic resistance to passive motion [79-81] (Figure 7).

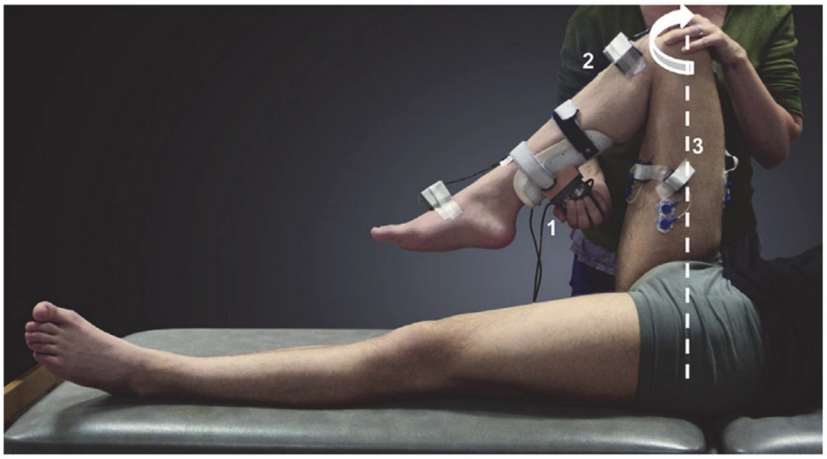


***Figure** 7 Test starting position, direction of stretch (white arrow), and instrumentation for the instrumented spasticity assessment of the medial hamstrings. Overview of the instrumentation: a 6 degrees of freedom force sensor attached to a shrank orthosis on the posterior aspect of the lower leg was used to measure torque (1); 2 inertial measurement units measured joint angle characteristics (2); and surface electromyography measured muscle activity of the agonist and antagonist muscle groups (3). From Bar-On et al., 2014 (modified).*

These integrated approaches consider both neurophysiological and biomechanical methods according to the incorporation of inertial sensors that allows researchers defining joint position, angular velocity, and acceleration of the imposed movement. Inertial measurements can improve accuracy and reliability problems due to the ease and accessibility. Inertial

measurement units allow estimation of kinematic parameters such as the body position, acceleration, and speed with high precision, using biaxial or triaxial accelerometers to measure planar or 3D movement, respectively, gyroscopes to measure rotation, and magnetometers to assess relative position [81-83]. The advantages in their utilization rely on low-power, pocket-sized, lightweight, and cost-effective systems, which can be adaptable in different evaluation environments. Instrumented tests that integrate biomechanical and electrophysiological measures have been shown to be reliable and valid for measuring spastic resistance to passive motion in laboratory setting [79], strongly supporting the employment of IMU systems in combination with EMG measurements [84].

Spasticity management

Ideal management of spasticity requires a multidisciplinary team to plan a comprehensive strategy to prevent and increase functional capacity, as well as relieve pain. Several pharmacological and non-pharmacological therapeutic approaches have been proposed and appraised in the literature. Among the pharmacological treatments comprehensively reviewed by Otero-Romero and colleagues [85], centrally-acting oral muscle relaxants are the most prescribed. Oral baclofen, a structural analogue of gamma-aminobutyric acid – GABA, decreases activity in motoneurons and interneurons; it has been found to significantly improve the symptom and in particular the frequency of spasms and clonus. However, in the majority of the analyzed trials, side effects such as tiredness, weakness and paresthesia were common (10%-75%). Tizanidine, a short-acting muscle relaxant, which reduces release of excitatory neurotransmitters, is also effective, as compared to baclofen and benzodiazepines; similarly to the latter, however, side effects appear to be quite common. Diazepam enhances the effect of neurotransmitter GABA and suppresses neuronal activity in the reticular formation, leading to muscle relaxation. Additionally, the usage of benzodiazepines showed more sedation. Overall,

there is a lack of convergence towards centrally acting muscle relaxants, particularly for their adverse effects on the central nervous system. Peripherally acting oral muscle relaxants, such as the cannabis-based nabiximols, have been introduced among the therapeutic treatments, despite an increased incidence of non-serious adverse events like dizziness [85].

Despite the consistent limitations, injection of botulinum toxin has strong recommendations to treat spasticity [7]. The formulation used to address spasticity is the Botulinum toxin type A, which blocks release of acetylcholine at neuromuscular junctions inhibiting muscle contraction. Local injection of Botulinum toxin in isolated muscle has a long-lasting effect over several weeks, with complete reversibility [85].

In those severe cases, intrathecal therapies are required with surgically pump implantation, although evidence supporting the use of injected phenol is still limited [85].

Regarding non-pharmacological treatments, a broad range of therapeutic interventions has been examined in different neurological populations, showing a lack of high-quality evidence for many modalities [86]. Among the most common approaches are exercise therapy, electro- and electromagnetic therapy, orthotics, which have been shown to provide short-term relief, reduce stretch reflex excitability possibly by decreasing excessive α motoneuron activity and hypersensitivity of muscle spindles to passive motion [86, 87]. A very recent systematic review of clinical trials in PwMS [88] reported a substantial paucity of data on the effectiveness of non-pharmacological interventions. However, significant improvements in spasticity outcomes were found for exercise-based interventions including strengthening, stretching, endurance and balance training. Such approaches, generally combined, appear to associate with improvements not only in hypertonia symptoms but also in fatiguability and motor functioning, balance, walking endurance and quality of life. However, the current body of knowledge on the management of MS-related spastic hypertonia with exercise-based interventions is still too limited to allow recommending its employment in clinical practice. Indeed, exercise has been studied so far more from the perspective of not exacerbating spasticity rather than relieving it.

Therefore, more studies are needed that evaluate whether exercise can also provide benefits to PwMS with hypertonia symptoms and, more broadly, to people with spasticity.

Chapter 1 - Spasticity

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Chapter 2

Experimental studies

Introduction to the studies

Based on Chapter 1 background and rationale, the primary goal of the first year of my PhD was to characterize spasticity in multiple sclerosis from an observational viewpoint in order to identify those major components (i.e., neural, non-neural) and their biomechanical manifestations that are not only typical of this population, but that may also be responsive to prospective rehabilitation treatments aimed at counteracting hypertonia.

In this perspective, two proof-of-concept pilot studies - Study 1 [1]; Study 2 [2] - have been devised, planned and executed employing isokinetic dynamometry as the core biomechanical evaluation method plus surface electromyography (sEMG) to characterize MS-related spasticity. In these works, resistance training targeting the spastic, weakened muscles was employed as exercise-based strategy to exert beneficial effects on muscle function and performance. Both eccentric and concentric contractions were chosen and evaluated individually to test their effects. Study 1 targeted on elbow flexors; while Study 2 was designed to examine ankle plantarflexors, which are known to be the most frequent site of lower limb spasticity in PwMS, affecting gait performance, independence and consequently quality of life.

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Study 1

Effect of eccentric strength training on elbow flexor spasticity and muscle weakness in people with multiple sclerosis: proof-of-concept single-system case series

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Effect of eccentric strength training on elbow flexor spasticity and muscle weakness in people with multiple sclerosis: proof-of-concept single-system case series

Abstract

Background: To date no attention has been devoted to the employment of eccentric contractions to manage spasticity in multiple sclerosis (MS). To explore in people with MS (PwMS) with elbow flexors' spasticity the effects of eccentric training on spasticity-related resistance to passive motion.

Design: Single-system case series with AB design.

Methods: Six PwMS (EDSS score 2.0-5.5; Modified Ashworth Scale, MAS, score ≤3) underwent a 6-week eccentric strength training of the spastic muscles. Before and after the intervention the following outcomes were assessed: resistive peak torque (RPT), isometric strength, resting limb position, passive (PROM) and active (AROM) range of motion, severity of hypertonia by MAS and numerical rating scale (NRS). At baseline, the primary outcome (RPT) was tested over three time-points to ensure a stable measurement. The 2-standard deviations (SD) method was used to test Pre-Post training effects at individual level. Group-level analyses were also performed.

Results: Following the intervention RPT decreased by at least 2 SDs in all subjects but one, with a significant reduction at group-level of 41.6±29.6% (p=0.018). Four PwMS reported a reduction in perceived spasticity severity. No changes in MAS score were detected. Group-level analyses revealed that maximal strength increased significantly in the trained elbow flexors (+30.9%±9.1; p=0.0006). Elbow flexion at rest was found significantly reduced (-35.5±12.4%; p=0.0008) while PROM (+4.6%; p=0.005) and AROM (+11.8%; p=0.009) significantly increased.

Limitations: Considering the design used and the lack of follow-up, these findings will need confirmation in a randomized controlled trial.

Conclusions: Eccentric training is feasible and safe to manage spasticity in PwMS. Preliminary data showed that this protocol can reduce resistance to passive motion, also improving strength, spasticity-free ROM and limb positioning.

Keywords: Multiple sclerosis; Spasticity; Resistance to passive motion; Eccentric training; Elbow joint; Single case studies

Introduction

It is estimated that 60-90% of people with multiple sclerosis (PwMS) experience spasticity [1], a debilitating symptom usually associated with weakness, spasms and pain. Spasticity negatively impacts a person's participation in family, work and social life and, consequently, on quality of life (QoL) [2]. Moreover, patients with spasticity suffer from tissue alterations including contractures and connective changes in muscles, tendons and joints, which can further impair limb positioning, movement and function [3].

Beyond pharmacological treatments, for which only short-term effectiveness is established, a wide range of non-pharmacological interventions are also used, such as physical modalities and structured exercise programs. A Cochrane Database review found 'low level' evidence of beneficial effects for exercise-based approaches given alone or in conjunction with physical modalities [4]. In regard to rehabilitation programs, to date no attention has ever been devoted to the employment of eccentric contractions (*i.e.*, the motion of an active muscle while it is lengthening under load) [5] to specifically manage spasticity in MS.

Compared with other training regimens, eccentric contractions have been extensively reported in healthy populations to induce the highest gains in maximal force generation and muscle capability to maintain force over the range of motion [6, 7]. Additionally, these effects are obtained at a reduced energy cost, which is of critical importance to PwMS, who exhibit muscle weakness and low reserves of energy and are exposed to early onset fatigue [8]. In addition, lengthening eccentric actions may lead to a better positioning of the affected limb and can reduce the spasticity-associated active and passive muscular insufficiencies in the spastic muscle and in its non-spastic agonist, respectively, which prevent multijoint muscles from achieving the optimal production of strength [9]. Overall, these properties were shown to have therapeutic implications in orthopedic conditions, especially for tendon disorders [5] and in neurological conditions characterized by muscle weakness and spasticity-induced contractures.

In particular, eccentric protocols were found to increase strength without exacerbating spasticity in children and adolescents with cerebral palsy [10] as well as in stroke survivors [11]. In PwMS, eccentric contractions have been previously employed to manage lower limb muscle weakness, with controversial findings ranging from significant increases in strength [12] to no additional effect if eccentric training was added to standard concentric exercise [13]. These studies, however, only employed lengthening contractions to manage muscle weakness but, to the best of our knowledge, no studies have investigated so far whether an eccentric training protocol is capable to reduce spastic hypertonia.

Based on the above rationale, the primary hypothesis of this study was that the employment of a program of eccentric training of the spastic elbow flexor muscles would *i)* prove feasible and safe in PwMS; *ii)* reduce resistance to passive motion; *iii)* increase the spasticity-free range of motion (ROM), and *iv)* improve muscle strength of the spastic elbow flexors. Therefore, this study proposed to explore in PwMS with focal limb spasticity the effects of eccentric training of the spastic muscle/s on their resistance to passive motion and muscle weakness and to verify whether these effects translated into higher functioning of the trained limb.

Methods

Participants

A convenience sample of six PwMS with moderate-to-severe degree of spasticity was selected within the framework of a larger randomized controlled trial (NCT02010398) for which a degree of spasticity ≥ moderate was set as exclusion criterion. The study was conducted according to the Declaration of Helsinki and approved by the institutional Bioethics Committee of the Local Health Authority (ASL n.1-Sassari, Italy; Prot. number 2420/CE 2016). Participants were given an informative note regarding all the modalities and timing of the study

and were required to sign an informed consent form before enrollment. All data are stored and protected at the Department of Biomedical Sciences, University of Sassari, Sassari, Italy.

Inclusion criteria were: definite diagnosis of MS according to 2017 revision of diagnostic criteria [14], Expanded Disability Status Scale score (EDSS) ≤6.5 with Pyramidal Functional System score of 2-4, unilateral spasticity of the upper limb shown by excessive flexor or extensor muscle tone score ≤3 as measured by the Modified Ashworth Scale (MAS) and compliance with the study instructions; age >18 years old.

Criteria for exclusion or discontinuation were: any medical condition contra-indicating participation in resistance training exercises; disability and comorbidities caused by medical conditions other than MS; fixed contracture or relevant atrophy in the affected limb; previous or current treatment with any botulin toxin serotype, or phenol, or cannabinoids, and surgery in the previous 6 months; current casting for spasticity of the limb of interest; occurrence of relapses or variations in disease-modifying drugs or symptomatic treatment within 6 months prior to recruitment; major depression (assessed with Beck Depression Inventory-BDI scale, cutoff for exclusion: ≥28; clinically relevant cognitive deficits (assessed with Frontal Assessment Battery-FAB scale, cutoff for exclusion: ≥14 and with the Trail Making-TMT Test A and B, cutoffs for exclusion: TMT-A ≥78 sec. and TMT-B ≥273 sec.); participation in rehabilitative or training programs in the previous 6 months.

Participants deemed eligible underwent clinical and dynamometric assessments within a 1-week period. Subjects were asked to refrain from any other exercise activity for the entire duration of the study.

Design

A single-system case series study was chosen because it is acknowledged as an appropriate methodology to observe changes in a subject's performance over time, providing clinically relevant information about individual subjects [15, 16]. The study design was implemented by

carrying out multiple pre-tests at baseline to control for the familiarization/learning effect, which is frequently associated with strength testing protocols [17] and to control for the high variability in muscle performance observed in PwMS [8, 18]. Multiple baseline assessments were also performed to establish the reliability of the measurements carried out.

A series of 6 case studies was completed employing a pretest-posttest design [19]. It is also known as AB design, where A represents the multiple baseline assessments, and B refers to the intervention phase followed by the post-intervention assessment. The timeline of the study is detailed in Figure 1.

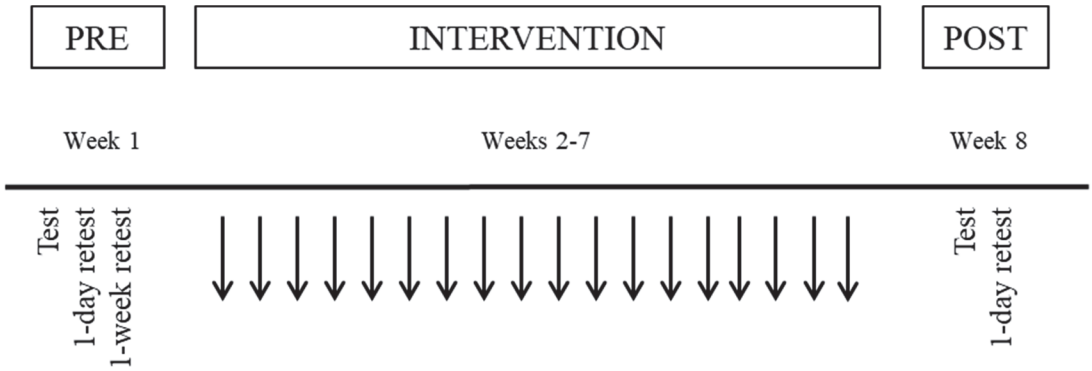


Figure 1 *Timeline of the study. PRE: baseline assessments (phase A of the AB design) with test-retest procedures consisting of 3 bilateral measurements (test, 1-day and 1-week retests) of the resistance to passive mobilization (isokinetic resistive spastic moment, primary outcome) from the spastic and non-spastic limbs; in this phase, baseline measures of dynamometric and clinical-functional outcomes were also performed (secondary outcomes). INTERVENTION: 6-week eccentric training of the spastic elbow flexors (phase B of the AB design). Each arrow indicates one training session (total sessions = 18). POST: post-training test-retest of the primary outcome and post-training test of secondary outcomes. From Manca et al., 2020*

Baseline assessments

Dynamometric assessments - All dynamometric tests were performed using an isokinetic device (KinCom Kinetic Communicator, Chattanooga, Tennesse, USA). The test was carried out in the affected limb first. The unaffected side was also assessed for intra-subject comparisons. The subject was asked to sit on the dynamometer seat, positioned according to the joint and muscle group under test and stabilized using custom straps and harnesses. The axis of rotation was aligned with the center of rotation of the elbow joint.

Resistance to motor-driven passive mobilization - The isokinetic resistive peak torque (RPT) was set as the primary outcome of the study since it allows to quantify the amount of resistance opposed by the spastic muscle group to passive movement [20, 21]. In the affected side, RPTs were measured during passive elbow extensions to quantify passive resistance to limb movement opposed by the flexor muscles. The patient's elbow joint was mobilized at increasing angular velocities (from 5 to 240°/s), according to patient's comfort and tolerability. In particular, for angular speeds >180°/s the flexibility, rigidity and self-reported perception of discomfort was carefully checked for each subject. During the procedure to measure the RPTs, subjects were instructed to relax while the dynamometer was moving the limb throughout the predefined comfortable ROM, which was kept constant from baseline to post-intervention assessments to ensure consistency and comparability. Passive torques obtained throughout the full ROM at the angular speed of 5°/s were used to correct for the effects of gravity and limb weight and to detect the amount of stiffness from the soft tissues, which detract from the actual torque produced by the flexor muscles [22, 23]. The lowest angular velocity that was found to elicit the spastic reflex was used for PRE to POST comparisons in RPT.

Given the high variability in neuromuscular performance observed in PwMS [8], the RPT was measured over three time-points by means of test-retest procedures (test; 1-day retest; 1-week retest) for reliability purposes, to obtain a stable baseline, avoid potential effects of residual fatigue or muscle soreness and minimize the presence of ongoing performance-based gains, which may make it difficult to track the real changes from baseline following the intervention. Of the RPTs recorded over the three sessions, the highest was retained for analysis as the baseline value. Offline data analyses were then conducted to establish the RPT for each subject, which was obtained as the difference between the torque recorded from the unaffected and from the spastic elbow flexors.

Maximal strength - Maximal voluntary isometric contractions from the affected and unaffected elbow flexor muscles were measured at the optimal muscle length (intermediate ROM). Three

trials, each lasting approximately 5 s, were collected. Each trial was followed by a 1-min rest period.

Electrogoniometric assessments - The resting limb position, passive and active ROM (PROM and AROM, respectively) were measured by electrogoniometry (Biometrics Ltd, Newport, UK).

Clinical assessments - a) the severity of spastic hypertonia, as assessed by the clinician-reported MAS [24], b) the variations in patient-reported perception of spasticity burden in the trained muscles as assessed by the numerical rating scale (NRS) with a score from 0 ‘no interference of spasticity’ to 10 ‘unable to move the spastic joint’.

Intervention

In general, throughout the training period special attention was devoted to the monitoring of the delayed onset of muscular soreness, which has been associated to eccentric contractions, although levels of soreness diminish with repeated bouts of eccentric exercise because muscle remodelling increases the muscle length [25]. Patient-reported delayed muscular soreness relating to a training session was estimated via NRS at the beginning of the following session. The eccentric intervention was performed on the same isokinetic device employed for the dynamometric assessments. PwMS underwent a 6-week eccentric training program targeting the spastic elbow flexors. Each patient was provided with an individually adapted eccentric training regimen tailored according to the strength level recorded at baseline. Participants were required to actively resist (*i.e*, “brake”) with the spastic muscles the forced elbow extension driven by the isokinetic device which was preset to move at a slow angular velocity (30°/s). The workload was adjusted to match 70% of the maximum level of strength recorded at baseline. The training schedule consisted of 3 training sessions/week, each session consisting of 6-8 sets of 6 to 10 repetitions (increased on a weekly basis), with a complete recovery of 3 minutes between sets. The training schedule was planned and developed by one of the authors,

a clinical exercise physiologist and physiotherapist with a specific background in testing and training procedures for populations with neurological conditions. Each session was supervised in a 1:1 ratio by a physiotherapist with a 5-year expertise with PwMS.

Post-intervention assessments

Post-intervention assessments of the primary and secondary outcomes were performed within one week from the end of the training (Figure 1).

Statistical analysis

Data analysis was performed using the SPSS software for Windows, version 18.0 (SPSS Inc, Chicago, IL - USA). The assessment of measurements' consistency was performed to determine the reliability of the primary outcome, the RPT, which has been previously reported as highly variable [21, 23]. According to Lexell and Downham [26], test-retest reproducibility was estimated by calculating the consistency of the RPT measurements at baseline. The intraclass correlation coefficient (ICC) was carried out over 3 time points using a 2-way random $ICC_{2,1}$ for average measures. The ICC coefficients were calculated taking a value <0.4 as an index of poor reliability, 0.4 to 0.75 fair to good reliability, and >0.75 excellent reliability [27]. ICC determination also allowed to establish the responsiveness of the changes from baseline. Accordingly, the standard error of measurement (SEM) was also calculated using the formula: $SEM=SD\sqrt{(1-ICC)}$ [28]. Based on the SEM, the smallest real difference at the individual level (SRD) [26] was calculated using the following formula: $SRD = 2.77\ SEM\sqrt{2}$ [29].

To assess the individual-level effects of the eccentric training, the two-standard deviation (2SD) band method was employed to quantify the amount of change in RPT from baseline [19]. A 2-SD band method was calculated for each participant based on the baseline measurements of RPT over three time-points.

Even though the design of this study was set as single-system, changes from baseline in the amount of resistance to passive motion following the intervention were also analyzed at the group-level by running two-tailed paired *t*-tests for continuous data expressed as mean ± SD, or the non-parametric Wilcoxon signed-rank test for ordinal data, with significance set at $p<0.05$.

Results

All the participants (6 women; 40.2±11.6 years old; mean weight: 60.4 ±12.3 kg) had a definite diagnosis of relapsing remitting MS with a mean disease duration of 12.2±1.5 years. They had moderate disability (median EDSS: 4.8; range 2-5.5), normal cognitive functions and depression ranging from minimal to mild, with the exception of subject #5, who exhibited a BDI score of 22 (moderate to severe depression). All PwMS were on anti-spastic pharmacological treatment (Baclofen *per os*) throughout the entire duration of the study, during which no relapses or changes in medications occurred. The intervention was well tolerated, with a 100% adherence to the scheduled program and no adverse events reported by the participants. Overall, a delayed onset of muscular soreness in the trained muscles was reported in the 48 hours following the training sessions of the first week of intervention (median NRS score 4/10; range 2-5). However, none of the participants had to take pain medication or to delay the following session due to muscular soreness.

Main demographic and clinical features of the participants are reported in Table 1.

Table 1. Demographic and clinical features of the participants at the study entry.

	Subjects					
	1	2	3	4	5	6
Age (years)	55	38	30	54	29	35
Disease duration (years)	12	13	11	13	14	10
EDSS	4.5	5.0	4.5	5.0	2.0	5.0
MAS	1+	2	2	1+	1	1
Walking Aids	None	None	None	None	Walking stick	AFO

EDSS, Expanded Disability System Status; MAS, Modified Ashworth Scale; AFO, Ankle Foot Orthosis.

Resistance to motor-driven passive motion – Data on RPT are reported at 90°/s of angular velocity, which was found to be the lowest speed capable to elicit the spastic reflex in all participants. Regarding the multiple assessments of RPT at baseline (Table 2), the ICC calculated over the three assessment sessions at baseline was 0.98 (95% CI 0.93-0.99), 0.99 (95% CI 0.96-1.00) when comparing sessions 1 and 2, and 0.96 (95% CI 0.70-0.99) when comparing sessions 1 and 3 and session 2 versus 3.

Table 2. Reliability of the resistive peak torque measured during passive isokinetic extensions of the affected elbow flexors at baseline

Subjects	Resistive peak torque* (Nm)		
	TEST	1-DAY retest	1-WEEK retest
1	12.9 ± 9.2	12.2 ± 8.9	12.3 ± 9.0
2	17.4 ± 11.9	17.0 ± 12.1	17.2 ± 11.5
3	22.5 ± 14.0	20.7 ± 12.6	17.0 ± 11.6
4	8.7 ± 5.8	6.2 ± 4.2	8.5 ± 5.9
5	6.5 ± 3.6	6.4 ± 4.0	6.5 ± 4.1
6	11.0 ± 6.2	10.3 ± 6.2	9.8 ± 5.7
1-6	13.2 ± 6.2	12.1 ± 5.8	11.9 ± 4.5

*The resistive peak torque was calculated as the difference between the torques recorded from the non-spastic and spastic elbow flexors, respectively; Nm, newton meter; all torques recorded at 90°/s of isokinetic angular velocity.

The SEM ranged from 7 to 25%, with a median value of 15% and the SRD ranged from 25.8 to 31%. Each subject had therefore to exceed this range of improvement in order to consider the observed training-induced change in the resistive peak torque as meaningful and not expression of a measurement error. Individual- and group-level results of the reliability analyses are reported for the RPT in Table 2.

Following the eccentric training, the amount of resistance opposed by the spastic muscle/s against the passive motion carried out by the isokinetic dynamometer, i.e. the RPT, was found reduced in all the participants but one (Table 3).

Table 3. Resistive peak torques measured during passive isokinetic extension of the non-spastic and spastic elbow flexors before (PRE) and after (POST) the 6-week period of eccentric training.

Subjects	PRE			POST			*RPT PRE to POST change (%)*
	Non-spastic torque (Nm)	Spastic torque (Nm)	RPT (Nm)	Non-spastic torque (Nm)	Spastic torque (Nm)	RPT (Nm)	
1	18.3±5.7	5.4±3.7	12.9±9.2	16.9±6.1	9.8±1.9	7.1±5.4	*- 45%*#*
2	18.0±5.7	0.6±6.5	17.4±11.9	17.0±6.5	10.6±2.5	6.5±5.3	*-62.7%*#*
3	18.7±5.6	-4.2±8.4	22.5±14	18.2±6.1	11.6±2.6	6.6±4.7	*-70.7%*#*
4	16.0±5.5	7.3±1.5	8.7±5.8	15.2±6.1	10.1±2.8	5.1±3.7	*-41.4%*#*
5	18.9±3.2	12.4±1.9	6.5±3.6	18.2±3.5	10.8±1.3	7.4±2.2	*13.8%*
6	17.1±5.6	6.1±1.6	11.0±6.2	16.3±6.3	10.1±2.8	6.2±3.9	*-43.6%*#*
1-6	17.8±1.1	4.5±5.8	13.2±5.9	17±1.2	10.5±0.7	6.5±0.8	*-41.6±29.6 p=0.018*

Nm, newton meter; all torques recorded at 90°/s of isokinetic angular velocity; RPT, resistive peak torque calculated as the difference between the torques recorded from the non-spastic and spastic elbow flexors, respectively; * PRE to POST change in resistive peak torque exceeding the smallest real difference (SRDi) cut-off for clinically meaningful change; #, significant change from baseline according to the 2-standard deviation method (2-SD band method) calculated for each participant at baseline over three time-points. 1-6, group-level results as assessed by repeated-measures analysis of variance; significance set at $p<0.05$.

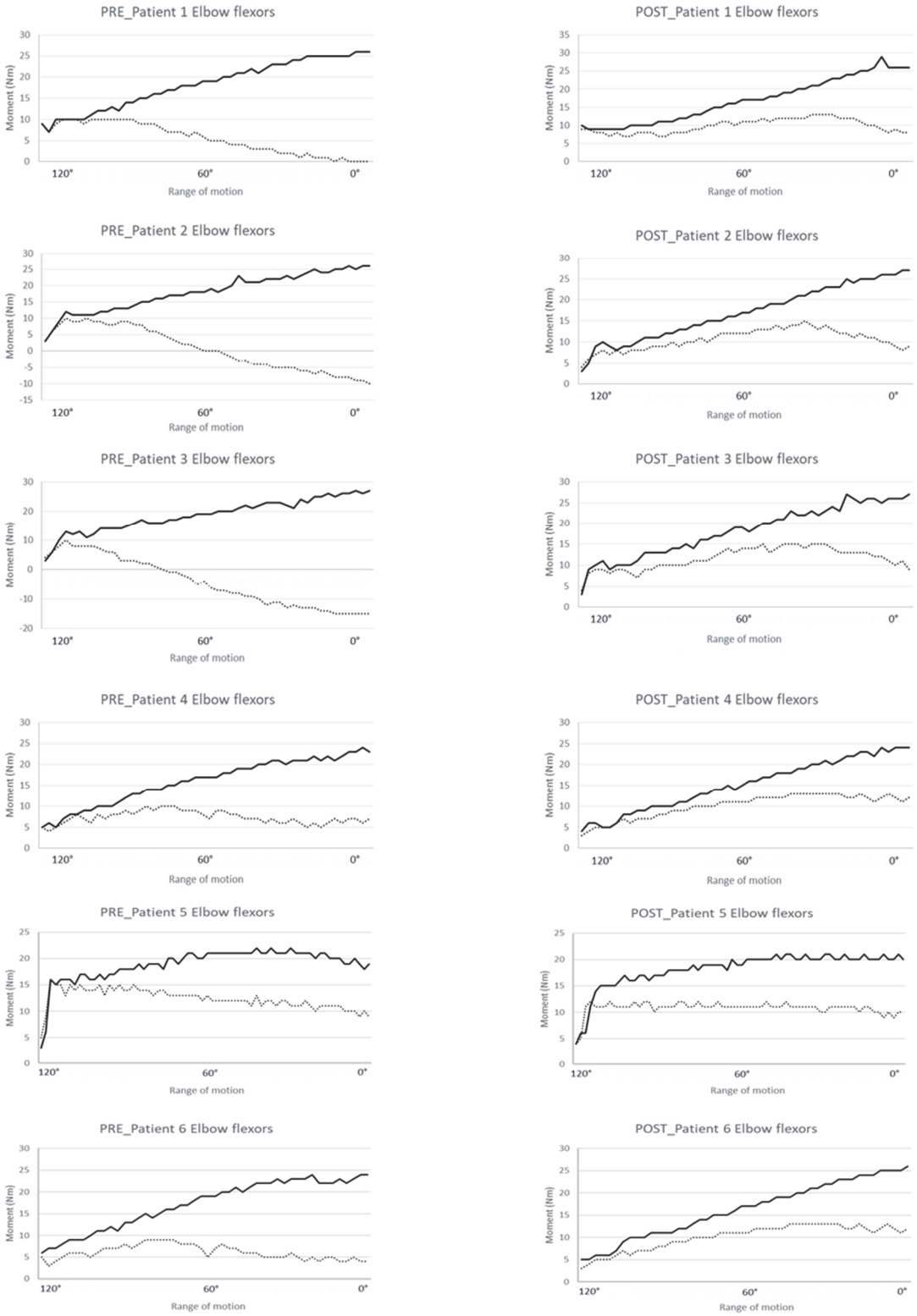


Figure 2 *Effects of a 6-week eccentric training on the isokinetic spastic resistive moment recorded bilaterally: individual results. Moment/angle isokinetic curve at 90°s of angular velocity is shown for each participant at baseline (PRE, left panels) and after the 6-week eccentric training (POST, right panels) carried out on the isokinetic device. Data are reported for the unaffected limb (continuous line) and the affected limb (dotted line). Graph axes are optimized for each case. From Manca et al., 2020*

Figure 2 displays for each of the six participants the torque/angle isokinetic curve during passive mobilization at 90°/s of angular velocity at baseline (PRE) and after the 6-week eccentric training (POST) carried out on the isokinetic device both for the unaffected limb and for the spastic limb. The graphs show that, at baseline, the unaffected limb is linearly moved by the isokinetic device throughout the predefined range of motion. By contrast, the spastic limb opposes a certain amount of resistance to passive motion, as shown by the opposite direction taken by the curve (downward rather than upward trend). The difference between the patterns exhibited by the two limbs was reduced following the 6-week eccentric training.

When appraising the results through visual inspection, based on the 2-SD band method, the post-training curves of five subjects (n. 1, 2, 3, 4 and 6) were found to be at least 2 SDs below the baseline values, thus indicating a significant reduction at the individual level in the amount of resistance to passive mobilization. For participants 5, a non-significant reduction in the RPT was observed.

Comparing the training-induced percent change in the resistive peak torque to the SRDi range (25.8-31%) calculated at baseline, five (subjects 1, 2, 3, 4 and 6) out of the six participants were found to exceed this threshold, while one patient (subject 5) did not.

Resistance to manual passive mobilization - Following the 6-week eccentric training, five of the participants (subjects 1, 2, 3, 4 and 6) reported a subjective reduction in self-perceived severity of spasticity, as assessed by the 0–10 NRS scale. Subjects 1, 2, 3 and 4 reported a reduction by at least one point. No change was detected in the clinician-rated MAS scores (Table 4).

Table 4. Muscle strength, goniometric and qualitative measures of muscle hypertonia in persons with multiple sclerosis presenting spasticity of elbow flexors before and after 6 weeks of eccentric training of the spastic muscles.

Outcomes assessed		Subjects						
		1	2	3	4	5	6	1-6
Spastic elbow flexors MVIC (Nm)	PRE	27.4	33.9	40.6	30.2	48.2	37.6	36.3 ± 7.5 (95% CI 28.4 – 44.2)
	POST	38.8	46.3	48.5	41.1	58.1	49.4	47.0 ± 6.8 (95% CI 39.8 – 54.2)
	p value							0.0006
Resting limb Position (deg)	PRE	17	24	30	12	18	17	19.7 ± 6.3 (95% CI 13.0 - 26.3)
	POST	9	14	22	7	15	9	12.7 ± 5.5 (95% CI 6.9 - 18.5)
	p value							0.001
PROM (deg)	PRE	110	102	105	107	111	114	108.2 ± 4.3 (95% CI 103.6 - 112.7)
	POST	113	109	113	110	113	121	113.2 ± 4.2 (95% CI 108.7 - 117.6)
	p value							0.005
AROM (deg)	PRE	87	74	90	92	101	101	90.5 ± 9.7 (95% CI 80.3 - 100.7)
	POST	104	93	101	99	103	103	101.2 ± 4.8 (95% CI 96.1 - 106.2)
	p value							0.009
MAS (score)	PRE	1+	2	2	1+	1	1	1.5 ± 0.6 (95% CI 0.9 - 2.1)
	POST	1	2	2	1	1	1	1.3 ± 0.5 (0.8 - 1.9)
	p value							>0.05
NRS (score)	PRE	7.1	6.1	6.9	5.8	5	3.6	5.7 ± 1.3 (95% CI -0.2 - 11.7)
	POST	5	4.2	5	4.5	5	3.1	4.5 ± 0.7 (95% CI -0.3 - 9.2)
	p value							0.01

Outcome measures are reported at individual level and at group level (mean ± standard deviation and 95% Confidence Interval); MVIC, maximal voluntary isometric contraction; Nm, newton meter; deg, degrees; PROM, Passive Range of Motion; AROM, Active Range of Motion; MAS, Modified Ashworth Scale; NRS, Numerical Rating Scale related to patient-reported perception of spasticity burden; PRE, outcome measures assessed at baseline; POST, outcome measures assessed after 6 weeks of eccentric training.

Maximal strength - Following the eccentric training, maximal voluntary isometric strength of the elbow flexors measured at the optimal muscle length (intermediate ROM) increased in all the participants (+30.9% ±9.1; 95% CI 20.3-41.4; p=0.0006, Table 4).

Resting limb position, passive and active ROM – Table 4 summarizes all the data by participant and at the group-level. At the POST-evaluation, electro-goniometry of the spastic side revealed consistent changes in terms of reduced flexion at rest in the spontaneous upper limb positioning in all subjects. At the group-level analysis, resting limb positioning was found significantly improved (-35.5 ± 12.4%; 95% CI 23.8-49.8; p=0.0008).

Both PROM (+4.6%; p=0.005) and AROM (+11.8%; p=0.009) were found significantly increased (Table 4).

Discussion

The present proof-of-concept single-system case series employed eccentric training for the first time primarily to modulate spastic hypertonia, unlike previous studies in neurological populations that used similar protocols to increase muscle strength in stroke survivors [11] and children with cerebral palsy [10]. We also showed that eccentric training is a feasible and safe way to manage spasticity-related resistance to passive motion in PwMS. Moreover, the eccentric training induced reductions in the resistance to passive motion of the spastic elbow flexors muscles, as measured objectively by isokinetic dynamometry, in self-reported perception of spasticity severity, in spasticity-free elbow ROM and in the spontaneous resting limb positioning. Finally, as expected, the intervention also improved significantly maximal strength of the spastic muscles.

The visual inspection of the single responses to eccentric training exhibited by each subject revealed a clear pattern towards reduction in the amount of resistance offered by the spastic muscle groups against the passive motor-driven limb mobilization, in all subjects. The 2SD-

band method, which is the preferred statistical benchmark in single-system design research, evidenced that five of the six participants (all exhibiting spasticity of the elbow flexors) improved significantly and exceeded the SRD, which is the smallest change that surpasses the measurement error and may thus be recognized as clinically meaningful at the level of the individual patient [26, 30].

Regarding the possible reasons why one patient (#5) did not respond to the intervention, this participant exhibited a BDI score of 22, which, despite lying below the cut-off for exclusion (≥28), fell into the 19-29 range, which represents a moderate to severe level of depression. These mood alterations may have led to reduced attention and motivation during the training sessions, possibly affecting patient's involvement in the study, which may be even more relevant if we consider that the execution of eccentric contractions is highly demanding and requires full patient-therapist interaction and collaboration.

Evidence is accumulating on the benefits of eccentric protocols, i.e. the lengthening of an active muscle while it is contracting under load [5], in musculoskeletal disorders, where it has been widely shown to induce consistent gains in strength as well as structural changes of soft tissues. In particular, eccentric contractions exert a lengthening action on sarcomeres and collagens, which has been demonstrated to have therapeutic implications in orthopedic conditions and also in neurological disorders characterized by spasticity-induced alterations such as contractures at the joint, tendon and muscle levels [10, 11]. Because of this lengthening action, the eccentric training affects the overall length range and the length-tension relationship of a muscle, inducing a sustained shift in the angle of peak torque and in the curve width, so that the range over which torque can be sustained above 50% of maximum (curve width) is significantly wider than that obtained with the conventionally employed concentric actions [10, 31]. Such effects have been explained by the training-induced increase in the number of sarcomeres in series to maximize muscle efficiency [32]. In addition, lengthening eccentric actions have the potential to counteract the contracture due to the hypertonia of the targeted muscles by reducing the

active insufficiency of the spastic muscle/s, *i.e.*, the too-shortened condition of the sarcomere, which prevent multijoint muscles from achieving the optimal production of strength [9]. In line with these findings, we found that the observed reduction in the resistance to passive motion was associated to significant improvements in strength of the spastic elbow flexors and resting limb position. Furthermore, subjective perception of spasticity was found reduced by one point (-21%, on NRS), which achieved the cut-off outlined for a clinically meaningful reduction in patient-reported spasticity (-20%) in PwMS [33]. However, no changes were detected in the clinician-rated impression of spasticity, as assessed by MAS testing. The minimal clinical important change in the MAS score has been established in stroke survivors as a decrease by approximately one point following focal pharmacological interventions, such as botulinum injections [34], and by 0.5 points following rehabilitation, which corresponds to a 10% decrease in the score [35, 36]. None of the participants in this study achieved nor surpassed this threshold. Even though failure to exceed the cut-off for clinically meaningful difference can be interpreted as a limited magnitude of effect of the intervention administered, responsiveness of MAS scores has been reported as controversial due to high variability across the studies, which results tend to range from poor to marked responsiveness to changes following rehabilitation [36]. For these reasons, establishing new end-points such as the RPT here proposed to appraise the effectiveness of interventions to manage spasticity is relevant and necessary.

Study limitations

A number of factors are to be acknowledged as they may limit the validity of the study findings. First, given the study design chosen (single-system case series), no cause-effect relationship between the intervention and any observed changes can be directly drawn or claimed, because case series only serve the purpose to document changes in a subject's performance over time

when exploring the effects of specific and/or innovative treatments for particular problems [15, 16].

Secondly, the specific AB design chosen further limits the causal inferences that can be drawn between the intervention administered and the observed effects [19], due to the lack of a follow-up period after the training was completed and to the limited number of assessments (in our study 3 at baseline and only 2 at the post). Upcoming properly planned randomized controlled trials comparing eccentric training to best practice in the exercise-based management of spasticity will contribute to look causally into effectiveness issues, with the recommendation to complement the laboratory-based RPT, which is only one component of the complex of signs contributing to spasticity, with a core set of functional outcomes.

Thirdly, the observed reductions in the resistance to passive robotic movement were detected after a period of slow eccentric contractions (30°/s of angular speed) at submaximal to maximal intensity (approximately 70-80% of the maximal baseline strength). Future dose-response studies will have to clarify these practical points, also considering that spasticity is velocity-dependent and that fast muscle contractions, including eccentric ones, may even result in exacerbated reflexes and spasms.

Finally, the present findings were obtained in the elbow flexor muscles and should not be generalized straightaway to other upper and or lower limb districts.

Conclusions

The eccentric training proved feasible and safe for the management of spasticity of elbow flexors muscles in MS. A training period of six weeks proved sufficient to reduce spastic hypertonia and weakness of the spastic muscles.

These objective effects translated in a subjective reduction of spasticity as perceived by the patients and in an increase of the spastic-free ROM, with a consequent better positioning of the

affected limb. The present preliminary findings encourage an extension of the study to confirm the observed results over a larger number of participants through a properly planned randomized controlled trial where eccentric training is confronted with other active exercise-based interventions.

Study 1

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Study 2

Isokinetic resistance training for ankle plantarflexor spasticity and muscle weakness in people with multiple sclerosis: A proof-of-concept case series

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Isokinetic resistance training for ankle plantarflexor spasticity and muscle weakness in people with multiple sclerosis: A proof-of-concept case series

Abstract

Objectives: To our knowledge, no data are available about the employment of isokinetic resistance training for managing ankle plantarflexors' spastic hypertonia in people with MS (PwMS). This proof-of-concept study aimed at exploring the feasibility and effects of concentric contractions on spasticity-related resistance to passive motion, strength and mobility in PwMS with ankle plantarflexors' spasticity.

Methods: Pre-test/post-test case series of five PwMS (mean age 53.6±8.8 years; median EDSS score 5; Modified Ashworth Scale, MAS, range 1-4), who underwent a 6-week isokinetic resistance training of the spastic plantarflexors. Before and after the intervention the following outcomes were assessed: average peak torque (APT) during passive robotic mobilization, isometric strength, surface electromyography (sEMG) from the spastic muscles, time to complete the 10-Meter Walk and the Timed-Up-and-Go (TUG) tests. The standardized effect size was used to test pre-post effects at the individual level. Group-level analyses were also performed.

Results: Following the training, the APT recorded from the plantarflexors during passive motion at 150°/s of velocity was found decreased by at least 1 SD in all subjects but one, with a significant reduction at group-level of 23.8% ($p=0.04$). Conversely, no changes in sEMG activity were detected. Group-level analyses revealed that the maximal strength of the trained plantarflexors increased significantly (+31.4%; $p=0.03$). Fast walking speed increased and time to complete the TUG decreased in four participants, although not significantly at the group-level.

CONCLUSIONS: Isokinetic resistance training proved safe and feasible in PwMS with ankle plantarflexors' spasticity. The observed reductions in resistance to passive motion from the spastic plantarflexors in the absence of sEMG changes might suggest a mechanical rather than neural effect of the training.

Impact Statement: Based on these preliminary findings, isokinetic resistance training does not exacerbate hypertonia in PwMS with ankle plantarflexors' spasticity and could be safely employed to manage muscle weakness in this population.

Keywords: Multiple sclerosis; Spasticity; Resistance to passive motion; Isokinetic resistance training; Ankle joint; Single case studies

Introduction

Spasticity is a complex of signs and symptoms that is commonly defined as an involuntary, velocity-dependent increase in muscle tonic stretch reflexes due to damage to the upper motor neurons of the corticospinal tract [1, 2].

Spasticity is a major complaint in approximately one-third of people with multiple sclerosis (PwMS) [3, 4]. Related symptoms such as weakness, spasms, and pain commonly accompany it and can affect one person's participation in family, work and social life [5]. Given its complex presentation, treatment of MS-related spasticity is challenging and requires a patient-focused, multidisciplinary treatment including spasticity reduction strategies, specialist rehabilitation therapy, oral medications, intramuscular and intrathecal infusions, and surgery.[1] Regarding non-pharmacological interventions, the most recent knowledge syntheses targeting MS spasticity have found low-level evidence for the effectiveness of physical activity given alone or in conjunction with physical therapy modalities [6-8].

The employment of a common rehabilitative method, *i.e.*, resistance training, to specifically target PwMS with spasticity has been sparsely reported. Miller and Light [9] linked the infrequent use of strengthening exercises for people with spasticity to the historical controversies brought by classical approaches, such as the Bobath concept, which were mainly developed for stroke rehabilitation [10]. Bobath's claims against strengthening approaches were that resistive exercise for spastic muscles could cause an increase in co-contraction and loss of coordination. However, such claims have been contradicted by several experimental and knowledge synthesis works dealing with people with spasticity [9, 11, 12]. Such debate was of marginal concern to the MS realm, where resistance training is frequently employed to counteract the cardinal symptom of muscle weakness. Nevertheless, to our knowledge only

very few works have dealt with the employment of resistive exercise for PwMS complaining of spasticity as their main symptom. In a recent proof-of-concept case series, which inspired the present investigation, the effect of eccentric resistance training was tested in PwMS with focal spasticity of the elbow flexors [13]. Eccentric training reduced spastic resistance to passive motion and improved muscle strength, spasticity-free range of motion, and limb positioning. Although preliminary in its nature, this case series showed that the administered strengthening protocol was not only associated to a reduction in muscle weakness without worsening spasticity, but also to some biomechanical modulation of this symptom, at least in terms of changes in the amount of resistance to passive motion opposed by the elbow joint soft tissues and muscles. Notably, no neuromuscular effect could be inferred as the authors of that case series did not record surface electromyography (sEMG) from the spastic muscles. sEMG allows differentiating the amount of resistance to passive motion due to the velocity-dependent neural reflex triggered by fast mobilization from the resistance attributable to soft tissue changes in the muscles, tendons and joints, also known as "intrinsic hypertonia", which is frequently observed in PwMS displaying spasticity [14, 15]. Moreover, sEMG is necessary for this population to distinguish spasticity from the inability to voluntary silence EMG activity, another common feature of PwMS [16].

Even in the early stages of MS, the most common and reported biomechanical alterations in the lower limb, which include contractures, muscle weakness and spasticity, are located at the ankle joint [17, 18]. The concurrence of these symptoms along with the commonly observed foot drop is considered a major determinant of walking dysfunction in this cohort while impairing independent mobility and increasing the risk of falls [19]. From the perspective of muscle function, it is the concentric strength of the ankle plantarflexors, the gastrocnemius and soleus, which is crucial for generating power, thus the forward acceleration of the body during the push-off phase of walking [20]. Hence, establishing tailored strategies to reduce ankle

dysfunction in PwMS is a distinct priority in the rehabilitation of these patients, justifying continued research on this topic.

Based on the above rationale, the present proof-of-concept case series primarily aimed at testing the safety and feasibility of an isokinetic resistance training program targeting the spastic ankle plantarflexors of a selected group of PwMS with moderate to severe focal hypertonia affecting this muscle group. Additionally, we planned to gather preliminary evidence on the potential effects of this protocol on the resistance to passive motion from the affected ankle and involuntary activity of the spastic muscles assessed by sEMG. Finally, before and after the 6-week intervention we evaluated the following secondary outcomes: 1) maximal strength of the spastic plantarflexion muscles and their antagonists to quantify the degree of muscle weakness; 2) patient-rated impact of spasticity and related pain to estimate the burden of spasticity; 3) walking speed and mobility to evaluate ambulatory capacity and independence.

Methods

Participants – A convenience sample of 5 PwMS with moderate-to-severe focal, unilateral spasticity of the ankle plantarflexion muscles was included, within the framework of a larger study on muscle weakness management in MS (ClinicalTrials.Gov registration number: NCT02010398). Briefly, in that investigation, the presence of spasticity had been listed among the criteria for exclusion, whereas the present case series was devised to specifically enrol PwMS with this symptom in concomitance with foot drop, defined as the reduced active dorsiflexion of the ankle caused by, among the other, weakness of the dorsiflexors [21].

Recruitment was conducted also using the following inclusion criteria: definite diagnosis of MS according to the 2017 revision of diagnostic criteria [22]; Expanded Disability Status Scale score (EDSS) ≤6.5 with Pyramidal Functional System score of 2-4; focal unilateral hypertonia of the ankle plantarflexion muscles ranging from 1–4, according to the Modified Ashworth

scale (MAS) as assessed by a Physical Medicine and Rehabilitation specialist (EA) with 15-year expertise, and later verified via surface electromyographic (sEMG) assessment; age >18 years old; compliance with the study instruction.

Discontinuation or exclusion criteria were: neurological conditions in addition to MS, including significant peripheral nervous system pathology that may affect motor function; medical conditions contra-indicating participation in resistance training exercises; the presence of bilateral spasticity; fixed contracture or relevant atrophy in the affected limb; previous or ongoing treatment with any botulinum toxin serotype, phenol, or cannabinoids, intrathecal baclofen and surgery in the previous 6 months; current casting for spasticity of the limb of interest; occurrence of relapses or variations in disease-modifying drugs or symptomatic treatment within 6 months prior to recruitment; major depression (assessed with Beck Depression Inventory-BDI scale, cutoff for exclusion: ≥28); participation in rehabilitative or training programs in the previous 3 months to avoid any carryover effects. No limitations related to disease course and degree of disability were applied for patient selection.

Participants deemed eligible underwent clinical and dynamometric assessments within a 1-week period and a post-training assessment after the intervention. Subjects were asked to refrain from any other exercise activity for the entire duration of the study.

The study was conducted according to the Declaration of Helsinki and approved by the institutional Bioethics Committee of the Local Health Authority (ASL n.1-Sassari, Italy; Prot. number 2420/CE 2016). Participants were given an informative note regarding all the modalities and timing of the study and were required to sign an informed consent form before enrollment. All data are stored and protected at the Department of Biomedical Sciences, University of Sassari, Sassari, Italy.

Design

A series of 5 case series studies with PwMS was employed. Case series methodology attempts to advocate an appropriate and individualized methodology to observe changes in a subject's performance over time and provide clinically relevant information about individual subject. This approach is of value in evaluating or exploring the effects of specific treatments for specific conditions [23, 24]. The study was executed with a pre-test/post-test design, taking measures from each participant before (initial phase, baseline assessments) and after (final phase, post-training assessments) a 6-week program of isokinetic resistance training based on concentric contractions targeting the spastic ankle plantarflexors. The study took place in an outpatient setting of the University Hospital.

The timeline of the study is detailed in Figure 1.

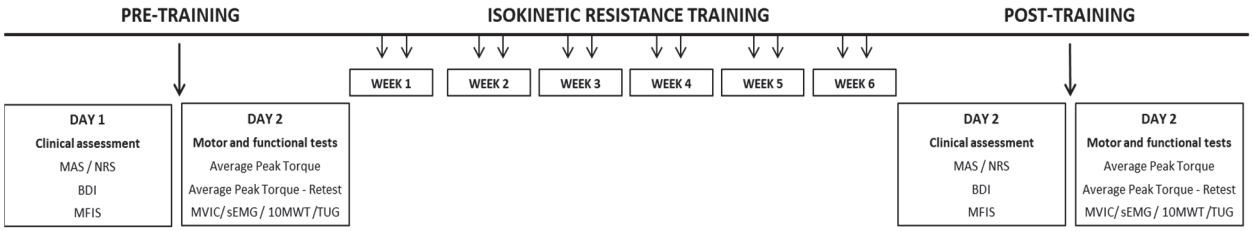


Figure 1. *Timeline of the study. PRE-TRAINING: baseline assessments of the resistance to passive mobilization (test-retest of the average peak torque, primary outcome) and measures of dynamometric and clinical-functional outcomes (secondary outcomes). 6-WEEK STRENGTH TRAINING: 6-week isokinetic training of the spastic plantarflexors. Each arrow indicates one training session (total sessions = 12). POST-TRAINING: post-training test-retest of the primary outcome and post-training test of secondary outcomes. BDI, Beck Depression Inventory; MAS, Modified Ashworth Scale; MFIS, Modified fatigue Impact Scale; MVIC, Maximal Voluntary Isometric Contraction; NRS, Numerical Rating Scale; sEMG, surface electromyography; TUG, Timed Up and Go; 10MWT, 10-Meter Walk Test. From Ventura et al., 2022*

Outcomes assessed

The average peak torque (APT) within the isokinetic window was set as the primary outcome of the study along with safety and feasibility. The APT allows quantifying the amount of resistance to passive motion opposed by the spastic ankle plantarflexors during passive mobilizations towards dorsiflexion imparted by the isokinetic device using low, intermediate,

and relatively high angular velocities [25, 26]. From a mechanical standpoint, the APT can also be expressed as the integral of the torque curve, which is also referred to as muscle work [27]. The involuntary activity of the soleus muscle and of the tibialis anterior was measured by sEMG.

Maximal voluntary isometric strength of both the plantarflexors and dorsiflexors, mobility and patient-rated burden of spasticity and pain were included as secondary outcomes of the study.

Safety and feasibility – Occurrence of adverse events, clinical relapses and worsening of the symptoms were monitored throughout the study period to evaluate the safety of the proposed intervention. Feasibility was assessed by determining participants' adherence rate (percentage of training sessions completed).

APT - All dynamometric tests were performed using an isokinetic device (KinCom Kinetic Communicator, Chattanooga, Tennesse, USA) by a physical therapist (GM) with a 5-year expertise in strength testing and training of PwMS. The test began with the affected limb, then the non-spastic side was assessed for inter-limb comparisons to exclude the presence of bilateral spasticity, which was set as an exclusion criterion. Prior to testing, the patient was asked to remain as relaxed as possible for the entire duration of the test. The subject was then positioned in the isokinetic dynamometer seat, according to the side, joint and muscle group under test, and stabilized using custom straps and harnesses. The patient was positioned in a sitting position with the trunk flexed at 85°, hip flexed at 135°, knee flexed at 45° and ankle in full plantarflexion. The isokinetic device passively moved the ankle joint from full plantarflexion toward dorsiflexion over the predefined comfortable ROM, which was individualized for each subject and kept constant from baseline to post-intervention assessments to ensure consistency and comparability. After a 15-second interval, passive return toward plantarflexion was completed, using the passive mode of the dynamometer. The muscles were tested over a set of seven predefined angular velocities (5-30-60-90-120-150-180°/s). During the movement toward dorsiflexion, the APT generated by the spastic ankle plantarflexors while lengthening

was measured over the specified range of motion and taken as an index of resistance to passive motion [28]. Passive mobilizations started with the low velocities and progressed to the faster ones according to the patient's comfort and tolerability. The lowest velocity that triggered the spastic reflex, as demonstrated by a sudden increase in sEMG activity which stood out clearly from the background activity, was used for the PRE to POST comparisons. Passive torques obtained throughout the full ROM at the angular speed of 5°/s were used to correct the effects of gravity and limb weight and to detect the amount of stiffness from the soft tissues, which detracts from the actual torque produced by the spastic muscles [29, 30]. Offline data analyses were then conducted to establish in each subject the APT, which was obtained, for each angular velocity tested, as the mean resisting torque of the affected plantarflexors throughout the isokinetic sector of the ROM.

To determine APT reliability, a retest procedure was carried out within 30 minutes for those angular velocities that were found to trigger the increase in resistance to passive motion.

Electromyographic activity – To determine the presence of involuntary neuromuscular activity in in the ankle plantarflexors during passive mobilizations, sEMG activity was recorded bilaterally (Biometrics DataLink SX230, Biometrics Ltd, UK) from the soleus and tibialis anterior muscles during the testing protocol to quantify resistance to passive motion (sampling rate 1000 Hz, bandwidth 3–3000 Hz) using active Ag/AgCl bipolar pre-amplified disc electrodes (Biometrics R300) in a belly-tendon montage with the reference electrode placed over the contralateral patella. The presence of spasticity was confirmed only when a non-artifactual EMG event was clearly standing out of the isoelectric line. Raw data were retained for the analysis. EMG raw traces were full-wave rectified and averaged using proprietary software (Biometrics DataLog 10.05 Analysis Package). sEMG recordings were completed by a physical therapist/neurophysiologist (AM) with 10-year expertise in neuromuscular assessment of individuals with neurological conditions.

Maximal strength - Maximal voluntary isometric strength was measured with the isokinetic device from the spastic ankle plantarflexors and from their antagonist muscles, the ankle dorsiflexors. Plantarflexors' strength was measured with the ankle positioned at 90° of flexion, dorsiflexors' strength was measured at full plantarflexion, according to the manufacturer's requirements. Three trials, each lasting approximately 5 s, were collected, with 1-min rests (highest value retained). The main reason for limiting strength assessment to isometric testing is justified by the common inability of people with a foot drop to move their ankle over a functional range of motion [21].

Mobility – Walking performance and dynamic balance were assessed by a physical therapist (LV) with 5-year expertise in functional testing of PwMS, using, respectively, the Ten-Meter Timed Walk (10-MTW) and the Timed Up and Go (TUG) test, which have proved highly reliable walking, mobility and dynamic balance/risk of fall tests in individuals with MS [31-33].

Patient-rated experience with spasticity – 11-point numerical rating scales (NRS) were administered at baseline to each participant to estimate the subjective impression about spasticity impact on the activities of daily living. "*Please indicate the extent of spasticity interference with the activities of daily living over the past 24 hours on a scale of 0 (no interference) to 10 (maximal interference).*"

Likewise, to estimate the degree of pain, if any, associated to spasticity, the 11-point numerical pain rating scale (NPRS) was employed by asking: "*Please indicate the intensity of current, best, and worst pain levels over the past 24 hours on a scale of 0 (no pain) to 10 (worst pain imaginable).*"

Intervention

The intervention phase was completed on the same isokinetic device employed for the dynamometric assessments. PwMS underwent a 6-week isokinetic resistance training with a

reinforcement of the concentric phase targeting the affected plantarflexors. Starting from the maximum dorsiflexion that could be reached passively, participants were required to plantarflex their affected ankle by pushing against the footplate of the isokinetic dynamometer, which was preset to operate at a low angular velocity of 30°/s (Figure 2).



Figure 2 *Experimental set-up used for the testing and training procedures. The inner box details the start and end points for the isokinetic resistance training targeting the spastic ankle plantarflexors with an isolated reinforcement of the concentric phase. From Ventura et al., 2022*

Return to the starting position toward dorsiflexion was carried out passively by the isokinetic device. Prior to training session 1 and subsequently every 2-3 sessions, the peak torque during concentric plantarflexion at 30°/s was recorded from the ankle plantarflexors. Based on this, the workload was adjusted to match 70% of the recorded peak torque. Workload progressed weekly according to the new values of peak torque achieved. Participants were provided with a personalized training according to their level of strength. The training schedule was specifically devised to achieve gains in maximal strength, according to the recommendations by Bird et al. [34]. The program consisted of two sessions per week, each session comprising 6

sets of 6 repetitions with a 3-minute rest between sets. The training schedule was planned and developed by one of the authors (AM), a clinical exercise physiologist and physiotherapist with a 10-year background in testing and training procedures for populations with neurological conditions. Each session was supervised, one on one, by a physiotherapist (GM) with 5-year expertise with PwMS.

Post-intervention assessments

Post-intervention assessments of the primary and secondary outcomes were performed by the same operators within one week from the end of the training at a consistent time of the day (Figure 1).

Statistical analysis

Data analysis was performed using the SPSS software for Windows, version 18.0 (SPSS Inc, Chicago, IL - USA). The assessment of measurements' consistency was performed to determine the reliability of the primary outcome, the APT. Test-retest reliability was estimated by calculating the intraclass correlation coefficient (ICC) over two-time points using a one-way random model for average measures. The ICC coefficients were calculated taking a value <0.4 as an index of poor reliability, 0.4 to 0.75 fair to good reliability, and >0.75 excellent reliability [35]. ICC determination also allowed to establish the responsiveness of the changes from baseline. Accordingly, the standard error of measurement (SEM) was also calculated using the formula: $SEM=SD_{diff}\sqrt{(1-ICC)}$, where SD_{diff} represents the standard deviation of the mean differences between the test and retest [36,37]. Based on the SEM, the minimal detectable change at the individual level (MDC_i) was calculated using the formula: $MDC=2.77\ SEM\sqrt{2}$ [38]. To quantify the amount of change in APT from baseline at the individual level, which is challenging in case series research, any differences detected from baseline were appraised against the MDC and SEM thresholds calculated to take baseline variability into account [39, 40]. Based on these works, a change from baseline exceeding the MDC would be interpreted

as a difference significantly larger than the measurement error, while a change of at least one SEM would closely approach the minimally important change (MIC).

Additionally, the magnitude in standard deviations (SDs) of the differences in APT and in the other outcomes of treatment were quantified as standardized effect sizes, *i.e.*, the contrast between PRE and POST in terms of SDs. Effect size interpretation was made considering a change ≤0.4 SDs as small, 0.51–0.79 as moderate, ≥0.8 as large [41].

Finally, even though the design of this study was set as case series research, changes from baseline in the outcomes tested were also analyzed at the group-level by running paired *t*-tests for continuous data expressed as mean ± SD, or the Wilcoxon signed-rank test for categorical data, with significance set at the conventional level of $p<0.05$. Blinding involved the outcome assessors and the statistician.

Results

The case series was completed over five participants (3 women, 2 men; mean age 53.6±8.8 years) having a definite diagnosis of MS. Demographic, anthropometric and clinical characteristics of the cohort of PwMS studied are reported in Table 1. Participants displayed moderate disability (median EDSS: 5; range 3.5-6.5; median pyramidal functional system score: 3), normal cognitive functions and depression ranging from minimal to mild. They were on stable DMT for the entire duration of the study. The severity of spasticity (as assessed by MAS score) proved mild to moderate in four participants while moderate to severe in one (subject #5). All participants also exhibited a foot drop and were unable to generate functional dorsiflexion at study entry.

Table 1. Demographic, anthropometric, and clinical features of the cohort of people with multiple sclerosis at the study entry.

Variables	Subjects				
	#1	**#2**	**#3**	**#4**	**#5**
Age *(years)*	42	61	47	62	56
Sex	F	M	M	F	F
Weight *(kg)*	53.5	70	64	76	61
Height *(cm)*	154	170	169	160	157
BMI *(score)*	23	24	22	30	24.8
Disease duration (*years)*	8	3	8	5	14
MS course	RR	PP	RR	PP	RR
EDSS *(score)*	3.5	4	5	5.5	6.5
Functional system - pyramidal	3	3	3	4	4
Ankle plantarflexors MAS *(flexed knee)*	1+	1+	2	0	3
Ankle plantarflexors MAS *(extended knee)*	2	1+	1+	1	4
Presence of drop foot	Yes	Yes	Yes	Yes	Yes
Patient-rated impact of spasticity (NRS) *(0 – 10)*	7	3	5	6	7
Patient-rated pain due to spasticity (NRS) *(0 – 10)*	0	0	0	1	0
Walking Aids	-	-	-	1 walking stick	wheelchair
DMT	Ocrelizumab	Rituximab	Fingolimod	Ocrelizumab	Teriflunomide
BDI	9	14	10	15	5
MFIS	30	22	32	59	44

BDI Beck Depression Inventory; BMI, body mass index; cm, centimeters; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Kg, kilograms; MAS, Modified Ashworth Scale; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; NRS, Numerical Rating Scale; PP, primary progressive; RR, relapsing-remitting.

Safety and feasibility - Overall, the intervention was safe and well tolerated, with no adverse events, relapses or clinical exacerbations reported during the study. The intervention also proved feasible with all the participants completing 100% of the planned sessions.

Resistance to motor-driven passive motion – Figure 3 depicts individual data at baseline for the APT in response to single passive mobilizations at each of the seven angular velocities (5-30-60-90-120-150-180°/s).

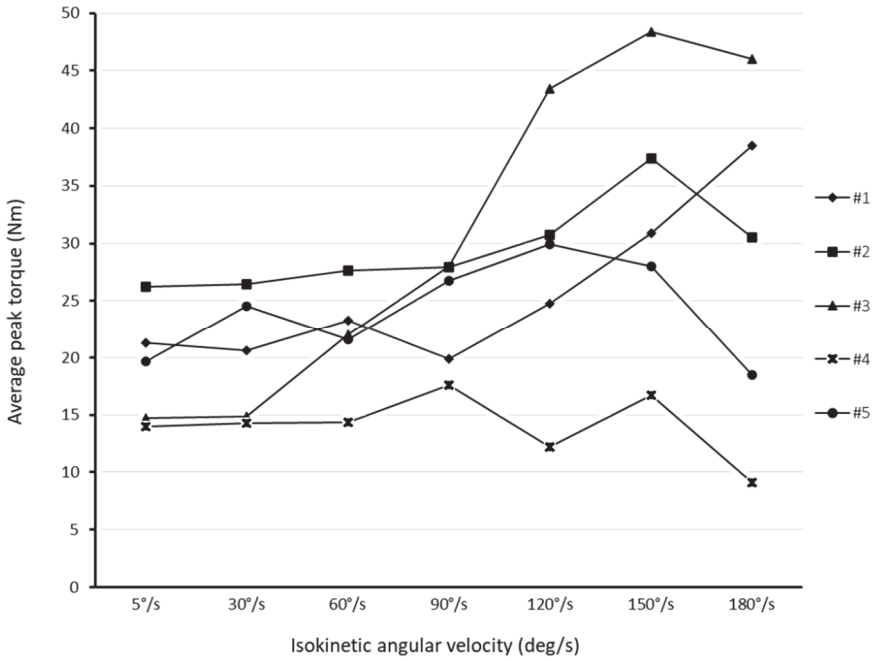


Figure 3 *Isokinetic torque-velocity curves obtained at baseline from the spastic ankle plantarflexors during passive motor-driven dorsiflexions in the cohort of five people with multiple sclerosis. deg/s, degrees per second; Nm, Newton meter. From Ventura et al., 2022*

A pattern of velocity-dependent increase in APT was detected in two participants (#1 and 3). The angular speed of 150°/s was identified as the one that triggered the reaction in all the participants and was therefore set as the target speed for which data are detailed below. The test-retest reliability of the APT (determined for the target velocity of 150°/s) proved excellent, as indicated by the ICC coefficient of 0.947 (95% CI 0.472-0.996; p=0.008). Based on the ICC, both the SEM (±1.43 Nm) and the MDC at the individual level (±5.60 Nm) could be calculated.

Complete data for APT and sEMG measurements are reported at both the individual- and group-level in Table 2.

Figure 4 displays the baseline and post-intervention individual torque/angle curves during passive mobilization at the angular velocities that prompted the spastic reflex. As shown in the individual graphs, the post-training curves of four subjects (#1, 2, 3 and 5) were located below the baseline values, indicating a reduction in the amount of resistance to passive motion.

Following the isokinetic resistance training, the amount of resistance opposed by the affected plantarflexors against the passive motion at 150°/s, *i.e.*, the APT, was reduced in all participants but one, who, instead, exhibited a 32.6% increase in resistance to passive motion (#4, Table 2). The mean pre-to-post reduction in APT at 150°/s (-10.4 Nm) was also found to surpass both the SEM (change of at least 1.4 Nm) and MDC (change of at least 5.6 Nm) thresholds for change. Overall, four out of five participants were found to surpass the MDC threshold.

When appraising the results based on the standardized effect size, *i.e.*, the number of SDs of the difference from baseline in the target velocity of 150°/s, four participants (#1, 2, 3 and 5) showed a reduction of at least 1 SD, with subject #1 exhibiting a 2.35 SDs reduction. Trivial or no changes were detected at 180°/s. Regarding participant #4, a 1.07 SDs increase in resistance to passive motion was observed.

Group-level analyses over the whole cohort confirmed a larger reduction in resistance to passive motion at 150°/s (1.23 SDs) compared to 180°/s (0.81 SDs). Pre-to-post one-tailed paired t-tests revealed a significant reduction in resistance to passive motion at 150°/s ($p=0.04$), but not at 180°/s ($p=0.14$).

Regarding the sEMG activity of the spastic muscles recorded during the passive mobilizations imparted by the isokinetic system (Table 2), no pre-to-post differences in involuntary activity were detected in any of the participants, neither by individual-level nor group-level analyses (at 150°/s: $p=0.33$; at 180°/s: $p=0.23$).

Table 2 Resistance to passive mobilization and surface electromyographic (sEMG) recorded from the spastic ankle plantarflexors of the cohort of people with multiple sclerosis before and after 6 weeks of unilateral isokinetic training.

			BASELINE				POST TRAINING				PRE – POST STATISTICS			
ID	**ROM (deg)**	**Speed (deg/s)**	**APT (Nm)**	**sEMG isoelectric (mV)**	**sEMG ARV (mV)**	**sEMG duration (ms)**	**APT (Nm)**	**sEMG isoelectric (mV)**	**sEMG ARV (mV)**	**sEMG duration (ms)**	**RPM SD of the change (APT in Nm)**	**% Variation - APT**	**sEMG SD of the change (ARV in mV)**	**% Variation - sEMG**
#1	**50**	**150°/s**	30.87±4.72	0.068	0.327±0.270	39	19.13±5.27	0.097	0.382±0.346	43	2.35	-38.03	0.18	16.82
		180°/s	38.50±5.59	0.068	0.615±0.362	33	19.81±4.30	0.092	0.703±0.606	39	3.75	-48.56	0.18	9.02
#2	**40**	**150°/s**	37.39±15.95	0.053	0.227±0.211	37	23.58±6.30	0.03	n.e.	-	1.14	-36.92	-	-
		180°/s	30.50±12.95	0.053	0.344±0.305	57	28.55±11.07	0.03	n.e.	-	0.16	-6.41	-	-
#3	**40**	**150°/s**	48.39±20.93	0.057	0.522±0.385	46	24.21±23.52	0.10	0.735±0.620	48	1.09	-49.97	0.41	40.81
		180°/s	46.00±5.49	0.049	0.531±0.241	72	42.78±20.09	0.135	0.667±0.579	56	0.22	-7.01	0.31	25.61
#4	**40**	**90°/s**	17.56±11.54	0.087	0.226±0.223	55	19.02±6.12	0.057	n.e.	-	0.16	8.29	-	-
		120°/s	12.23±5.26	0.084	0.262±0.229	39	15.44±3.95	0.06	n.e.	-	0.69	26.19	-	-
		150°/s	16.74±5.45	0.084	0.239±0.205	70	22.18±4.68	0.06	n.e.	-	1.07	32.55	-	-
#5	**30**	**90°/s**	26.78±15.46	0.086	0.419±0.282	44	25.36 ±14.54	0.099	0.248±0.218	49	0.09	-5.30	0.68	-40.86
		120°/s	29.92±14.60	0.095	0.353±0.249	72	21.56±10.43	0.126	0.403±0.317	56	0.66	-27.92	0.18	14.02
		150°/s	28.00±8.70	0.092	0.520±0.345	57	20.51±7.69	0.095	0.399±0.418	48	1.01	-26.73	0.32	23.34
1-5 mean (95% CI)		**150°/s**	32.28 ±11.70 (17.75 to 46.80)	0.071±0.017 (0.05 to 0.09)	0.367±0.146 (0.19 to 0.55)	49.80±13.73 (32.74 to 66.86)	21.92±2.11* (19.30 to 24.54)	0.076±0.031 (0.04 to 0.11)	0.505±0.2 (0.01 to 1.00)	46.33±2.9 (39.16 to 53.50)	1.23	-32.09	0.79	37.60
		180°/s	38.33±7.75 (19.08 to 57.59)	0.057±0.01 (0.03 to 0.08)	0.497±0.147 (0.26 to 0.62)	54.80±15.34 (35.76 to 73.84)	30.38±11.59 (1.58 to 59.18)	0.086±0.05 (-0.05 to 0.22)	0.531±0.18 (0.24 to 0.82)	45.00±10.80 (27.81 to 62.19)	0.81	-20.75	0.62	6.84

APT, Average Peak Torque; ARV, Average Rectified Value; CI, confidence interval; deg, degrees; ms, milliseconds; mV, millivolts; n.e., reflex not elicited; Nm, Newton meter; ROM, range of motions; s, seconds; SD, standard deviation. APT data were analyzed both at group- and individual-level (see text for Methods and Results). *Significant for $p<0.05$ (as assessed by one-tailed paired t-tests).

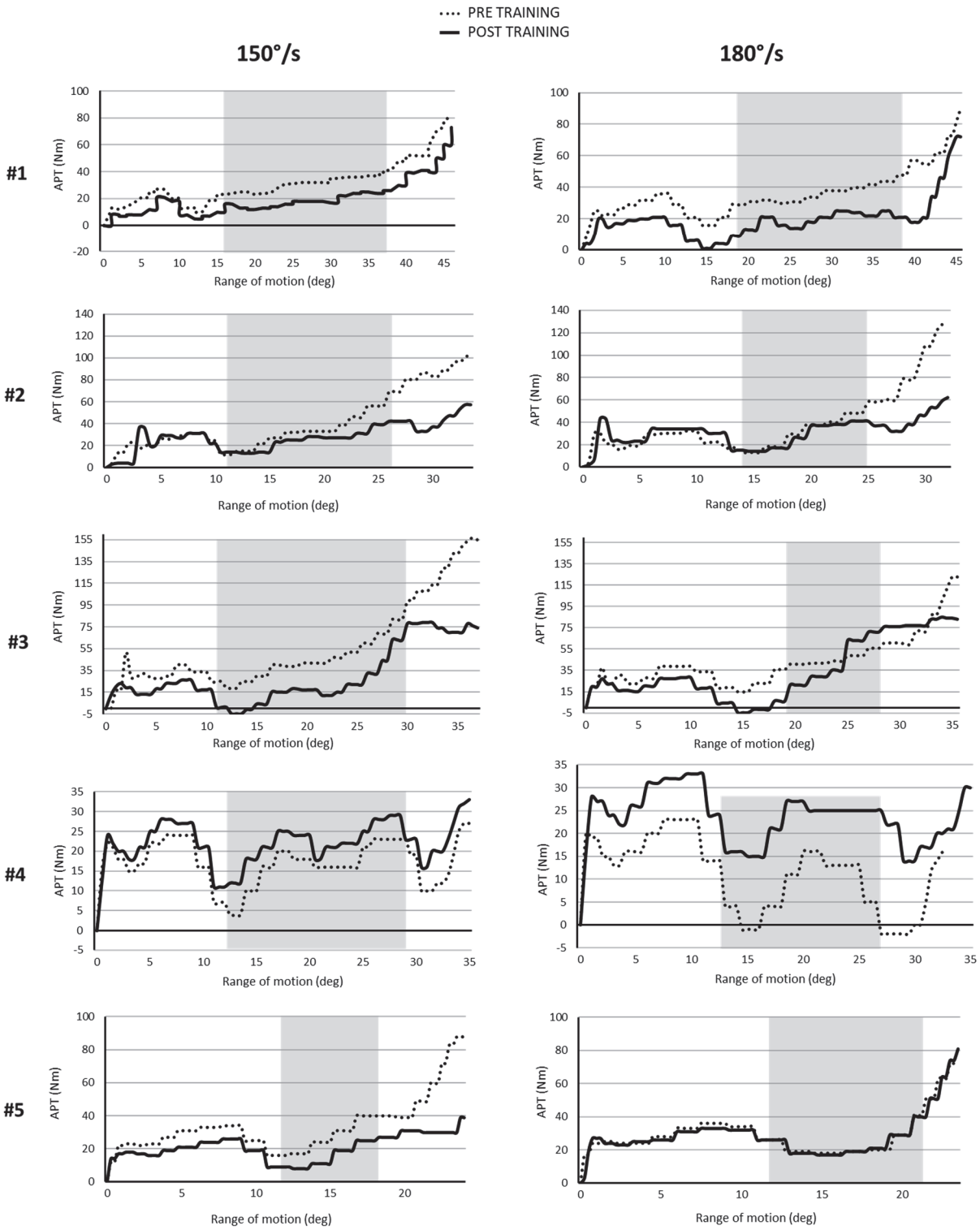


Figure 4 *Isokinetic torque-angle curves obtained at baseline (dotted line) and after the 6-week isokinetic training period (continuous line) from the spastic ankle plantarflexors during passive motor-driven dorsiflexions in the cohort of five people with multiple sclerosis. The left panels show the data recorded at the angular velocity of 150°/s; the right panels show the data recorded at the angular velocity of 180°/s. Deg, degrees; Nm, Newton meter; APT, average peak torque; s, second. From Ventura et al., 2022*

Maximal strength – Table 3 summarizes the results of the dynamometric testing for the spastic ankle plantarflexors and their antagonist muscles, the ankle dorsiflexors. Following the 6-week intervention, maximal voluntary isometric strength of the plantarflexors increased in all the participants but one (#4). The increases in strength ranged from 0.7 to 4.8 SDs. Likewise, ankle dorsiflexors' strength increased in all the participants but one (#3), with the observed gains in strength ranging from 0.7 to 10.3 SDs.

Group-level analyses employing one-tailed independent t-tests revealed a significant increase in the affected plantarflexors' strength (+31.4%; p=0.03) and a non-significant trend towards increase in the unaffected dorsiflexors (+20.9%; p=0.07).

Walking speed and mobility – The results of the pre-post comparisons in the 10-MTW and TUG tests are presented in Table 3. Following the intervention, comfortable walking speed increased in three participants (+0.14 m/s for #1 and 3; +0.10 for #5), with the observed change ranging from 2.7 to 7.5 SDs of increase. Likewise, increases in fastest walking speed were observed in four participants (+0.09 m/s for #1 and 3; +0.17 m/s for #4; +0.13 for #5), with changes ranging from 0.6 to 32.9 SDs.

At the individual level, reductions in the time needed to complete the TUG test were observed in four participants (#2-5), with changes ranging from 0.7 to 4.3 SDs.

While the observed changes in walking speed surpassed the MIC, paired t-tests revealed no significant differences at the group level from pre to post in any of the mobility tests (10-MTW comfortable: p=0.16; 10-MTW fastest: p=0.16; TUG: p=0.09).

Patient-rated experience with spasticity – The NRS score resembling the subjective impression about spasticity impact decreased in four participants and was confirmed by the Wilcoxon test (Z=-2.032; p=0.04). No change was detected in the NRS scores rating degree of pain associated with spasticity (Z=-1.000; p=0.32).

Table 3. Muscle strength and mobility data of people with multiple sclerosis before and after 6 weeks unilateral isokinetic training of the spastic ankle plantarflexors.

Outcomes assessed		Individual-level analysis					Group-level analysis
		#1	**#2**	**#3**	**#4**	**#5**	**1-5**
SOL MVIC (Nm)	*PRE*	162.20±23.32	425±33.15	808±13.59	394.50±32.36	376.33±30.50	433.21±233.83 (142.86 to 723.55)
	POST	283.75±27.61	602.50±128.13	1116.67±98.42	392.00±21.86	452.00±76.32	569.38±326.90* (163.49 to 975.28)
	SD of the change (%)	4.756 (*74.94*)	1.896 (*41.76*)	4.393 (*38.20*)	0.091 (*-0.63*)	0.722 (*20.11*)	0.48 (*31.43*)
TA MVIC (Nm)	*PRE*	126.67±12.86	289.25±26.03	256.00±16.07	31.40±14.94	156.50±20.76	171.96±103.52 (43.42 to 300.50)
	POST	134±5.20	315.75±7.50	260.20±12.64	147.25±5.56	182.67±4.16	207.97±77.69 (111.51 to 304.44)
	SD of the change (%)	0.747 (*5.79*)	1.383 (*9.16*)	0.29 (*1.64*)	10.277 (*368.95*)	1.749 (*16.72*)	0.39 (*20.94*)
10-MWT-*c* (s)	*PRE*	8.44±0.04	7.50±0.25	9.46±0.47	10.99±0.21	46.13±2.81	16.50±16.61 (-4.12 to 37.13)
	POST	7.57±0.29	7.54±0.16	8.33±0.37	11.15±0.22	31.08±0.51	13.13±10.14 (0.54 to 25.73)
	SD of the change (%)	4.20 (*-10.31*)	0.19 (*0.50*)	2.67 (*-11.97*)	0.744 (*1.44*)	7.453 (*-32.62*)	0.24 (*-20.42*)
10-MWT-*f* (s)	*PRE*	6.63±0.20	5.79±0.28	6.31±0.25	9.85±1.01	42.69±0	14.25±15.98 (-5.58 to 34.09)
	POST	6.27±0.20	5.64±0.19	5.96±0.10	8.42±0.37	27.35±0.66	10.73±9.36 (-0.89 to 22.34)
	SD of the change (%)	1.800 (*-5.352*)	0.626 (*-2.590*)	1.838 (*-5.524*)	2.768 (*-14.590*)	32.87 (*-35.933*)	0.27 (*-24.74*)
TUG (s)	*PRE*	8.70±0.35	7.61±0.20	8.01±0.55	12.61±0.52	43.74±2.12	16.13±15.56 (-3.19 to 35.45)
	POST	8.60±0.44	6.71±0.40	7.67±0.34	10.35±0.64	35.86±1.45	13.84±12.38 (-1.54 to 29.21)
	SD of the change (%)	0.252 (-1.13)	2.846 (-11.91)	0.743 (-4.31)	3.876 (-17.94)	4.339 (-18.00)	0.16 (-14.23)

MVIC, maximal voluntary isometric contraction; Nm, newton meter; PRE, outcome measures assessed at baseline; POST, outcome measures assessed after 6 weeks of isokinetic training; s, seconds; SD, standard deviations; SOL, soleus; TA, tibialis anterior; TUG, Timed Up and Go test; 10MWT-c, Ten Meter Walk Test at comfortable speed; 10-MWT-f, Ten Meter Walk Test at fastest speed; %, percent variation of the change. Data were analyzed both at group- and individual-level (see text for Methods and Results). *Significant for $p<0.05$ (as assessed by one-tailed paired t-tests).

Discussion

The present proof-of-concept, case series of 5 PwMS displaying ankle plantarflexors' weakness and spasticity tested the safety, feasibility and potential effects of isokinetic resistance training on muscle weakness, as conventionally done in frail and weakened populations, and on the amount of spasticity-related resistance to passive motion. Patient-reported impression of spasticity impact and pain, gait speed and mobility were also set as secondary outcomes of treatment.

The main finding of the study was that the isokinetic resistance training administered proved safe and feasible in this population, with none of the participants reporting any adverse events, worsening of the symptoms and exacerbation of hypertonia in the affected muscles. Additionally, following the intervention the resistance to passive motion of the spastic plantarflexors was found reduced in 4 of the 5 participants who completed the training, who also reported a significant reduction in the impact of spasticity on daily living activities. However, at the post we found significantly worsened resistance to passive motion (*i.e.*, >1 SD of increase) in subject #4, possibly due to the clinical features of the participant, who had a progressive form of MS (primary progressive) and displayed one of the highest EDSS and pyramidal scores. Such clinical scenario might have contributed to the negative results detected for this participant.

Since the involuntary sEMG activity elicited from the spastic muscles during the passive motor-driven mobilizations imparted by the isokinetic dynamometer was unchanged despite evidence of resistance to passive motion reduction, it may be claimed that no neuromuscular modulation occurred in response to the intervention. We offer that the observed reduction in resistance to passive motion might be attributable to changes in the viscoelastic and mechanical properties of the joint soft tissues and of the chronic hypertonic muscles [42] following the training. However, such assumption was not tested in this study, thus warranting experimental studies to

employ technologies based on electrical bio-impedance analysis that allow the myotonometric evaluation of the properties of superficial muscles, such as tone, elasticity, and stiffness.

While a neuromodulation effect might be excluded, such evidence adds to a growing body of knowledge showing that resistive exercise does not exacerbate hypertonia in stroke survivors with spastic hemiplegia [9, 11, 12] and, more recently, in PwMS [13].

When interpreting the potential implications of the reductions in resistance to passive motion, firstly one has to relate the magnitude of the observed findings to some thresholds for change, which, however, are lacking for biomechanically assessed resistance to passive motion in patients with spasticity. In the absence of these, individual-level studies are compelled to refer to thresholds outlined in adjacent fields. The use of *a priori* fixed thresholds, such as the one-half SD benchmark [43] or the two-SDs method [44], has been questioned. Indeed, identifying a single cut-off for a clinically important change is potentially misleading due to the various factors influencing the meaning of a change score in an individual [45]. Moreover, a difference of one-half SD may be too small to attain practical and functional relevance, whereas a 2-SDs difference may be too large to achieve. Wyrwich et al. [40] demonstrated that a value of one SEM in one outcome closely approximates the minimally important change (MIC) for several health-related outcomes. This one SEM-based criterion entails that patients improving more than one-SEM achieve the MIC [40]. Another approach is centred on the distribution-based minimal detectable change (MDC), which reflects the lower bounds of measurement error and the threshold below which change cannot be distinguished from measurement noise [39]. Accordingly, in the present study the reductions in resistance to passive motion (-10.4 Nm) exceeded both the one-SEM (1.4 Nm) and MDC (5.6 Nm) thresholds calculated taking baseline variability into account, suggesting that a change not due to chance or measurement noise took place.

Reduced resistance to passive motion was accompanied by significant strength gains in the ankle plantarflexors, with four of the five participants improving more than 2 SDs from

baseline. Importantly, while at study entry all participants could not plantarflex their affected ankle over the whole range of motion at the preset isokinetic speed, they could do so after the intervention, with four out of five increasing maximal strength of the spastic muscles. When comparing the abovementioned gains to established thresholds for change, such as the MIC, three out of five participants were found to surpass this cut-off, which has been shown to correspond to a change in strength ranging from 20% for grip strength [46] to 26.9% for quadriceps strength [47]. Increased plantarflexors' strength was associated with higher gait speed in all the participants. In this regard, gait performance may have benefitted from increased plantarflexors' strength during the concentric phase, which is the main determinant of the push phase at terminal stance [20]. In this context, it cannot be excluded that the improved viscoelastic and mechanical properties of the soft tissues, suggested by the reduced resistance to passive motion in the absence of neuromuscular changes, may have contributed to higher gait speed observed following the intervention. In particular, during the fastest Ten-Meter Timed Walk, the observed increases in gait speed ranged from +0.09 to 0.17 m/s, matching the MIC that is expected after retraining programs for older adults [48] or physical rehabilitation for neurological conditions [49].

Based on these cut-off values for clinically important improvement (≥0.06, small; ≥0.14, moderate; ≥0.18, large), the improvement in walking speed observed here following the training should be interpreted as clinically meaningful albeit of a moderate extent. Comparing our findings to neurological populations other than MS is justified by the lack of valid estimates of the MIC for gait speed in this population. To date, the only MIC threshold outlined for the Ten-Meter Timed Walk in PwMS is a change of at least 20% in walking time [31,50]. If such criterion is applied, the increase by 20.4% in comfortable walking speed would equal the MIC, whereas the 24.7% increase in fastest walking speed would surpass it.

Study limitations

Several factors other than the small sample size may limit the validity of the study results. First, the pre-test/post-test design without a follow-up after training completion further limits any causal inferences that can be drawn between the intervention and the observed effects [44], especially considering the case series design chosen for the present proof-of-concept investigation. Future randomized controlled trials comparing isokinetic resistance training to best practice in the management of spastic hypertonia for PwMS will contribute to look causally into effectiveness issues. The recommendation would be to complement the isokinetically-determined resistance to passive motion, which is only one of the factors contributing to spasticity, with a comprehensive set of subjective and functional outcomes.

Secondly, only in few participants increasing the angular velocity of the mobilization resulted in increased resistance to passive motion and involuntary sEMG activity of the spastic muscles, suggesting that spasticity might have been over-diagnosed at baseline and that stiff rather than spastic patients underwent the training regimen here examined. Future studies will have to establish eligibility not only via clinical testing (MAS score), but also through sEMG and, when possible, isokinetic dynamometry. By doing so, only participants with velocity-dependent and sEMG-demonstrated increase in resistance to passive motion would be enrolled.

Thirdly, the present findings were obtained in the ankle plantarflexors and should not be generalized straightaway to other lower or upper limb districts. Moreover, due to the participants' inability at baseline to fully plantarflex their affected ankle under isokinetic conditions, the performance of this muscle group was tested only isometrically. Whenever possible, future studies will have to assess strength dynamically in order to evaluate muscle power, which is a major determinant of propulsion during the push phase of the gait.

Conclusions

Isokinetic resistance training proved feasible and safe in the management of our group of 5 PwMS displaying ankle contractures and plantarflexors' weakness. PwMS who participated in a 6-week isokinetic program demonstrated reduced resistance to passive motion and weakness of the affected muscles in the absence of EMG changes. Additionally, the observed changes were found to associate with increased walking speed. However, it should be noted that 1 out of 5 participants showed increased resistance to passive motion, which needs to be considered when selecting candidates with higher degrees of disability and progressive courses of the disease for isokinetic training of the spastic, weakened muscles.

The present preliminary findings encourage an extension of the study into a pragmatic effectiveness trial to confirm the observed results over an adequate number of participants through a properly planned randomized controlled study where isokinetic resistance training is compared to best practice and other exercise-based interventions.

Study 2

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Final considerations on 1st-year experimental series of pilot studies

The two studies [1, 2] provided conceptual ground for developing outcome measures that can be responsive to rehabilitation. Specifically, the spasticity-related resistance to passive motion displayed by the preliminary cohorts of selected PwMS here enrolled was quantified through determination of the resistive torque generated by the spastic muscles once the abnormal stretch reflex was elicited with fast passive mobilizations imparted by the isokinetic device. Such measurement approach – shared by the two works – allowed characterizing spastic hypertonia in PwMS, unveiling peculiar patterns that are generally not observed in other neurological conditions with associated spasticity, such as stroke and cerebral palsy. In more detail, while some of the participants were diagnosed with MS spasticity according to clinical tests including MAS, not all of them exhibited a neural component, with resistance to passive motion more likely attributable to alterations in the soft tissue at the muscle, tendon, and joint levels. When neural components were observed, these were often highly variable and unstable, requiring the execution of multiple retests to obtain an average measurement. These findings need to be taken into account for the sake of accuracy when attempting to evaluate how PwMS react to fast mobilization. Based on these observations, for PwMS with evidence of pyramidal dysfunction the assessments should incorporate sEMG to determine whether a neural component is present or, instead, resistance to passive motion is mainly contributed by soft tissue alteration and contractures. This is a key point as resistance was found increased when increasing velocity of passive motion even though no sEMG activity was detected, according to the results of Study 2 [2]. Another aspect deserving attention is the high fluctuation in the resistive torque, which demands a robust validation of this outcome measure in this population through test-retest procedures on different time points in order to define the amount of variability around the average measurement. This would prove particularly important not only to better characterize resistance to passive motion of presumable spastic nature, but also to allow better tracking of

the changes that may follow rehabilitation. In this regard, the pilot studies allowed to detect the minimal detectable change in resistance to passive motion (approximately 0.5 kg) that should be achieved in order to exceed the baseline variability.

From an interventional point of view, the administration of eccentric (i.e., lengthening) resistance training in Study 1 [1] and concentric (i.e., shortening) resistance training in Study 2 [2] allowed to achieve specific effects. PwMS benefitted from eccentric training of the elbow flexors in terms of increased free range of motion and, importantly, subjective reduction of spasticity burden and interference with gait and mobility. A plausible mechanism that may have mediated such changes is a shift in the length/tension relationship, with sarcomeres remodeled in terms of their average length and, thus, potentially capable to generate higher levels of tension at different angles and over an increased range of active motion. In this context, eccentric lengthening contraction may prove useful to PwMS displaying resistance to passive motion that is velocity-dependent, yet not showing a neural component.

The main lesson learnt from Study 2 [2] was that concentric resistance training allowed performance improvements in the spastic muscles (ankle plantarflexors) when a neural component was detected by sEMG and also when resistance to passive motion was ascribable to non-neural changes in the involved soft tissues. In both cases, the training program did not exacerbate hypertonia. However, it should be pointed out that the two components are not mutually exclusive and tend to present concurrently, being one generally prevalent over the other. As a proof of it, resistance to passive motion was found significantly reduced in those participants with neural components and also in those with non-neural resistance. The absence of sEMG changes seems to indicate that resistance training may have impacted in a positive manner on muscle architecture but was not able to modulate hypertonia.

Beyond the main findings of the two pilot studies, non-negligible limitations in the experimental setting and, specifically, in the way the affected muscle groups were evaluated led us to rethink the modalities by which spastic hypertonia should be assessed in MS, which proved to be quite

a challenging condition due to fluctuating performance, high variability in the measurements, and peculiar patterns of hypertonia. Among the latter, unlike in stroke and cerebral palsy, hypertonia in MS is often subclinical and elicitable only at high speed of passive motion. This resulted, surprisingly, in the isokinetic device being unable to reach angular velocities that could trigger the spastic reflex, if any. Indeed, the electrical engine of an isokinetic apparatus can reach speeds of approximately 200-240 degrees per second in passive motion. However, for low-grade hypertonia to be elicited, angular speeds as high as 400-500 degrees per second are needed, which is the common speed rate at which MAS tests are administered to patients in clinical settings.

Altogether, such considerations not only justify continued efforts in investigating this topic but also demand a technological upgrade and the development and introduction of a novel device capable to capture the biomechanical features of spastic hypertonia in such a challenging condition as MS-related spasticity.

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Chapter 3

The device for the Smart Assessment of Spasticity (SAS)

Justification of Study 3

Based on the background and rationale conveyed in Chapters 1 and 2 of the present dissertation, an experimental series (Study 3) was conceived, planned, and carried out in a cohort of moderately disabled people with multiple sclerosis (PwMS) exhibiting mild hypertonia.

Our main working hypothesis was that the introduction of a novel device for a smart assessment of spasticity (SAS) capable of characterizing MS-related hypertonia through reliable, accurate, cost-effective, and responsive measurements would alleviate the main issues that the clinician has to face in the evaluation of hypertonia and in the choice of a more effective management of this disorder. In particular, the main tenets and associated reasons for carrying out Study 3, *i.e.* piloting observational and interventional validations of the SAS in PwMS are the following:

1) MS-related hypertonia is often subclinical in nature and limited in its external manifestations, thus frequently escaping diagnostic procedures;
2) Even when diagnosed via clinical examination and rating tools, the assessment of MS-related hypertonia is troubled by limitations in the ability of such tools to grade objectively its severity as well as its response to therapeutic approaches;
3) Unlike in patients with hemiplegia due to other neurological conditions, such as stroke and cerebral palsy, MS-related hypertonia is heterogeneous, unstable, and presents with additional neural and non-neural features that collectively blur the clinical picture.

Therefore, we proposed to carry out Study 3, which was developed in two phases: (1) phase 1 – observational study, to determine test-retest reproducibility of the kinematic, dynamometric and electromyographic measurements collected with the SAS device during slow to fast passive manual mobilization over three time-points, and (2) phase 2 – interventional study, to test the ability of the SAS device in tracking changes in hypertonia induced by an acute (single-session) rehabilitative intervention which is conventionally employed in clinical practice to induce short-term relief of hypertonia symptoms.

Materials and methods

Participants and eligibility criteria

Participants were recruited from the Department of Multiple Sclerosis Center, Sheba Medical Center – Tel Hashomer (Israel); the Medical Ethics Committee of the Sheba Medical Center – Tel Hashomer approved the study. Full written informed consent signed by all participants was obtained.

Eligibility criteria for the study projects were: 1) definite diagnosis of multiple sclerosis according to the 2017 revision of diagnostic criteria [1]; 2) Expanded Disability Status Scale (EDSS) score ≤ 6.5; 3) focal spasticity affecting the ankle plantarflexors (at least at one side), as shown by excessive flexor or extensor muscle tone scored ≤ 3 according to the Modified Ashworth Scale (MAS); 4) age older than 18 years.

Excluded criteria were detected for: 1) any medical condition contraindicating participation in passive mobilization; 2) comorbidities caused by major medical conditions other than MS; 3) fixed contracture or MAS >4; 4) previous or current treatment with any botulin toxin serotype (e.g., injections), phenol, cannabinoids, or surgery in the previous 6 months; 5) current casting for spasticity of the limb of interest; 6) occurrence of relapses or variations in disease-modifying drugs or symptomatic treatment within 6 months before recruitment.

All voluntary participants were tested by neurological specialist, whose evaluation determined the eligibility or non-eligibility for the study and, if both sides were impaired, defined the most affected one to test. The eligible participants were asked to undergo two different sessions (baseline and one-week retest) for 75 minutes each, conducted by the same operator and in the same condition. Participants were asked to refrain from any other exercise activity before the time of the test.

Phase 1 - Observational study

Aims of the study

The observational study aimed at determining, in a cohort of PwMS with muscle spasticity, test-retest reproducibility of the kinematic, dynamometric and electromyographic measurements of resistance to passive motion (RPM) collected with the SAS device during slow to fast passive manual mobilization in three time-points: test, instant retest and one-week retest.

Design

Phase 1 research design stands as an observational cross-sectional test-retest reproducibility study, where comparison analyses were performed for three measurement time-points, starting from the first session including test and instant retest and a second measurement session, within a week, at the same test condition. Therefore, the association between the outcome measurements obtained with the SAS device and the principal clinical parameters were investigated.

Protocol and instrumentation

In the observational study, each participant was tested twice within 8 days (Figure 1). Before each session, calibration, bench static and quality check of the SAS device and all components were performed, as well as the participant's file process creation on the relative software.

Prior to the quantitative spasticity tests, participants underwent anthropometrical measurements of the most affected limb - defined at the medical evaluation - and the cleansing preparation of the skin for surface electromyography (sEMG) assessment.

Once lying on the medical bed, a passive range of motion (PROM) record of the ankle joint with the SAS device was completed; then, a baseline sEMG track for both plantarflexors (soleus) and tibialis anterior (TA) was recorded, at rest (duration: 60 seconds).

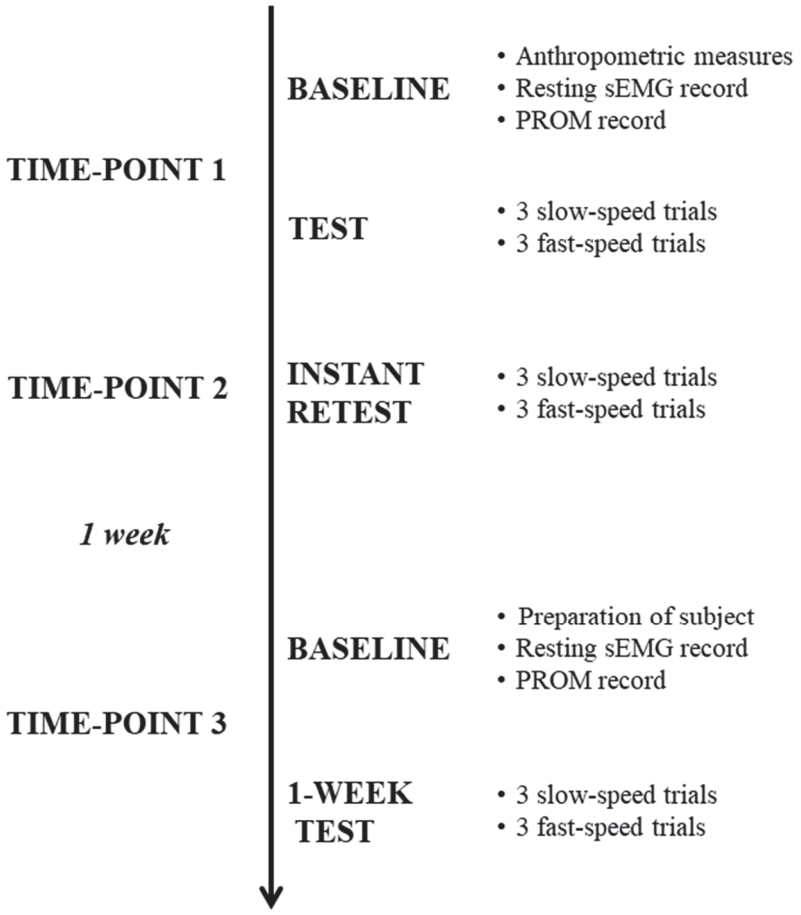


Figure 1 *Timeline of Phase 1. sEMG, surface electromyography; PROM, passive range of motion.*

For each time-point (test and instant retest in the same session day, and one-week retest), the examiner performed 6 trials using the SAS device: 3 slow-speed trials of passive mobilization at about 5°/s (using a metronome with an earphone worn by the operator), followed by 3 fast-speed trials of passive mobilizations, at the maximal affordable velocity.

The ankle was sustained by the operator firmly by one hand, while the other hand maintained the knee flexed stable between 45 to 50°, depending on the individual available mobility, to

keep the best possible stabilization of the position. A 30-second break was included between each trial, and test and retest were performed after 3 minutes of rest. The same conditions were applied to the one-week retest.

The SAS device consists of inertial sensors to track the motion of the proximal and distal segments of the limb during the tests. The force sensor cells were set in to detect the resistance opposed by the spastic muscle during the passive displacement over the range of motion (ROM), at both trial speeds. Each SAS device was worn by the patient and firmly fixed to prevent any change of orientation of the sensor, with respect to the ankle district. Participants were lying down on the medical bed in a supine position for the entire duration of the test, in a comfortable state.

All the mobilizations were completed with respect to the individual soft-tissue mobility of the joint of interest. Each of the trial mobilizations was preceded by a 5-second steady position at 90° at the ankle, to stabilize the goniometry assessment; depending on the set speed, the passive mobilization started from the full plantarflexion to full dorsiflexion, as individually identified in the previous PROM record. At the end of the motion, a 5-second steady position was maintained too.

Outcome measurements

Biomechanical measurements - To define joint angles, angular velocity and acceleration, SAS device, which is constituted of two inertial measurement units, were used to track the movement of the distal limb segment with respect to the proximal segment. Quantitative measurements obtained from the inertial sensor device were recorded during the fast speed stretches, in different time-point trials. Variables were detected for the deflection point, as the first point of deflection, through the joint displacement, where a clear and sudden change of displacement appears based on the proximal and distal inertial sensor's acquisitions (*Theta*); maximal

deceleration point, defined as the position of the maximal point of deceleration during the fast stretches, after the maximal acceleration point [2]; in relation to the angular velocity, maximal power was detected as the product of maximal angular velocity and relative force applied, recorded from force sensor cell.

sEMG evaluation - To measure muscle activity, sEMG was recorded during all the time-point tests, as well as at resting condition prior to tests to detect the presence of involuntary neuromuscular activity or inability to have silent muscle activity. The average root mean square (RMS) EMG was recorded and analysed. sEMG activity was recorded bilaterally (Biometrics DataLink SX230; Biometrics Ltd, Newport, United Kingdom) from the soleus and tibialis anterior muscles during the testing protocol to quantify resistance to passive motion (sampling rate = 5000 Hz; bandwidth = 3–3000 Hz). Active Ag/AgCl bipolar preamplified disc electrodes (Biometrics R300) were used in a belly-tendon montage, with the reference electrode placed over the contralateral lateral malleolus or patella. Before electrode placement, the skin was carefully cleaned with alcohol.

The presence of a spasticity-related event was confirmed only when a non-artifactual sEMG event was clearly standing out of the isoelectric line.

Patient-rated perception of spasticity burden

An 11-point numerical rating scale (NRS) was administered at each time-point to all participants to estimate their subjective impression about spasticity over the preceding 24 hours on a 0-10 NRS with anchors of 0 = “no spasticity” and 10 = “worst possible spasticity. Spasticity was defined by the patients as the muscle stiffness they were experiencing [3].

Data analysis

Data analysis was carried out using custom-made software (MATLAB R2022a: MathWorks), to detect biomechanical parameters such as ROM, Deflection Point, minimal and maximal angular velocity, as well as maximal acceleration and deceleration, and maximal power, individually for each participant and for every trial performed. sEMG raw data were retained for the analysis. EMG raw traces were full-wave rectified, then averaged and plotted for RMS using proprietary software (Biometrics DataLog 10.05 Analysis Package) for each trial performed, at each time point.

Statistical Analysis

Statistical analyses were performed with SPSS Software (Version 26; IBM, New York, USA). Test-retest reliability over three time points (test; instant retest; 1-week retest) was assessed by calculating the intraclass correlation (ICC) coefficients for average measures employing a 2-way mixed design. To test for measurements' stability over the selected time-points repeated-measures analysis of variance (RM-ANOVA) was also employed to test for significant differences in the mean. For all tests and comparisons, the significance level was set at the conventional level for $p<0.05$. To quantify the amount of error surrounding the measurement, the standard error of measurement (SEM) was calculated according to the formula pooled *standard deviation*√1-ICC*. The smallest amount of change that can be detected not due to inherent variation or "noise", *i.e.*, the minimal detectable difference (MDD), was also calculated according to the formula $SEM*1.96 * \sqrt{2}$.

Phase 2 - Interventional study

Aims of the study

Phase 2 was targeted at determining, in a cohort of PwMS with muscle spasticity, the validity of the SAS device to track any real changes induced by an acute (single-session) rehabilitative intervention that has been demonstrated to induce at least short-term relief in spastic symptoms [3, 4]. To this aim, the ankle joint district both at slow and fast speed passive mobilizations was tested.

Design

Phase 2 research design stands as a Pre to Post single-group study, where comparison analyses were performed before and after an acute single-session intervention (same test session of Study 1), to detect the accuracy of the SAS device to identify changes during fast-stretch trials.

Protocol and instrumentation

The interventional study provided each participant to be tested once, in a single test session (Figure 2). The calibration and quality processes of the SAS device refer to the previous Study 1, as well as the instrumentation used for the outcome measurements.

Prior to the spasticity tests, participants underwent anthropometrical measurements of the most affected limb and the cleansing preparation of the skin for sEMG assessment. Once lying on the medical bed, a PROM record of the ankle joint with the SAS device was completed; then, a baseline sEMG track for both plantarflexors (soleus) and tibialis anterior (TA) was recorded, at rest (duration: 60 seconds).

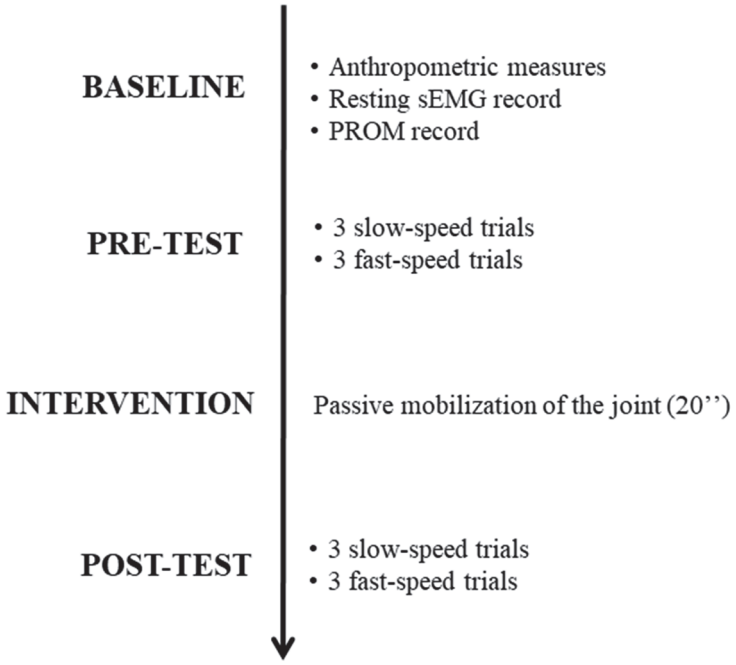


Figure 2 *Timeline of the Phase 2. sEMG, surface electromyography; PROM, passive range of motion.*

Before and after the intervention, the examiner performed 6 trials using the SAS device: 3 slow-speed trials of passive mobilization at ≤ 5°/s (using a metronome with an earphone worn by the operator), followed by 3 fast-speed trials of passive mobilizations, at the maximal affordable velocity. A 30-second break was included between each trial. The SAS device was worn by the patient and firmly fixed to prevent any change of orientation of the sensor, with respect to the ankle district. Participants were lying down on the medical bed in a supine position for all the duration of the test (around 75 minutes), in a comfortable state.

All the stretch mobilizations were completed with respect to the individual soft-tissue mobility of the joint of interest. Each of the trial mobilizations were preceded by a 5-second steady position at 90° at the ankle to stabilize the goniometry assessment; depending on the set speed, the passive mobilization started from the full plantarflexion to full dorsiflexion, as individually identified in the previous PROM record. At the end of the motion, a 5-second steady position were maintained too.

Intervention

The administered intervention provided a 20-minute of passive mobilization of the ankle joint district, exerted at a very slow speed (≤5°/s to a maximum of 10°/s), at the same position kept during the trials to avoid any different test conditions, before and after the intervention.

Among the several conservative treatments, passive mobilization of the ankle is a common technique in the clinical physical therapy management of spasticity [4]. Continuous slow motion of the joint offers a well-controlled movement and elongation of the muscle fibres and soft-tissue structures as tendon, connective, vascular, dermal and neural tissue [4, 5]. The aim of passive joint mobilization and stretch of the muscular tissue may be to normalize muscle tone, reduce pain and improve function [5]. Despite the low evidence, passive mobilization, which resembles clinical practice, is the most common and safe treatment to address spasticity [3].

sEMG evaluation – sEMG records was carried out under the same conditions as phase 1 (see: "Phase 1 - sEMG evaluation").

Data analysis

The data analysis was carried out under the same conditions as phase 1 (see: "Phase 1 - Data analysis").

Statistical Analysis

Statistical analyses were performed with SPSS Software (Version 26; IBM, New York, USA). Normality of data distribution was tested with the Kolmogorov-Smirnov and Shapiro-Wilk normality tests. For normally distributed data, parametric tests were chosen. In case of violations, the corresponding non-parametric test was executed. RM analysis of covariance (ANCOVA) was chosen as the main approach to compare pre and post data also takin into

account the unavoidable discrepancy between fast stretch mobilizations delivered by a human tester. Power (angular velocity * torque) was set as the covariate to insert in the model to compensate for such discrepancies.

The effect size (Cohen's d) of the within-subjects differences, if any, was also evaluated in its magnitude according to the conventional categorization [6] where $d<0.4$ suggests a small effect, d between 0.41 and 0.8 a moderate effect, and $d>0.8$ a large effect.

Results

Phase 1 – Cross-sectional test-retest reproducibility study

Sample characteristics

Complete data were obtained from 22 participants (mean age: 53.3 ± 12.8 years; 14 men, 8 women). The main anthropometric, demographic, and clinical features at study entry are summarized in Table 1. Overall, they displayed a moderate degree of disability (EDSS median: 4.3; range: 3.5 – 6.5), mild resistance to passive motion from the ankle plantarflexors (MAS 1 in 31.8%; MAS 1+ in 31.8%; MAS 2 in 36.4%). The most prevalent disease course was primary progressive (9/22, 40.9%), followed by relapsing remitting (7/22, 31.8%) and secondary progressive (6/22, 27.3%).

Table 1 Anthropometric, demographic, and clinical data of the cohort of PwMS. All data were shown as mean ± SD, unless specified otherwise.

Variable (*unit of measure*)		**Values**
Age (*years*)		53.27 ± 12.77
Gender (*n*)	Male	*n* = 14
	Female	*n* = 8
Weight (*kg*)		71.09 ± 14.35
Height (*cm*)		172.73 ± 10.43
Disease history (*years*)		13.45 ± 9.50
MS course (*n*)	RR	*n* = 7
	PP	*n* = 9
	SP	*n* = 6
EDSS (*score; median ± std. error*)		4.25 ± 0.22
Pyramidal score (*score; median ± std. error*)		3 ± 0.16
MAS (*n*)	1	*n* = 7 (31.8%)
	1^+	*n* = 7 (31.8%)
	2	*n* = 8 (36.4%)

SD, standard deviation; Kg, kilograms; cm, centimeters; MS, multiple sclerosis; RR, relapsing-remitting; PP, primary progressive; SP, secondary progressive; EDSS, Expanded Disability Status Scale; MAS, Modified Ashworth Scale.

Resistance to passive motion recordings

Descriptive statistics for the main variables measured by the SAS device are detailed in Table 2. The results are presented for the primary outcomes of the studies, *i.e.*, mean maximal deceleration, deflection point, maximal power, and sEMG activity from the affected muscles during the passive test of RPM. Raw data also for these variables are presented in Table 2, while Table 3 summarizes the results of the reliability analyses.

Table 2 Descriptive outcome measurements at three time points.

Variable (*unit of measurement*)	**Test (mean ± SD)**	**Instant retest (mean ± SD)**	**1-week retest (mean ± SD)**
ROM (*deg*)	51.10 ± 9.16	49.87 ± 9.32	51.47 ± 8.83
Maximal Deceleration (deg/s^2)	-16515.85 ± 4683.62	-15559.33 ± 5325.37	-17284.18 ± 5592.30
Deflection Point (*ROM %*)	13.68 ± 5.16	13.95 ± 4.76	13.78 ± 4.69
Maximal Angular Velocity (*deg/s*)	529.94 ± 93.85	518.43 ± 94.92	540.38 ± 90.44
Maximal Power (*W*)	691.70 ± 302.07	587.85 ± 282.36	670.13 ± 306.24
sEMG amplitude (*mV*)	0.43 ± 0.27	0.41 ± 0.26	0.44 ± 0.25
sEMG Ratio (*mV/s*)	6.81 ± 5.68	5.39 ± 9.76	5.46 ± 9.79

SD, standard deviation; ROM, range of motion; deg, degree; s, second; W, watt; sEMG, surface electromyography; mV, millivolts;

Table 3 Results of the reliability analysis for the principal outcome measurements.

Variable (*unit of measurement*)	**ICC (95% CI)**	**SEM**	**MDD**	**SEM%**	**MDD%**
Maximal Deceleration (deg/s^2)	0.947 (0.890, 0.977)	-1197.23	-3318.55	7.28	20.17
Deflection Point (*ROM %*)	0.804 (0.594, 0.914)	2.16	5.99	15.65	43.39
Maximal Power (*W*)	0.692 (0.375, 0.863)	164.77	456.72	25.35	70.27
sEMG RMS Amplitude (*mV*)	0.939 (0.874, 0.973)	0.06	0.17	14.06	39.84
sEMG RMS Ratio (*mV/s*)	0.932 (0.860, 0.970)	2.19	6.07	37.18	102.77

ICC, intraclass correlation coefficient; CI, confidence interval; SEM, standard error of measurement; MDD, minimal detectable change; deg, degree; s, second; ROM, range of motion; W, watt; sEMG, surface electromyography; RMS, root mean square; mV, millivolts.

Maximal deceleration – ICC analyses revealed a high test-retest reliability over the three time-points tested (test, instant retest, 1-week retest), with an average-measure ICC of 0.947 (95% CI: 0.89 to 0.977). Clinimetric analyses aimed at determining stability and responsiveness of the measurement revealed a SEM value of -1197.23 deg/s^2, and an MDC value of -3318.55 deg/s^2. If expressed as percentages, SEM and MDC were 7.28% and 20.17%, respectively.

Deflection point – High ICC coefficients were also found for deflection point expressed in percentage of the entire ROM (0.804; 95% CI: 0.594 to 0.914). Absolute SEM and MDC (2.16 and 5.99) as well as the related percent scores (15.65% and 43.39%) were low in magnitude.

Power – The average measurement of power as recorded during the tester's impulse while mobilizing the participant's affected limb was associated to moderate to high ICC (0.692; 95% CI: 0.375 to 0.863). Clinimetric analyses revealed low SEM and MDC values both as absolute (164.77 and 456.72) and relative percent scores (25.35% and 70.27%).

sEMG – ICC analysis revealed high coefficients for mean RMS amplitude recorded from the plantarflexors of the affected side (ICC 0.939; 95% CI: 0.874 to 0.973; SEM = 0.06, SEM% = 14.06, MDD = 0.17, MDD% = 39.84) and for RMS Ratio (ICC 0.932; 95% CI: 0.860 to 0.970; SEM = 2.19, SEM% = 37.18, MDD = 6.07, MDD% = 102.77). Lower coefficients indicating low to moderate reliability were found for RMS duration (ICC 0.604; 95% CI: 0.182 to 0.827).

Association of the SAS-recorded outcomes with clinical items

Correlation analyses revealed significant associations between the EDSS pyramidal score and all the EMG variables (RMS amplitude: r=0.879; p=0.009; RMS duration: r=0.805; p=0.028; RMS Ratio: r=0.692; p=0.039).

No significant correlations with EDSS, MAS and spasticity NRS scores were observed for any of the variables recorded.

Phase 2 – Interventional validation study

The same 22 participants enrolled for Study 1 underwent an intervention phase consisting of a 20-minute passive, slow mobilization of the affected ankle (see: "Methods – Intervention"). Changes in the primary outcome measures following the intervention are presented in Table 4 and represented in Figures 3 and 4.

Table 4 Changes in primary outcomes describing resistance to passive motion following the 20-minute passive mobilization of the affected ankle.

Variable (*unit of measure*)	**PRE**	**POST**	**Statistics**
Maximal Deceleration (*deg/s²*)	-16515.85 ± 4683.62	-14341.89 ± 5068.65	-13.2%; $F_{1,20}$=10.184; *p*=0.005; d=0.859
Deflection Point (*ROM %*)	13.68 ± 5.16	22.08 ± 8.65	+61.4%; $F_{1,20}$=21.899; *p*<0.0001; d=0.994
sEMG Ratio (*mV/s*)	6.81 ± 5.68	5.24 ± 9.10	-23.1%; $F_{1,20}$=8.934; *p*=0.007; d=0.811

Deg, degree; s, second; ROM, range of motion; sEMG, surface electromyography; mV, millivolts. Significance for p<0,05.

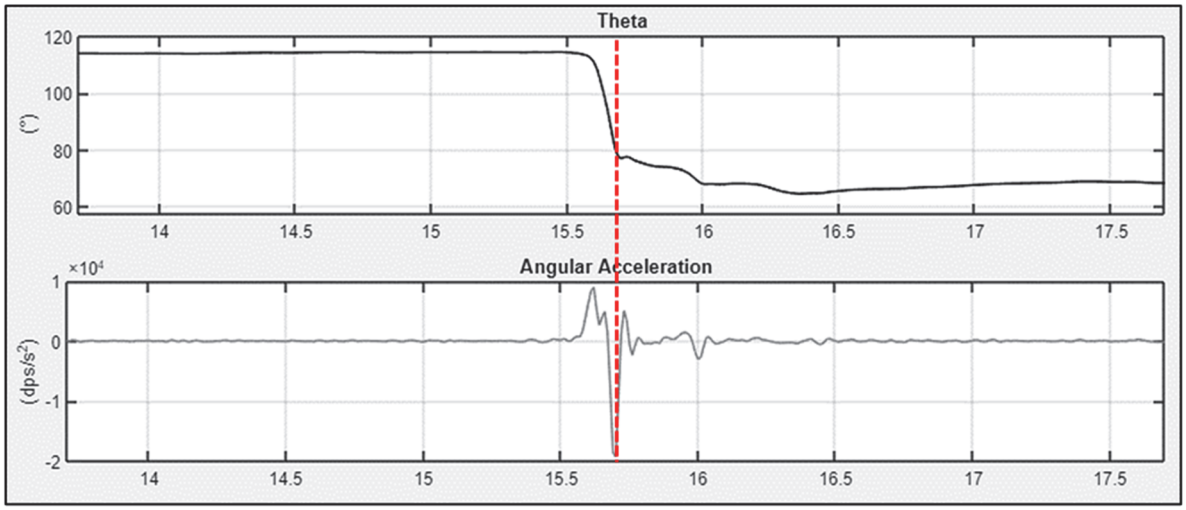


Figure 3. *Graphic detection of deflection point and maximal deceleration (dotted line) during a fast-speed passive stretch, in a single case participant. °, degrees; dps, degree per second; s, second.*

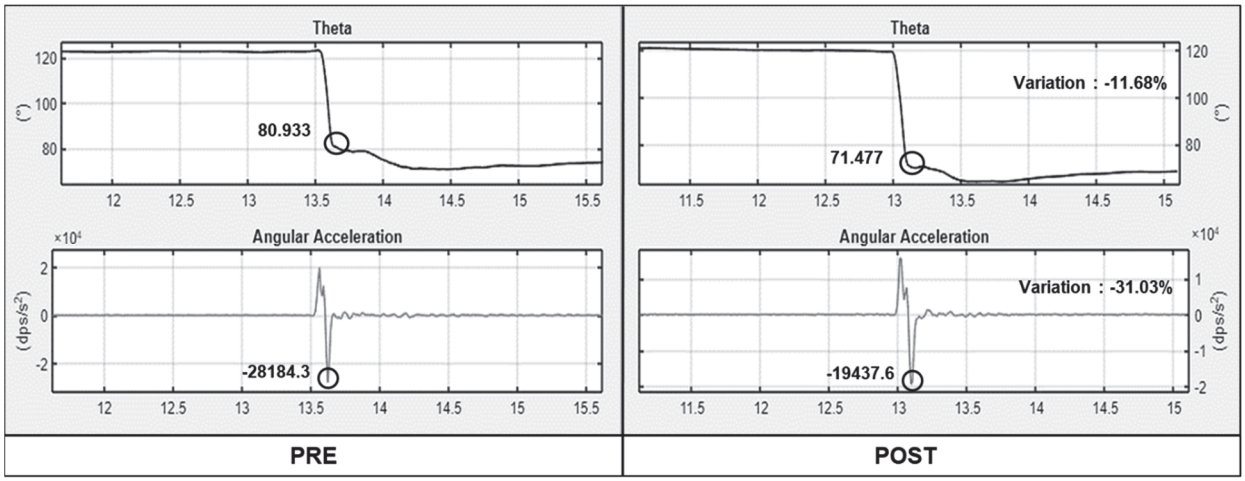


Figure 4. *Pre to post changes for primary outcome measurements. Graphic detection of deflection point and maximal deceleration (circles) during a fast-speed passive stretch, in a single-case participant. Pre-test appears on the right side, post-test on the left side. °, degree; dps, degree per second.*

Maximal deceleration - Following the passive mobilization, RM-ANCOVA (covariate: maximal power imparted by the tester) revealed a significant reduction in the angular deceleration imparted by the affected ankle plantarflexors after the reflex was triggered by the tester's fast mobilization (-13.2%; $F_{1,20}=10.184$; $p=0.005$; $d=0.859$).

Deflection point – RM-ANCOVA (covariate: maximal power) showed a significant shift in the deflection point, i.e., an increased ROM free from the reflex (+61.4%; $F_{1,20}=21.899$; $p<0.0001$; $d=0.994$).

sEMG - RM-ANCOVA (covariate: maximal power) showed a significant reduction in the EMG activity recorded from the plantarflexors of the affected side (-23.1%; $F_{1,20}=8.934$; $p=0.007$; $d=0.811$).

Discussion

Study 3 primarily aimed at: (1) establishing the reliability and clinimetric properties of the outcomes describing RPM as measured by the newly introduced sensorized device, the SAS device, through a test-retest study carried out in a clinical population of PwMS, and (2) testing the ability of the device to capture changes in the biomechanical descriptors of RPM following a paradigmatic intervention conventionally employed in clinical practice for alleviating hypertonia symptoms in the short term.

The main finding of the observational phase was that the SAS device allowed reliable, reproducible, and accurate measurements of RPM in PwMS complaining of hypertonia, according to self-rated and clinician-rated scales. The high to excellent reliability along with the low variability indexes observed for the primary biomechanical descriptors of RPM patterns make these measurements trustable quantitative and objective tools to complement the subjective, clinical assessment of patients. Specifically, maximal deceleration (generated by the muscles of the affected side during the fast stretch) and the deflection point in percentage (also known as "angle of catch") [7] emerged as those parameters best capturing pathological RPM patterns. However, the clinimetric properties of maximal deceleration (highest ICC coefficients, lowest SEM and MDC percent scores) seem to suggest this parameter as first choice. These parameters describe the biomechanical response attributable to the patient's limb reaction after the stretch reflex is elicited by the fast mobilization imparted by the clinician/tester. Such parameters are also in line with previously published reports that employed accelerometry for characterizing RPM in neurological populations with UMN syndrome, confirming them as appropriate biomechanical measures for monitoring individuals with hypertonia [2, 8]. In addition to these descriptors, which can be obtained with accelerometers and gyroscopes, the SAS device here tested also includes a load cell that allows recording the force applied by the tester to the patient's limb while mobilizing it passively. This is an important feature that

permits to control and quantify the amount of strength that the tester/clinician needs to generate for accelerating the patient's limb up to the critical angular velocity that eventually triggers the pathological stretch reflex. The combined recording of the angular velocity measured by the accelerometer embedded in the SAS device with the force pressure measured by the load cell placed over the device allows for determining the power (velocity * torque) of the impulse imparted. Accordingly, maximal deceleration and deflection point, which represent the patient's limb response, should be corrected for the tester's power to ensure reproducible and accurate measurement of RPM.

Accurate characterization of the motor pattern following the stretch reflex elicitation is particularly relevant to MS-related hypertonia as PwMS exhibit peculiar features that make their assessment challenging [9]. Indeed, unlike the paradigmatic hypertonia displayed by hemiplegic stroke survivors, the RPM that is generally detected in PwMS is often not velocity-dependent. Intrinsic hypertonia (i.e., soft tissue changes in the muscles, tendons and joints that can increase muscle tone) is also a major component eventually shortening the affected muscles and ensuing reduction of both passive and active ROM [10]. Recently, it has been pointed out that a tonic stretch reflex can be observed whether PwMS present spastic hypertonia or not [9]. This introduces spastic dystonia, i.e., the inability to relax a muscle leading to a spontaneous tonic contraction, as an additional feature that can potentially reduce the clinician's ability to characterize hypertonia in this population [11]. Relatedly, inability to silence EMG activity from the affected muscle groups has also been reported [9]. Ideally, the most controlled setting for testing the biomechanical responses of a hypertonic limb is to have quantitative control of the angular velocity at which the tester imparts the perturbation to the limb, the amount of force needed to accelerate the limb to the critical speed - both being features linked to the tester - and then the reflex-related, involuntary deceleration opposed by the hypertonic muscles. Such a controlled setting is possible with isokinetic dynamometers which, when used for capturing

RPM, move the patient's limb at a known, predefined angular velocity also recording the dynamometric response opposed by the affected muscle groups [12, 13, 14]. With this technique it is therefore possible to test the RPM in the joints with preset speeds at different lengths of the same muscle. As spasticity is defined as a velocity-dependent response of muscle to passive stretching [15], isokinetic dynamometry seems to be a technique suited for this purpose. When controlled with sEMG, the testing procedure can inform on the involvement and hierarchy of neural and non-neural components of the observed RPM.

However, this technique has been mainly employed for testing paradigmatic and stable manifestations of hypertonia, such as those observed in hemiplegic stroke survivors, individuals with cerebral palsy and spinal cord injury. In these conditions even low to moderate angular velocities in the range of 30 to 120 (°/s can trigger the spastic reflex, thus allowing accurate depiction of the biomechanical response to perturbation. This is not the case of MS-related hypertonia, where PwMS exhibit atypical, often unstable patterns of response to fast stretches. Moreover, RPM is not triggered by low to moderate velocities as high or very high speeds are, instead, needed. In two recent case series enrolling PwMS with hypertonia of the ankle plantarflexors [16, 17] we documented the need of angular velocities up to 200°/s to elicit responses in our cohorts of participants with moderate to severe disability. Such speeds are at the top of most isokinetic systems which allow recordings at velocities up to 400°/s but, when operating in passive mode for limb mobilization, are self-limited at lower top speeds of 220-240°/s for safety purposes. Therefore, this technique seems not suited for MS-related hypertonia, particularly for patients not showing severe degrees of disability and pyramidal symptoms. For these individuals establishing novel and more suitable assessment approaches is, therefore, imperative.

With these considerations in mind, the present preliminary findings pointing towards reliable and accurate measurements of hypertonia in moderately disabled PwMS with mild hypertonia

as recorded by the newly introduced SAS bracelet are of potential relevance to clinicians as well as researchers involved in MS as they can help differentiate among the wide spectrum of hypertonic features exhibited by PwMS. Indeed, ascertaining the different contribution of spasticity, dystonia and intrinsic soft tissue changes would also allow to devise and execute appropriate therapeutic plans to manage related symptoms and disability.

In addition to its high to excellent reproducibility properties, the SAS device conceived, built and developed with the present PhD project also allowed tracking of the changes induced by the intervention here administered. A 20-minute passive, slow mobilization was chosen as a common approach that is conventionally employed in clinical practice to mitigate hypertonic symptoms in the short term [4, 5]. The outcome measures identified in the observational phase as those most reliably and accurately portraying the RPM pattern of PwMS – maximal deceleration and deflection point - were found significantly changed following the intervention, suggesting that the SAS device is sensitive to changes following rehabilitation, even after a single basic session, unlike common clinical tools which are well-known for being insensitive and poorly responsive to non-pharmacological treatments [18]. Based on the clinimetric properties exhibited by the outcome measures, however, only deflection point achieved and surpassed the MDD cut-off that was determined at baseline (pre-post change of +61.4% against a MDD% of 43.4%). This was not the case of maximal deceleration (pre-post change of +13.2% against a MDD% of 20.2%). Data indicate that while the vast majority of the participants (21 responders out of 22 participants) experienced a positive shift in the deflection point, *i.e.*, an increase in the ROM free from RPM, changes in maximal deceleration were of lesser extent and sparser, with 14 responders (*i.e.*, displaying substantial reduction) out of 22 participants. For these reasons, after balancing clinimetric properties and sensitivity to change, we would recommend deflection point as the ultimate outcome measure for capturing RPM patterns in MS as well as for tracking changes following the intervention.

Study limitations

Given its preliminary nature, the present experimental series is not free from limitations. Among these, the lack of a healthy control group that would have allowed to concurrently characterize the main differences between pathological and physiological patterns of RPM, which is present also in healthy subjects when approaching the limits of the ROM.

Another limitation relates to the lack of concurrent validation using the gold-standard isokinetic dynamometry. Unfortunately, as extensively elaborated upon in the discussion, MS-related hypertonia can be unveiled only at high or very high angular velocities, thus exceeding the top speeds that isokinetic systems can achieve.

Importantly, we focused on the ankle district according to pertinent literature indicating this joint as the most common site of contractures, weakness and spasticity. However, the ankle is somewhat peculiar if confronted with other joints, particularly if we consider that is it subjected to continuous loading in closed kinetic chain, and presents with generally higher prevalence of soft tissue disorders. Therefore, the present findings cannot be generalized straightaway to other body districts. Conversely, we hypothesize that they can be reasonably stretched to populations other than MS, such as – among others - stroke, spinal cord injury and cerebral palsy, where hypertonic symptoms tend to present in a more stereotyped and homogeneous manner.

Finally, the acute intervention here administered should be in no way considered as a viable therapeutic option for spasticity as a robust body of literature has clearly dismissed it, showing no sustained aftereffects. Indeed, for the present study passive mobilization served the mere purpose to offer a short-lived modulation of hypertonia, as extensively reported in published reports dealing with hypertonia.

Conclusions

According to the preliminary data here collected, the newly introduced SAS device allows a reliable assessment of hypertonia, even in challenging conditions such as those observed in MS. The clinimetric properties of the SAS-derived outcome parameters also ensure to efficiently track differences in hypertonia induced by non-pharmacological interventions, making the SAS a sensitive and responsive tool that can complement and corroborate the conventional clinical evaluation of this disorder.

Study 3

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