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EFFECTS OF MUSCLE SHORTENING MANOEUVRE ON MOTOR CONTROL: A CLINICAL MODEL

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Abstract

The Muscle Shortening Maneuver (MSM), a physiotherapy approach, was introduced by Grimaldi et al. (ref) in the eighties and is derived from Feldman's λ model of motor control (Melchiorre, 2014). In the λ model the regulation of the stretch reflex threshold, that is the lower muscle length or joint angle at which motoneuronal recruitment occurs, plays a pivotal role (Feldman, 1995; Latash, 2010). The dynamic stretch reflex threshold (DSRT) is influenced by stretch speed. The tonic stretch reflex threshold (TSRT) represents the specific value of the DSRT at zero velocity. DSRTs and TSRTs are expressed in relation to the configuration of the joints, within a body frame of reference (FR) [4]. MSM is non-invasive and free of side effects, and is locally used in clinical practice (Ferrarello, 2021); it consists of two essential simultaneously applied elements: a muscle shortening and a solicitation in traction. A physiotherapist applies a series of fast accelerations to a skeletal segment (e.g., the foot) in the presence of forces acting in the opposite direction (added mass), thus producing a tensile stress. MSM provokes a dynamic lengthening associated with sudden shortening of the agonist and antagonist muscles. Tissue deformation stimulates the muscle spindles, with an enrolment of motor units and an attempt to produce muscle tension. However, the development of tension is prevented by the sudden shortening of the muscle due to the therapeutic maneuver. It is widely used in clinical practice but with little scientific evidence. The aim of the thesis is to investigate the neurophysiological mechanisms underlying it.

With these assumptions, an intervention study on patients with chronic stroke in which, through the use of a portable device, it has been possible to use the TSRTs as an objective outcome measure, has been designed. In order to test this protocol and before embarking on a real randomized clinical trial, a pilot study was performed. Despite the limitations of this type of study design do not allow to make assumptions on the real efficacy of the treatment, it was already possible to identify real physiological changes in patients. Moreover, the pilot study has been useful to detect the criticalities of the original research project and therefore to make changes to support a better execution of the future trial.

In the meanwhile a retrospective analysis which led to a re-elaboration of data obtained in the recent past was conducted. In particular, in a case series of 9 subjects with infantile cerebral palsy, the evaluation of objective outcomes (muscle strength, range of motion) is found for the first time in relation to functional outcomes measured by scales (Selective Motor Control Scale, Physician Rating Scale). Despite the many limitations that a series of cases with such a small sample can have, it was considered important to proceed with a more in-depth analysis of the data obtained in order to reflect on the possible presence of strong outcomes that would really change the physiological and functional characteristics of the subjects. This would have allowed to lay the foundations for future work to

better investigate the effects of MSM on movement control in individuals with central nervous system injury.

The effects of the maneuver were also investigated in terms of pure electromyographic activity in a pediatric patient with post-surgical peroneal nerve resection. Also in this patient it was possible to find a clear modification of the outcomes in question with a strong reduction in clinical and functional findings and greater daily autonomy in the activities of life. Obviously, the limits of the observation of a single case are evident and the results cannot be considered as evidence of efficacy but it is considered important, even in this case, to detect the presence of hard outcomes of the therapeutic path.

Furthermore, the literature on MSM shows the possible effects of this type of treatment also on orthopedic injuries. In particular, two articles by Melchiorre et al. showed that this type of intervention seems effective on patients with Shoulder Impingement Syndrome (SIS) in terms of morpho-structural changes in the musculotendinous compartment of the joint, detectable by ultrasound, and of increased strength and pain relief. This protocol was selected for the design and execution of a study on subjects with SIS from a population that practices an overhead sport, water polo. In this randomized and controlled study, it was possible to observe objective and immediate changes in the musculotendinous components in correspondence with a significant decrease of pain.

In conclusion, the results of these studies seem to highlight a real effect of MSM on motor control understood as modulation of TSRT, in the perspective of Feldman's threshold referent control theory.

Chapter 1. Introduction

1.0 Motor control: dynamic systems theory and Equilibrium Point Hypothesis (EPH)

The view that posture and movement are controlled by separate mechanisms has dominated the study of motor control for many years, sometimes for convenience and sometimes for tradition. The Equilibrium Point Hypothesis is the only approach to motor control that stably and definitively resolves the controversy over the control mechanisms between posture and movement.

1.0.1 The λ model

Anatol Feldman, with his λ model, overcomes an earlier model, proposed by Bizzi, who first elaborated the notion of length/tension muscle characteristics, each corresponding to an invariant level of alpha muscle innervation. In this model, the muscle length/tension features are isoelectric, the level of α activation is invariant for each of them, and the existence of a single resting length from which all features depart is assumed. The Feldman model, developed through experiments with load/ relief and with the instruction not to intervene voluntarily on the movement produced, states the existence, for each muscle, of several length/tension curves of equal slope but with different thresholds λ. Involuntary behavior was analyzed by means of unloading experiments in which the forearm was positioned on a horizontal manipulandum and subjects resisted in a specific position an initial load torque with the elbow flexors. In this initial state, called the system's Equilibrium Point (EP), elbow position, loading torque, and electromyographic activity of the flexors and extensors were measured. The EP was thus composed of the equilibrium position and its associated equilibrium torque. In subsequent trials, from this initial EP, the elbow flexors were unloaded with varying amounts of torque. Subjects were instructed not to intervene voluntarily when the unloading arrived. This meant that they were to let the arm move to its new position after unloading and not to try to make corrections to return the arm to its initial position or to relax it completely. After each time the arm was partially unloaded, it naturally found a different final EP, depending on the amount of unloading. These final EPs were recorded on a torque/angle graph and, along with the initial EP, formed a regular non-linear torque/angle feature (Latash et al., 2010). Unlike the Bizzi model, in the λ model (or "Equilibrium Point Hypothesis - EPH"), the curves are not isoelectric and there is no single resting length.

In EPH, movement occurs on the basis of threshold regulation by the Central Nervous System (CNS). The threshold length λ represents one of the essential variables that allows the creation of the constraint equation. There are also nonessential variables that relate to changes in the segmental excitatory state, which is the cause of the increased slope of the pre-existing length/voltage relationship. The constraint imposed by the essential variable is maintained until a critical value that causes the transition to another coordinative structure. A single central control command is sufficient to organize the movement at the periphery, allowing the identification of new threshold lengths λ that are determined as a function of intentionality. Arranging this resting length means constraining the dynamics to accomplish the motor act. Indeed, in an experiment by Feldman, participants were asked to voluntarily change their initial position against a load and the procedure was repeated by a new initial EP, which provided a new torque/angle characteristic. In this way, a range of torque/angle features was recorded. Finally, subjects were asked to totally relax their muscles, while the elbow was extended from the manipulandum and a passive torque/angle feature of the subject's arm muscles was obtained. The first two unloading features were similar: for both, torque was related to arm position in a nonlinear way, and EMG activity was changed with load. The features were somewhat different in terms of shape, which could result from differences in the mechanical properties of the muscles in different parts of the angular range, rather than from voluntary action. Each unloading curve intersected with the passive joint characteristic at a specific joint angle (R). At these R points, the muscles became silent and ceased to generate active torque. These threshold angles were different for different characteristics (Fig. 1.0.1). From these experiments, Asatryan and Feldman concluded that the threshold angle, R, at which the muscles ceased to be active, was invariant for a given initial command. When the subject intentionally changed the initial arm position, a new value of R was specified (Latash et al., 2010).

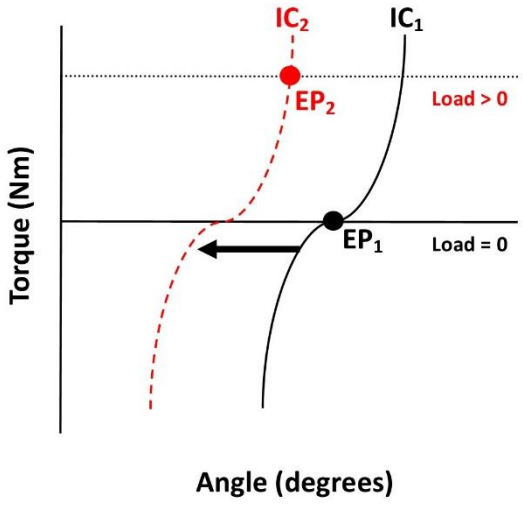

Figure 1.0.1. Schematic diagram of how a change in force is produced in the λ model when a load is suddenly introduced and the subject is instructed to hold the position. At first, the load is 0. When a constant load is introduced (dashed line, Load > 0), to maintain the same position, the subject must shift the equilibrium point from EP1 to EP2. This is accomplished by moving the invariant feature of the joint from IC1 to IC2. For the same position, one finds more muscle activity and more torque at EP1 rather than EP2. The muscle activation required to change torque is therefore a consequence of shifting EPs. *IC= Invariant Characteristic; EP= Equilibrium Point*

1.0.2 Neuromuscular mechanics: the Houk and Rymer's model

Electrophysiological studies have shown that pathways descending from the brain to the spinal cord possess direct actions on α and γ motor neurons, as well as actions on interneurons in reflex pathways and on presynaptic terminals. It is sometimes assumed that interneuronal and presynaptic actions are particularly important in controlling reflex responsivity and that movements, on the other hand, are controlled by direct actions on motor neurons. Certainly, there is now good evidence that movement commands are sent to both skeletal-motor and spindle-motor neurons, and it is also clear that reflex transmission, as tested by electrophysiological techniques, can be modified by descending activity. Changes in reflex transmission, however, demonstrate only the anatomical convergence of descending and reflex pathways; the normal actions of a descending input converging on a reflex pathway could add to a subentrant input from the periphery and thus affect the threshold of the reflex, rather than changing its "gain." Studies of decerebrate animals, in which control signals to the motor servo are altered in a variety of ways, have, in most cases, demonstrated a simple shift in the threshold of the force-length relation rather than a change in its slope, the latter corresponding to gain control. Matthews reported on the effects of activation of synergistic, antagonistic, and extensor-crossed reflex pathways, and on the consequences of spontaneous changes in stiffness and depression caused by procaine paralysis of γ-fibers. The salient effect of each of these procedures was a shift in the force-length relationship along the abscissa, that is, a change in the threshold of the stretch reflex with little change in the conformation of the curve. Excitatory inputs lowered the threshold, whereas inhibitory inputs shifted it to a greater muscle length. Feldman and Orlovsky obtained the same result with tonic stimulation of the descending pathways. Various excitatory and inhibitory combinations obtained by stimulating the ipsilateral and contralateral nucleus of Deiters, the pyramidal bundle, and the medial reticular formation of the medulla oblongata simply resulted in threshold changes. However, Kim and Partridge, reported that stimulation of the utricular nerve sometimes caused conformation changes (at low levels of central excitatory state), as well as shifts in threshold. The fundamental uniformity of these results is striking because of the variable motoneuronal contribution from α versus γ for different simulated motor commands. It is known that descending and extensor-crossed pathways result in co-activation of α and γ motoneurons, synergistic and antagonistic pathways primarily activate α motoneurons, and paralysis of γ motoneurons modifies only the γ signal. Evidently, static motor servo performance is rather independent of the α-γ relationship (Houk and Rymer, 1981). This seems to be related to the finding that the basic effect of a central motor command is a shift in the stretch reflex threshold, more or less independent of the α and γ motor neuron composition of the command (Houk and Rymer, 1981; Grimaldi et al., 1986).

1.0.3 Constraints on Dynamics and Threshold Lengths

The embodiment of the constraint is represented by the shift of the threshold of the relationship length/tension whose purpose is, precisely, to obtain oscillatory systems with very precise characteristics of equifinality. The coordinative structures thus identified will then have characteristics of: equifinality, stability, autonomy, emphasizing the role of dynamics, self-organization and non-linearity. In this way, the central command does not require a continuous update in relation to obstacles because, if they are transient, the periphery will adjust, while, if they are constant, the torque/angle curves will be properly prepared. In this model, therefore, the CNS parameterizes the values of λ (Levin, 2000), that is the resting length, if the length of the muscle varies from the resting length, the muscle enters in the activation area. Therefore, calling x the actual length of the muscle for $x > \lambda$, the muscle will be in the activation area and will develop active tension; for $x < \lambda$, the muscle will be in the silent area and will be released.

In the Feldman model, the motor control function takes the form $F = f(x; \lambda)$; where x is the actual length of the muscle and λ represents the tonic stretch reflex threshold (TSRT). Feldman's experiments, moreover, showed that, to totally relax the arm muscles, the threshold had to be moved beyond the upper biomechanical limit of the elbow joint, so that the muscles could remain silent in the entire biomechanical range of the elbow joint angles (Fig. 1.0.2). Conversely, to fully activate the muscle, even at the smallest muscle length, the threshold had to be moved beyond the lower limit of the biomechanical range (Latash et al., 2010). Imposing a resting length means, therefore, constraining the dynamics for the performance of a motor act. Dynamics, however, has, for the authors, a dual effect: computational saving but also disruptive action to the movement. This is the reason why the coordinative structures are born, which have exactly the purpose of cancelling the undesired effect of dynamics.

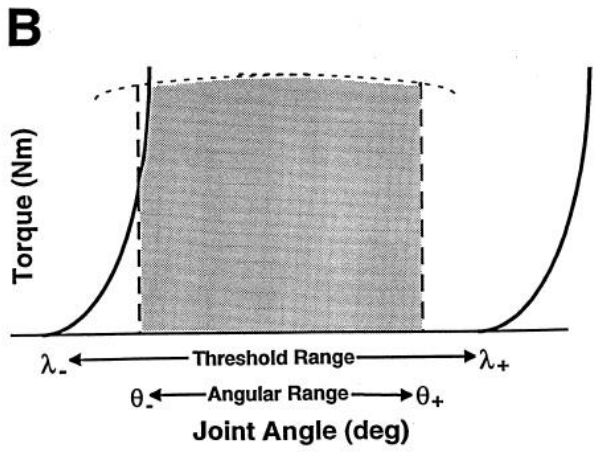

Figure 1.0.2. Schematic diagram to illustrate that the threshold parameter λ needs to be adjusted within a range (λ-; λ+) greater than the joint angular range (θ-; θ+) in order for the muscles to fully relax (when λ is in the rightmost position) or develop force at all joint angles (e.g. when λ is in the leftmost position). The colored area shows the possible combinations of torque and muscle positions (Latash et al., 2010).

1.0.4 Threshold control theory and the area of muscle activation

The motor control needs structures adequately dedicated to it. In this perspective, Feldman (2010), describes the simplest unit of motor control that includes the α motor neuron and its connections: the output to the muscle, the feedback from proprioceptive afferents (especially length-dependent ones from spindles) and the input from central systems. When the descending signals are minimal and the muscle is lengthened slowly, the membrane potential of the motor neuron increases. The motor neuron is recruited when its electrical threshold (V^+) is reached. This electrical threshold is achieved at a certain muscle length, λ^+. In the situation where descending facilitation is minimal, this threshold will be higher than the upper limit of the biomechanical range [x^- ; x^+] and the muscle will be relaxed within this range. If descending systems cause an excitatory input into the motor neuron, the membrane potential will increase, and the same muscle stretch will cause motor neuron recruitment at a shorter threshold length, λ' (Fig. 1.0.3).

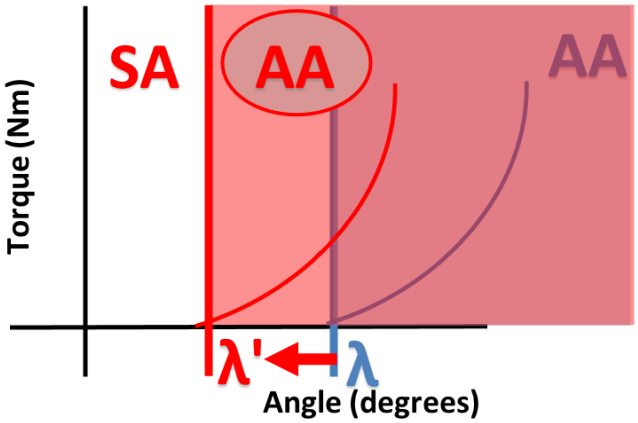

Figure 1.0.3. Activation and silent areas of the muscle. Highlights the dependence of the stretch reflex threshold on length. When the system goes from λ to λ' the muscle enters the activation area at a shorter length.

The motoneuron discharge frequency will increase as the muscle length increases beyond the threshold λ. Note that the threshold length of the muscle can be changed even if the electrical threshold remains constant. However, changes in motor neuron electrical thresholds may be an alternative source of spatial threshold shift. The motoneuron membrane is, therefore, the place where independent electrochemical signals descending from the brain are converted (decoded) into spatial thresholds that associate our motor actions with the body (Fig. 1.0.4). This decoding would be impossible without position-dependent feedback (Feldman, 2010).

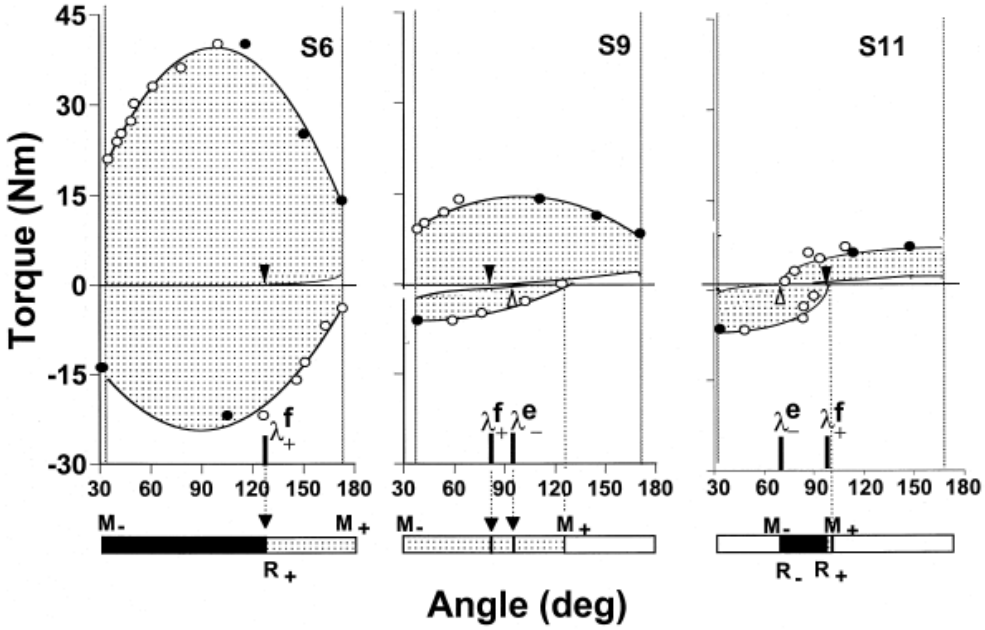

Figure 1.0.4. Areas of flexor and extensor muscle torque production in three different subjects. In the left panel, torque can be generated at each joint angle for both muscle groups. In the middle panel, torque can be generated for the entire flexor range but only in a portion of the extensor range. In the right panel, the range of torque generation is limited in both directions. The filled and empty triangles represent the static RTS thresholds of flexors and extensors, respectively, also highlighted by thick vertical marks on the angular axis. For each subject, the torque/angle characteristics of flexors and extensors obtained when each group is stretched at low velocity (< 8°/s) and generates torque beyond the threshold angle (continuous curves without dots) were also added. The areas to the right of the flexor feature and to the left of the extensor feature represent the angular ranges in which muscle relaxation is not possible. The horizontal bars below each panel represent the range of active movement (M-, M+; black and light gray bars together), the range of reciprocal innervation, R (black bars), and the ranges in which movement was either not possible or possible in only one direction (white bars). The lower limit of R (R-) extends beyond the lower limit of the angular range (θ -) in the left panel. In the middle panel, the range λ+f < λ-e, indicates co-activation with a fixed value of R (Levin, 2000).

1.0.5 The dynamic threshold λ* and the coefficient μ

It is commonly known that the stretch reflex is velocity-dependent; this led Feldman to introduce the concept of a dynamic threshold (or total threshold), λ*, which is dependent on the rate of change of muscle length or joint angle, mutual inhibition of the reflex, and other hetero-genetic reflexes. This threshold is identified by the expression: $\lambda^* = \lambda - \mu\, d\theta/dt + \rho$.

In this expression, the time-dimensional coefficient, μ, characterizes the sensitivity of the threshold to change in muscle length: the threshold decreases with muscle stretch when, for the flexor group, $d\theta/dt > 0$. Theoretically, μ correlates with the index of sensitivity changing from dynamic to static (positional) spindle afferents of the muscle (Fig. 1.0.5). As such, μ, may be controlled in part by the

activity of dynamic γ motor neurons. The parameter ρ defines the threshold changes of the muscle evoked by proprioceptive afferents from other muscles, including synergists and antagonists. Thus, in static, when $d\theta/dt = 0$, the threshold λ^* consists of two additional components (λ and ρ). If we assume that only afferent signals from active muscles can affect the threshold of the stretched muscle, ρ will equal 0 under conditions of muscle relaxation (Levin, 2000).

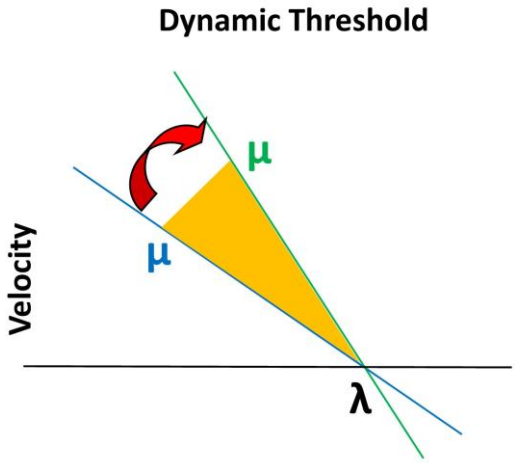

Figure 1.0.5. The coefficient μ represents the slope of the dynamic Activation Area boundary. It is influenced by the sensitivity of velocity-dependent receptors in muscle spindles, can be controlled directly by the CNS, and determines a temporal variation in the entry of the muscle into the activation area (it has the dimensions of time).

1.0.6 C and R commands

Further studies of the λ model aimed to get answers about how the CNS controlled coordination in different muscles. Earlier work suggested that agonist/antagonist activation was reciprocally organized (Sherrington, 1909). Later, Tilney and Pike (1925) proposed that muscle coordination depended primarily on the synchronous co-activation of opposing muscle groups. Movements requiring precision or performed at high speeds with heavy loads are characterized by some degree of co-contraction. On the other hand, reciprocal patterns of activation are more likely to accompany isometric contractions (Smith, 1981). Based on studies of rhythmic and discrete movements, Feldman (1980) concluded that patterns of reciprocal muscle activation and coactivation were not mutually exclusive but could be combined or overlapped in different proportions depending on the motor task. Empirical support for the existence of biological structures dedicated to the control of reciprocal muscle activation and co-activation comes from work in primates and humans. Overlapping regions of the precentral cortex have been shown to control these two types of muscle activation patterns in wrist movements (Humphrey and Reed, 1983). Specific areas of the cortex, cerebellum, and red nucleus may also be selectively activated in upper limb movements that require reciprocal movements

or co-activation. The central origin of reciprocal activation and co-activation has been reinforced by findings of common and reciprocal commands between motor units of antagonistic muscles during voluntary activation of the thumb flexors and extensors in humans. By integrating these physiological findings into the λ model, at least two central commands regulating agonist and antagonist muscle thresholds for single joint movement were defined. In other words, the control variable λ is subordinate to two higher-order central commands, one of reciprocity (R) and one of coactivation (C), that coordinate the regulation of λ of individual muscles. The dependence of λ on commands R and C does not preclude its consideration as a control variable, since it remains independent of peripheral events. The R and C commands can be specified independently of events occurring in the periphery. Physiologically, the R command combines facilitation of agonist motor neurons with inhibition (or de-facilitation) of antagonist motor neurons. The C command simultaneously facilitates motor neurons of both muscle groups. The R and C commands can be measured in terms of position variables. Isolately, the R command specifies the threshold angle (R) at which the transition between agonist and antagonist activity or vice versa occurs (Fig. 1.0.6). The C command specifies an angular range in which agonist and antagonist muscles can be simultaneously activated (co-activation zone) or silent (silent zone) if $C < 0$. The C command moves the λs in opposite directions. The larger the command, the wider the separation and the higher the agonist/antagonist co-activation. In order for no change in position to occur when a C command is applied, the λs should be shifted in such a way that equal and opposite torques are produced in the agonist and antagonist muscles (Fig. 1.0.6). To do this, the nervous system should take into account the length-tension characteristics of the muscle. Thus, changing the C command will not affect the existing EP of the system or the EP shifts evoked by the R command. Since it limits arm deflection by increasing joint stiffness, the C command affects the shifts in EP evoked by changes in external load. Control systems, in this way, distinguished between voluntary (the R command mediated EP displacements) and involuntary (load perturbations) reactions. With the descending command to the motor neurons held constant, deviation of the joint from the R position evoked active muscle torque, which tended to bring the joint back to the R position. If the external load was equal to 0, the arm returned to the R position, which in this case coincided with the equilibrium position, a component of the equilibrium point. If the load was not equal to 0, the EP resulted in the point of intersection between the invariant characteristic and the load. The trace of net joint torque produced by each muscle group to counteract external forces changed at the R angle, so control inputs to motor neurons could shift the R point and/or change the amplitude of the coactivation zone. In this scheme, μ remains a control variable by which the CNS

can specify the time of transition from one EP to another. Whether μ is specified individually for each muscle or globally for all muscles involved in the motor task remains unknown (Levin, 2000).

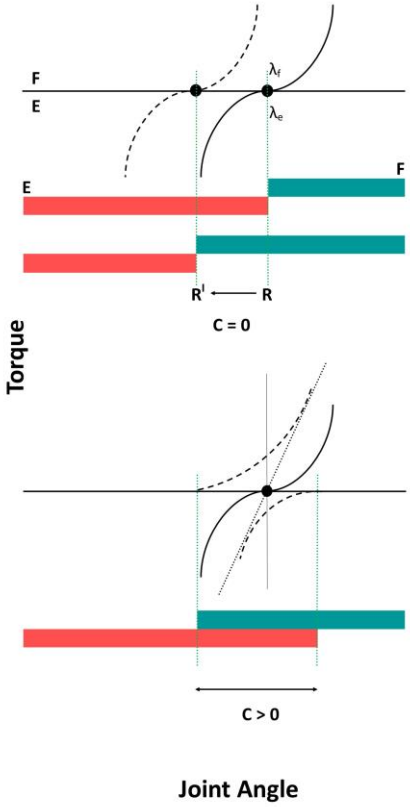

Figure 1.0.6. Motion production in the λ model. The R command (top panel) moves the thresholds of flexors (λf) and extensors (λe) and their associated invariant features in the same direction (R to R'). In this example, the C command is 0 and λf and λe coincide. The C command (bottom panel; C > 0) shifts λs in opposite directions creating an angular zone in which both flexor and extensor muscles are active. The horizontal bars below each panel represent the angular zones where flexor (green bars) and extensor (red bars) muscle activity is found.

Some significant experiments regarding the ability of the CNS to set up commands of co-activation and reciprocal activation and their role in the mechanisms of postural stability can be referred to the work of Levin and Dimov, "Spatial zones for muscle coactivation and the control of postural stability" of 1997. This paper reports the results of elbow joint unloading tests, performed using a torque motor machine connected to a manipulandum, starting from a 130° elbow extension position. The extent of unloading was calculated at 30% of the MVC and unloaded 2 Nm at a time until complete unloading. Participants were divided into two groups: a group of healthy adults and a group of chronic post-stroke hemiparetic patients. All subjects were instructed not to intervene during the test. The activity of agonist (biceps brachii and brachioradialis) and antagonist (triceps brachii and anconeus) poly and mono-articular muscles, velocity, torque, angular position, and oscillations were measured, so that toque/angle and velocity/angle graphs could be obtained. Functionally, the modified Ashworth scale (MAS) was administered for spasticity and the Fugl-Meyer for arm function. In healthy subjects it was observed that, during the test, the activity of the agonists decreased while that of the antagonists increased; in this way a zone of co-activation was specified and clearly visible on the torque/angle graph associated with the EMG tracings. In hemiparetic subjects, however, this zone was missing, replaced by a silent zone and a more marked number of abnormal oscillations in both EMG traces and velocity/angle graphs (Fig. 1.0.7).

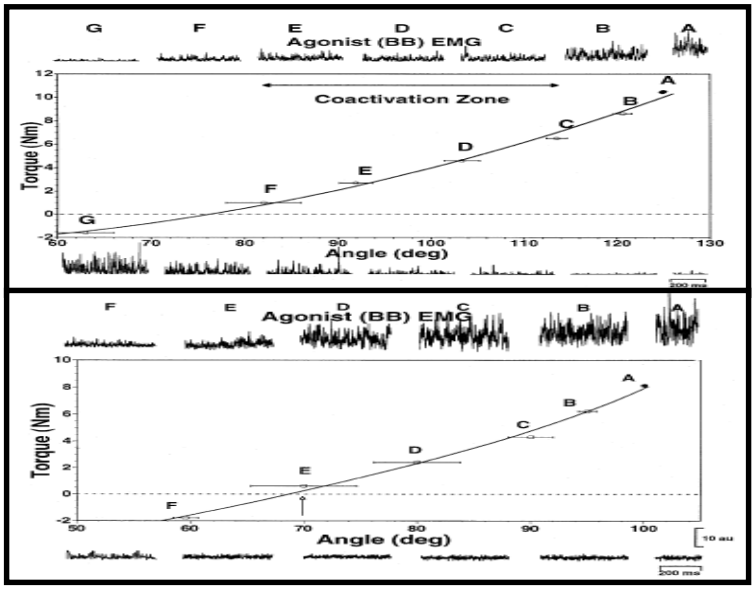

Figure 1.0.7. Torque/Angle and EMG characteristics of agonist and antagonist for each EP measured in the last 400 ms of each trial in healthy (upper panel) and hemiparetic (lower panel) subjects. In healthy subjects, agonist activity decreased while antagonist activity increased. The zone of co-activation is indicated by the double-headed arrow. In some hemiparetic subjects, no zone of co-activation is observed. (Levin and Dimov, 1997)

With these results, the authors demonstrated the invariant character of the R and C commands, which, through the specification of an area of spatial co-activation before movement (feed-forward mechanism) guaranteed adequate levels of stiffness in specific ranges and therefore postural stability. In the hemiparetic subjects, in fact, it was noted that, despite the preserved stiffness, the abnormal oscillations and the loss of co-activation zones, replaced by silent zones, the antagonist muscles did not provide adequate decelerations to reach the threshold of the extensors (uncontrolled extension) and the agonists could not brake the extension. All of this led to the picture of postural instability typical of the hemiplegic subject. (Levin and Dimov, 1997)

In a more recent study by Raptis et al. (2010), the duration of the R command, implied by fast changes in wrist position, was estimated by applying strong perturbations before the onset of movement in healthy adult subjects. It was shown that the displacement in the R command ended well before the peak velocity of the movement. The maximum displacement velocity of the R command was estimated to be 700°/s. Finally, the idea that the CNS directly programs EMG discharges was opposed in another study by Adamovich et al. in 1997. They found that perturbations before the onset of a movement gave rise to stretch reflex-dependent changes in the latency of even the first agonist discharge in the three-discharge pattern observed in the rapid movement of the single elbow joint. The possibility that the changes in latency could be due to voluntary triggered reactions was unlikely since these reactions, which occurred between 30 and 50 ms after perturbation, were below the minimum latency for the appearance of triggered reactions (70 ms). Thus, the finding that the onset of the first EMG activity was susceptible to changes in reflex feedback supported the central idea of the λ model that EMG discharges are not centrally programmed (Levin, 2000).

Furthermore, anticipatory control of movement allows for the prediction of errors before the end of the motor act itself. Experimental data and computer simulations have shown that the final value of the reference position of an arm performing fast movements is established essentially before the end of the movement, approximately when the speed reaches its peak. In this way, the next motor action, in a sequence of actions, can be initiated without waiting for the end of the motor output of the previous one, as happens for example when speaking quickly or playing the piano. Moreover, these control processes provide the system with the time necessary to predict whether the goal will be achieved, so that corrections can be made in time (Fig. 1.0.8). The feed-forward nature of threshold position control is a natural consequence of the integration of control and sensory inputs at the level of the motor neuron membrane (Feldman, 2010).

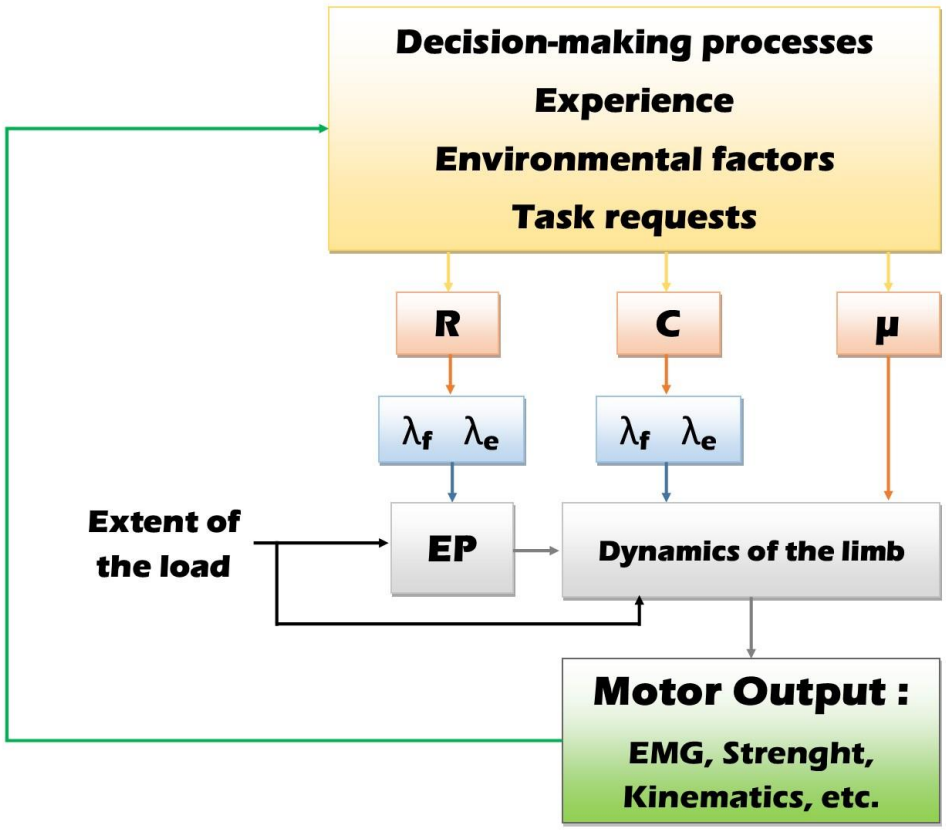

Figure 1.0.8 Schematic description of the causal chain of events during motion production of healthy subjects according to the λ model. Central commands (R, C, and μ) are specified according to decision processes and other factors listed in the yellow block. Once issued, these commands are executed independently of motor output until another decision is made. The R command affects the equilibrium point (EP) of the joint. EP shifts, as well as μ commands, affect the dynamics of the limb. System EPs and limb dynamics can depend on parameters related to load and gravity. Depending on the motor task, information regarding motor output may or may not be ignored by decision making.

1.0.7 Reference and current configurations: the "global" control of movement

In addition to local biomechanical and reflex factors that influence muscle activation, the nervous system can also use global factors to control all muscles in a consistent, task-specific manner. It was hypothesized that one of these factors was a virtual, or reference, R configuration of the body determined by muscle recruitment thresholds specified by various levels of neural control. Due to the threshold characteristic of the R configuration, the activity of each muscle will depend on the difference between the actual configuration (Q) of the body and its R configuration (Fig. 1.0.9). The nervous system modifies the R configuration to produce movement. This hypothesis implies that biomechanical, central, and afferent interactions between neuromuscular elements tend to minimize the difference between Q and R (principle of interaction minimization).
One prediction of this hypothesis is that the two configurations, Q and R, may meet each other, most likely in movements with changes of direction, producing as an effect a minimal peak in the level of electromyographic activity of the muscles involved. The magnitude of this minimal peak is relative

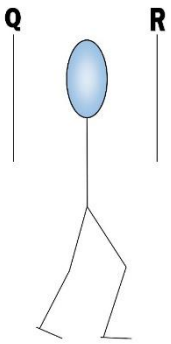

Figure 1.0.9. The specific form of the threshold position control is chosen depending on the desired action. A single step or a continuous path is produced by a discrete or continuous displacement of the reference position (R) of the body in space, respectively.

to the degree of co-activation of the opposing muscle groups. Another prediction is that the minimal EMG spike in the activity of multiple muscles may occur not only when the movement is assisted but also when it is opposed by external forces (e.g., gravity). These predictions have been confirmed for many movements such as jumping, marching in place, sitting-standing, head movements, and walking (Feldman et al., 2021). Feldman, in the 2010 review, reports the neurophysiological explanation for this type of hypothesis. He assumes that there is a group of neurons that receive visual signals regarding body position in the environment (body position neurons). Independent inputs directed to these neurons will be identified as producing changes in thresholds that shift the reference position (Rl) of the body in the environment. These neurons may or may not be activated, depending on the

difference between the actual position of the body in the environment and its reference position. Suppose further that the body position neurons control other neurons, called body configuration neurons, which, all together, receive composite afferent signals about the actual body configuration (Qc) and project the same to the motor neurons of all skeletal muscles. The signals from the body position neurons can be considered as independent of the afferent signals carried by the body configuration neurons. Thus, these independent signals can be identified as the cause of the change in reference configuration (Rc). At this configuration, all skeletal muscles, regardless of their biomechanical functions, will reach their activation threshold. Thus, by shifting the body's reference position in the environment, the system can cause changes in Rc and, consequently, in motor behaviors such as walking. Threshold positions can be defined for each body segment or for any combination of segments. Some data suggest the actual existence of body position neurons within the hippocampus of some animals. These neurons would be able to drive the central pattern generator (CPG) for locomotion by influencing the locomotor areas discovered by Shik and Orlovsky. With this, the CPG itself could likely be better understood as a producer of motor output, depending on the difference between the current position and the velocity-dependent reference position of the body. Another possible suggestion is that the mirror neurons themselves, which are activated in unison with observed actions, are related to body configuration neurons (Feldman, 2010). This view, while very reminiscent of the purely cognitivist theory of motor imagery, differs from it because, by specifying a threshold position, the brain predetermines where, in spatial coordinates, the neuromuscular elements will work but does not give instructions on how they should work: muscular activity and forces will emerge only if peripheral feedback indicates that the position of the segment (or body) will be within the specified spatial range. However, central changes in threshold position, per se, do not represent motor commands; in fact, they are named central commands or control variables. In this way, threshold position control represents a major departure from the conventional view that actions are the result of a pre-programmed pattern of motor commands (efferent copying) computed in accordance with the desired movement trajectory or other kinematic and kinetic characteristics. The nervous system is freed from the burden of pre-programming every variable characterizing motor output, including movement trajectories. The brain can influence, but not directly predetermine, EP since it is also influenced by external forces, which limit the nervous system's ability to control it (Feldman, 2010). The neural levels of control, therefore, will only set "where", within the spatial coordinates, the neuromuscular elements must work to produce an action. Specifically, these thresholds may be considered as parameters defining the origin of spatial frames of reference (FRs) in which muscles may be silent or recruited, depending on the difference between their respective real and reference positions. Other parameters that define, for example, the distance of the current

state of the system with respect to the origin, or parameters that define the orientation of a FR within another, can, in the same way, be controlled by the nervous system. Changes within these parameters will produce a change in motor neuron activity (actions). Just for this reason, these FR are called "producing action" or "physical" and they differ from the mathematical and formal FR for which a displacement of the origin modifies the description of the behavior of the system but not the behavior in itself. The number of FR can be enormous but they exist determined relations between them so that the entire series of FR can be compared to a tree with FR greater or stems and FR branches connected to the previous ones. The control levels can choose the most appropriate FR for the motor task (leading FR) and comparatively swap it quickly with another when the task demand changes, as demonstrated for pointing movements at with fixed and moving targets. Some novel motor tasks, however, may require the integration of sensory stimuli not found in available FRs so that new FRs should be formed during learning (Feldman, 2006).

The notion of referent control also affects the understanding of the role of reflexes in action and perception. In particular, central control of reflexes is usually interpreted as a modulation of gain (change in EMG response per unit of muscle stretch) or as reflex gating—phase dependent inhibition and facilitation of reflex pathways to α-MNs by central generators, as is often observed during locomotion. From these observations one could conclude that reflexes are suppressed at certain phases of motion. However, knowing that reflexes are controlled by shifting their spatial thresholds, one can conclude that afferent feedback (reafference) is not suppressed as such but is transferred to evolving body postures at which it remains fully functional. Reflex gating or changes in reflex gain can thus be considered as secondary, emergent effects of referent control manifested by changes in the spatial thresholds for muscle activation. Findings of afferent suppression at some phases of motion are therefore insufficient to claim the validity of EC-based schemes of motor control and active sensing. Theories of sensing based on prediction of sensory consequences of motor actions derived from computations with the help of internal models and optimality criteria should also be reexamined (Feldman, 2016). Motor learning may be associated with the ability of the nervous system to choose, memorise, reproduce and modify referent variables to meet the task demands. The system does not need to ‘‘learn” the force field – it learns how to adjust referent control

to reach the motor goal in the given force field without internal representation or modelling of the field. By considering reciprocal and coactivation influences on MNs of opposing muscle groups, Feldman et al. showed that there is specific hierarchy between these influences, although they can be used in isolation or in combination. Reciprocal influences (R command) pre-determine the position of body segments at which agonist and antagonist muscles can be coactivated. This is essential for understanding why, by coactivating agonist and antagonist muscles, the system can speed up, rather

than inhibit motion, as well as for the understanding of the relationship between posture and movement (Feldman et al., 2021).

1.1 Muscle tone disorders: evolution of the concept in light of threshold control theory

1.1.1 Muscle tone disorders in the context of EP theory

The most common definition of spasticity is that suggested by Lance: "a motor disorder characterized by a velocity-dependent increase in the tonic stretch reflex with exaggerated tendon response, resulting from hyperexcitability of the stretch reflex as a component of the first motor neuron syndrome" (Lance, 1980). Spasticity following a stroke is often predominantly found in a single muscle group of a joint and is related to changes in spinal and supraspinal excitability as well as intrinsic changes in muscle and/or reflex properties. Another muscle tone disorder, stiffness, often occurs in patients with Parkinson's disease or other causes and is characterized by increased resistance of antagonistic muscle pairs to externally imposed joint movements. Tendon responses and H reflexes are nearly normal in patients with Parkinsonism but low-latency EMG responses to small mechanical stimuli are suppressed. Previous studies provided observations that led to the idea that stiffness was not velocity-dependent but other studies demonstrated the influence of the velocity-dependent stretch reflex on it. Furthermore, long-latency stretch reflexes, bending reactions, and stretch-induced inhibition are involved in the genesis of both spasticity and rigidity, thus making it difficult to discriminate between the two disorders (Mullick et al., 2013).

The pathophysiology of spasticity and rigidity can be considered in relation to the basic principles of normal motor control. One of the main mechanisms in posture and movement control is the ability of segmental and descending systems to set and re-set the spatial threshold of reflexes (λ). Spasticity, in fact, is the outcome of a reduction in the central regulatory range of reflex thresholds - λ. Specifically, the threshold regulatory range in the healthy nervous system is defined by the task-specific ability to activate or relax muscles at each position within the biomechanical range of motion of the joint (Fig. 1.1.1). This leads to the argument that the range of threshold regulation is larger than the biomechanical range of motion of the joint and that, after neurological injury, the range of possible λ-shifts is limited, giving motor deficit as an effect. If, for example, the upper limit of the range of λ of the flexor muscles (R+) is within the biomechanical range of the joint, an externally imposed extension would find an active muscular resistance that would begin at length R+ and increase with increasing extension. This phenomenon is clinically defined as spasticity (Fig. 1.1.2). Another

important aspect is that the threshold λ decreases as the rate of muscle stretch increases (Levin et al., 2000). This, in the healthy subject, provides stability of posture and movement, helping to suppress and limit oscillations. Post-stroke patients, however, are hypersensitive to changes in velocity, which results in reduced stability of arm movement evoked by discharge perturbations (Mullick et al., 2013). Another study of Turpin et al (2017) showed that subjects with post-stroke spasticity retained some ability to modulate stretch-reflex behavior in elbow muscles and this ability was correlated with the level of upper limb motor impairment. The study also suggests that clinical spasticity, although evaluated at rest, may provide some information about the ability of subjects to regulate the SR threshold during active motion and an increase in TSRTs during active motion may result from the involvement of inhibitory mechanisms that are suppressed at rest. Finally, the study highlights the notion of the threshold position control theory that TSRT regulation, spasticity and movement disorders are coupled in a unified framework (Turpin et al., 2017).

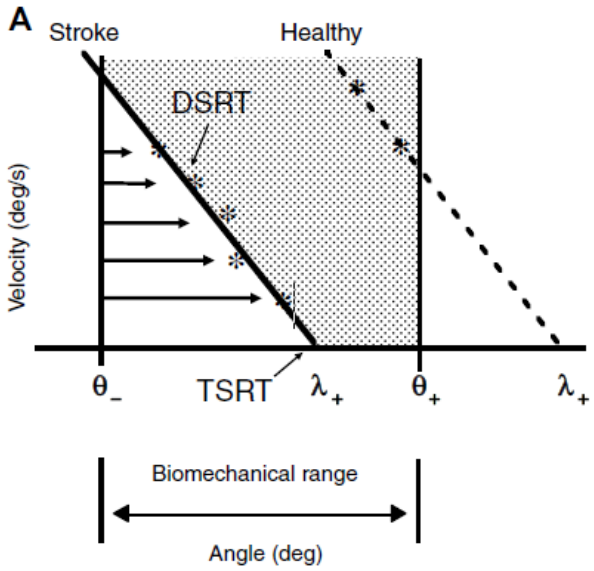

Figure 1.1.1. Dynamic stretch reflex thresholds (DSRTs or λ*) are the joint angles at which muscle recruitment begins at a given stretch rate. Stretches are repeated at different speeds. Higher velocities evoke reflex responses at lower joint angles. Linear regression between DSRTs is used to estimate the tonic stretch reflex threshold (TSRT or λ+) at zero velocity. In healthy subjects, TSRT lies outside the biomechanical range of the joint (double-headed arrow, θ-; θ+). In patients with stroke, TSRT may lie within the biomechanical range defining the joint angle at which spasticity begins to appear (Mullick et al., 2013).

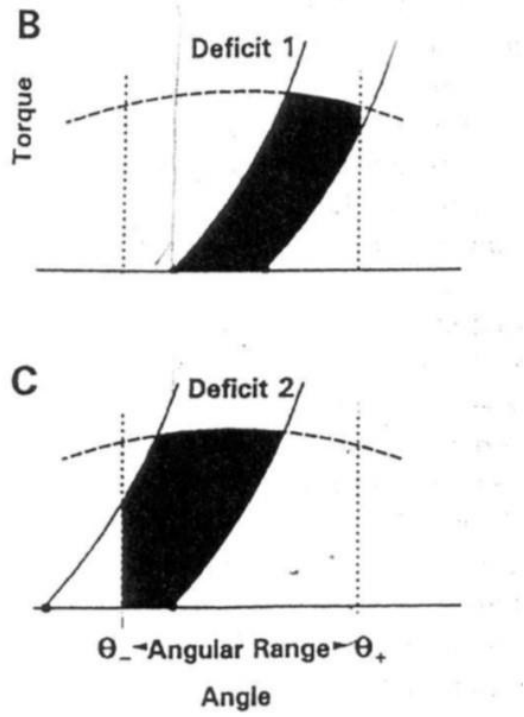

Figure 1.1.2. Working areas of hypotonic (upper panel) and hypertonic (lower panel) muscle. In hypotonia, the thresholds λmin and λmax are within the biomechanical range of the joint and the muscle fails to enter the activation area. In hypertonia, λmax < θmax and the muscle fails to relax (Mullick et al., 2013).

1.1.2 The EPH applied as a discriminator between spasticity and rigidity

There are many studies addressing these issues. Mullick et al. (2013), for example, in their work, use the measurement of the spatial threshold of the stretch reflex to discriminate between spasticity and rigidity.

The authors set out to test the hypothesis that the phenomenon of rigidity is also associated with a reduced range of central regulation of λ thresholds and/or their sensitivity to speed. The veracity of this hypothesis would then lead to the possibility of discrimination between rigidity and spasticity based on these deficits. Ten chronic post-stroke hemiparetic subjects (without relapses; at least 6 months prior), eleven with parkinsonism (Parkinson's disease and alternative parkinsonisms), and six healthy subjects were included in the study. Patients were clinically assessed by two rating scales: the Composite Spasticity Index (CSI) for post-stroke patients and the Unified Parkinson's Disease Rating Scale (UPDRS) for parkinsonian patients. Instrumental testing for λ limitations was performed on four muscles of the arm most affected by the tone disorder: brachioradialis, biceps brachii, anconeus, and triceps brachii. The arm was placed in a neutral position on a manipulandum connected to a torque-motor machine with the elbow in an initial 90° position. The machine produced elbow muscle stretches in the horizontal plane while the subject was asked to relax his or her muscles from the

beginning of the test, so that the maneuver would be totally passive. The stretches were performed at five different peak speeds, each of which was performed six times in random order for a total of thirty trials for each direction of stretch (from full flexion to full extension and vice versa). At the end, the elbow was slowly returned to its initial position by the experimenter. During the trials the EMG activity of the above muscles, angular position and velocity were recorded (using axial sensors inside the manipulandum). From these data it was possible to derive bell-shaped curves drawn on speed/angle phase diagrams. Through these, the dynamic threshold λ* was determined from which, by linear regression, the static threshold λ was obtained. λ*, moreover, provided the value of the sensitivity of the threshold to the speed of stretching, μ, calculated as the negative cotangent of the angle α, which, in turn, indicated the slope of the regression line. The study demonstrated that the velocity sensitivity of the dynamic threshold, μ, was high in poststroke subjects and close to zero, if not negative, in parkinsonian subjects. In addition, λ threshold values for flexor muscles were higher in the former than in the latter, whereas no particular differences between the two groups were noted in those of the extensor muscles. An 18.6% larger zone of hypertone was also found in parkinsonian subjects than in stroke subjects. The results showed, therefore, that spasticity and rigidity had common features but, at the same time, important differences in the regulation of λ. A common feature was that both types of hypertone were associated with a decrease in the range of central regulation of tonic λ, a factor that implied an inability to relax muscles in specific parts of the biomechanical range. However, limitations in the range of flexor muscles were more pronounced in parkinsonian compared with poststroke subjects, although clinical impressions regarding the amount of resistance to passive stretching were similar for both groups. Making a comparison with healthy subjects, thresholds were hypersensitive to the rate of muscle stretch in most subjects with spasticity while they were hyposensitive or even "inversely" sensitive in most Parkinsonian subjects with rigidity (Mullick et al., 2013).

These findings may have great clinical relevance, not only for their discriminating character between types of hypertone, but also for the measurement of muscle tone disorders since the "gold standards" in this field, to date, all refer to the quantification of the resistance felt when a muscle is passively stretched. These measurements have poor reliability and do not accurately reflect small changes in tone. Measurement of λ-thresholds is a method that provides data that is certainly more objective and takes into account the dependence of hypertone on speed. For a better overview, however, the author suggests combining the two types of measurements (Mullick et al., 2013).

1.1.3 The EPH applied for objective measurement of spasticity

Calota et al. (2008) addressed the issue of measuring spasticity in a study in which they compared the measurement of resistance to stretching (MAS scale) with the identification of the threshold of the tonic stretch reflex (TSRT, λ), carried out with a portable instrument. This instrument, consisting of a single-channel electromyograph, an electrogoniometer, and a portable computer, was named the "Montreal Spasticity Measure" device (MSMD) by the authors (Fig. 1.1.3). The aim of the study was to determine the inter- and intra-operator reliability of the device in measuring spasticity, understood as a limitation in the central regulation of TSRTs, and to determine any correlation between this measure and the measure of resistance to passive stretching provided by the MAS. Spasticity was assessed in 20 chronic poststroke subjects using the MSMD and MAS; all assessments were performed over 2 days by three physical therapists. EMG signals of the biceps brachii and elbow positions were recorded during twenty stretches applied at different speeds for each trial. In this way, velocity-dependent dynamic stretch reflex thresholds (DSRT, λ*) were recorded. These values were used by the instrument software to calculate TSRTs (thresholds at speed 0) by linear regression. Results showed that reliability was moderately good for subjects with moderate to severe spasticity and that the measurement of TSRT was not correlated in any way with that of passive stretch resistance. In conclusion, the MSMD provides a more representative measure of spasticity than the MAS, especially for cases in which the clinical symptom is classified as moderate or severe. The advantages of using such a device in the clinic are to be found, first of all, in its portability and ease of use in relation to the accuracy of the measurement it provides, then in the type of measurement itself, the machine takes into account the threshold joint angles and the speed of stretching, which fits more closely with the definition of spasticity of Lance, to date the most widely used (Calota et al., 2008).

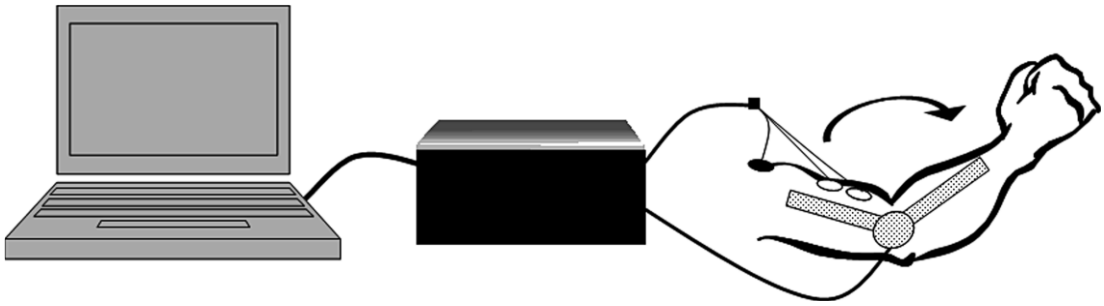

Figure 1.1.3. The portable "Montreal Spasticity Measure" (MSMD) instrument. The two active electrodes (white circles) are placed on the belly of the biceps brachii and the reference electrode (black circle) is placed on the acromion. The electrogoniometer is aligned with the individual's arm and forearm and secured to them using self-adhesive strips. The elbow flexors are manually stretched by the operator at different speeds to derive DSRTs. EMG signals and angular position data are collected (black box), transmitted to the computer, and displayed in real time. The TSRT is estimated by linear regression based on DSRT values. (Calota et al., 2008)

1.2 The Muscle Shortening Manoeuvre (MSM)

1.2.1 Functioning Mechanisms

Muscle Shortening Manoeuvre (MSM) is a physiotherapy rehabilitation technique developed by Professor Luigi Grimaldi (Grimaldi et al., 1986); this manoeuvre consists of subjecting a target muscle to shortening and simultaneous stress in traction and is aimed at pathological pictures that are only apparently distant (central neurolesions, peripheral neurolesions having the character of partiality, more properly orthopaedic lesions).

What they have in common is the need to therapeutically recover muscle strength by emphasising the role of the nervous system in its development. The development of strength mediated by muscle hypertrophy is of no interest here, nor are the effects of so-called strength training on muscle structures of any relevance. Ultimately, short-term changes in strength are induced by neural adaptations, which are the target of this procedure.

The MSM is based on three elements:

- length variation
- tension variation
- external load or tensile stress

It aims at recovering the ability to voluntarily and permanently evoke muscle units that, before the maneuver, did not show activity. The target muscular unit undergoes a double action: it is subjected to an increasing traction stress which, in order to be balanced, requires the muscular unit to develop an increasingly higher internal force; it is simultaneously shortened so that it tends to lose tension. The system is in a critical situation because it cannot solve the perception problem. To overcome this situation it must create a new constraint, i.e. to set a different TSRT. The presupposition of the MSM is, therefore, to create a situation of catastrophe, of informational crisis in the system, in order to force it to project new essential variables, i.e. to create new constraints. During the MSM, the system finds itself in a critical situation because there is no correspondence between the force developed and the actual length. In order to overcome the problem it has to create a new constraint or find a new TSRT. In this way, the aim to obtain the evocation of absent motor components is pursued. The new kinematic configuration must be energetically more advantageous than the previous one, otherwise it will be reabsorbed by the system itself. This type of exercise aims to give the muscle the possibility to contract with a non-stereotyped behavior.

Another element to consider is the acceleration that is always impressed on the system. The greater inertia of the system caused by the increase of mass by means of the use of weights opposes the movement, requiring more driving force to maintain the same acceleration. To impose higher accelerations only means to overcome a possible greater inertia by imposing a greater force.

The inhomogeneous muscular behavior causes sarcomeres of different stiffness and viscosity to accelerate in different times and ways. It is hypothesized that this microscopic dynamics results in excitation of neuromuscular spindles with consequent activation of the stretch reflex and creation of action potentials in the muscle.

In addition to analyzing the therapeutic manoeuvre with kinematics variables, it is possible to observe the phenomenon through the dynamics of oscillations. Applying a sinusoidal force to a body segment, as it happens with the use of a flexible element, makes it possible to analyze the motion in terms of frequency and amplitude of oscillations.

Even if the force is applied in pulses, it is still possible to analyze it in these terms. Oscillations of the whole system can induce internal oscillations in the muscle, which is considered a viscoelastic system with a high damping coefficient. The frequency of oscillations depends on the internal damping of the system: if damping increases, the frequency decreases.

The frequency of the exciting force is important because it determines the possibility of energy transfer to the system to which it is applied.

The energy transfer (acceleration) during the therapeutic manoeuvre is important both for muscle shortening and for realizing the traction stress. Maximum energy transfer occurs when the frequency of the excitatory force is equal to the natural frequency of the elastic system (resonance frequency).
Tensile stress can be achieved in several ways: tensile springs, energy increase (gravity, mass, mass per radius squared), acceleration acting on the muscle anisotropy. All this results in tissue deformation, either due to inhomogeneous muscle behavior or, and more markedly, pre-shortening muscle stretch.
Tissue deformation causes spindle stimulation with the consequent recruitment of motor units and the attempt to produce tension. It is at this point that the critical factor in the temporal relationship comes into play: the importance of the speed of muscle shortening. Since from the receptor stimulation to the EMG activity there is a delay of about 40 - 50 ms and from the EMG activity to the development of tension (electromechanical delay) another 70 - 80 ms, there is sufficient time to prevent the development of tension, given the fast shortening of the muscle caused by the therapeutic protocol.
It should also be taken into account that from the beginning of development to the maximum expression of force, 200 to 300 ms can elapse, which is a sufficiently long time to prevent the development of tension.
Muscle shortening is followed by a decoupling between the discharge of length receptors and tension receptors, an information gap. The maneuver creates a break in symmetry, it affects invariant relationships by disturbing information and making perception possible. Therefore, it involves a decrease in the stability of the function and an increase in the dissipation of energy for which the CNS feels an urgent need to intervene by arranging a new TSRT. This organization causes a process of synaptic rearrangement and can occur over a period of several minutes (Sanes and Donoghue, 1993). The consequence of this process leads to short-term force modifications induced by neuronal adaptation.
The ability to counteract the perturbation-deformation through the commensurate development of muscle tension (stability) is thus reestablished. In other words, the Equilibrium Point Hypothesis (EPH) assumes that, for a given control signal, the motor performance (whatever it is) is characterized by an invariant relationship between internal muscle forces and external forces.
This relationship remains invariant throughout a series of transformations, or perturbations, until a critical perturbation elides the invariance and creates the conditions for a new stability. In the case of the maneuver of shortening and traction stress, the relational invariance is lost because the induced traction (increase in muscle length) is not compensated by the development of muscle strength

(sudden muscle shortening), so that the relationship between the forces involved remains invariant (Grimaldi et al., 1986).

1.2.2 Practical application of MSM

MSM consists of passively mobilizing specific body segments to elongate and shorten target muscle groups. The body segment to be passively mobilized is made to oscillate through a series of elastic elements at a frequency between 1 and 3 Hz. Summarizing, some application principles of MSM are:

- It was created for neurological patients but can be applied to different pathologies with different etiopathogenesis.
- The only real contraindication is the presence of muscle-tendon retractions and/or joint ankylosis
- It can also be performed on patients with pain or functional limitations; it is sufficient to always work under threshold (pain, joint range, etc.)
- Can be applied to all muscle groups and in multiple kinematic contexts
- The proposed execution time is between 10 and 20 minutes
- A correct solicitation requires a stimulation frequency of 1-3 Hz

The necessary tools to be used in order to promote traction stress, are:

- Flexible rods
- Support springs
- Weights
- Pulleys

These are intended to promote traction stress. Once the target muscle has been identified, the flexible rod is attached to the body segment to be mobilized (Figure 1.2.1). This muscle will be shortened by the physiotherapist through oscillations (acceleration and deceleration). The stress is done along the entire range of motion that can be used but in successive steps. The spring is fixed on the opposite side of the flexible rod and has the purpose of exerting resistance and promoting traction stress. For some exercises the use of pulleys is foreseen, to which the springs are fixed, replacing the flexible rods in the logic of the exercise (Figure 1.2.1). The spring is applied in such a way as to ensure a good lever arm in traction. When the muscle is shortened, the progressive traction force exerted by the spring causes part of the external force to act in a coacting sense on the joint, while the presence of

the rod or pulley ensures that the force is not discharged on a periphery that is too rigid. The flexible rod favors the creation of radial and tangential accelerations, the latter able to act on the muscle deforming it and determining a shortening reaction. The transfer of the optimal amount of energy to the muscle occurs when the imposed acceleration is at the same resonance frequency as the internal system. The resonance frequency is directly proportional to the coefficient of elasticity (stiffness) of the system and inversely proportional to its inertia. With the external elements (rod, springs, weights) it's possible to act on the stiffness or inertia of the system to modify its resonance frequency so that the imposed accelerations obtain the transfer of the optimal share of energy to obtain the best possible results. An important feature of MSM is that it gives objective feedback of the results obtained immediately after the application of the exercise.

It is therefore very important to carry out functional assessment both before and after the exercise, as this allows you to see whether movements that have appeared at the segmental level fit into the system and are able to modify function (e.g. walking).

Figure 1.2.1. Applications of Muscle Shortening Manoeuvre on different muscle groups: a) trunk flexors; b) knee extensors; c) ankle plantar flexors; d) shoulder adductors.

Chapter 2. Experimental Evidences

2.0 Aim of the thesis

MSM is widely used in clinical practice but with little scientific evidence (Ferrarello et al., 2021). The aim of the thesis is to investigate the neurophysiological mechanisms underlying it.

With these assumptions an intervention study on patients with chronic stroke in which, through the use of a portable device, it has been possible to use the TSRTs as an objective outcome measure, has been designed. In order to test this protocol and before embarking on a real randomized clinical trial, a pilot study was performed.

In the meanwhile a retrospective analysis which led to a re-elaboration of data obtained in the recent past was conducted (Longo et al., 2021). In particular, in a case series of 9 subjects with infantile cerebral palsy, the evaluation of objective outcomes (muscle strength, range of motion) is found for the first time in relation to functional outcomes measured by scales (Selective Motor Control Scale, Physician Rating Scale).

The effects of the maneuver were also investigated in terms of pure electromyographic activity in a pediatric patient with post-surgical peroneal nerve resection.

Furthermore, the literature on MSM shows the possible effects of this type of treatment also on orthopedic injuries. In particular, two articles by Melchiorre et al. (2014, 2018) showed that this type of intervention seems effective on patients with Shoulder Impingement Syndrome (SIS) in terms of morpho-structural changes in the musculotendinous compartment of the joint, detectable by ultrasound, and of increased strength and pain relief. This protocol was selected for the design and execution of a study on subjects with SIS from a population that practices an overhead sport, water polo (Longo et al., 2022).

2.1 The muscle shortening manoeuvre: applicability and preliminary evaluation in children with hemiplegic cerebral palsy: a retrospective analysis

Therapeutic interventions for children with cerebral palsy (CP) embrace the extent of the International Classification of Functioning, Disability and Health (ICF), aiming at addressing body function/structure deficits, minimize activity limitations, and encourage participation (Morgan et al., 2016). Several physiotherapy interventions, such as strengthening, task-specific practice, and mobility training, to name a few, have been shown to be effective in improving motor ability (Novak et al., 2020).
The aim of this retrospective analysis was to describe the applicability and estimate the effect of MSM applied to improve motor weakness and joint excursion of the ankle in children with hemiplegia due to CP.

2.1.1 Methods

This study analysed de-identified data from 9 children with hemiplegic CP, who were referred to local health authority outpatient rehabilitation services (February to June 2009). Parents provided written informed consent, including consent for data extraction from chart review, and eventual dissemination through publication. Children gave informed oral assent before the intervention was administered. The procedures were in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

2.1.1.1 Participants

The participants' age ranged from 8 to 12 years, and the children were able to walk independently without assistive devices. None of them had undergone orthopaedic surgery within the previous 12 months or botulinum toxin therapy within the previous 6 months. They did not take anti-spastic medications, and did not have dyskinesia, dystonia, severe muscle contractures, or other relevant comorbidities. The children did not participate in any other rehabilitation intervention during the follow-up period.

2.1.1.2 Intervention

A mechanical device was used to perform repetitive passive mobilization of the ankle (Fig. 2.1.1). The device comprises 3 rectangular parallel platforms. The horizontal axis of movement of the platforms coincides with the projection of the ankle transverse axis, thus isolated dorsal and

plantarflexion movements can be performed during mobilization. An accelerometer (PCE Inc., (Southampton, UK) MSR 145S, sampling rate 50 points/s) positioned on one end of the device's axis records the frequency and excursion of the oscillations. The other end of the axis is connected to a perpendicular lever arm. Two weights and 2 springs have been placed at the lever arm upper extremity. One of the springs is connected to a tensioning rod; the therapist acts on the other spring by means of a handle and small arm movements, thus inducing oscillations of the platform at the desired amplitude and frequency (Fig. 2.1.1). The subject was seated on a chair with the hip and knee joint at 90° of flexion. Cushions were utilized to adjust the height of the seat. The plegic foot was positioned on the moving platform, on a foam layer. Velcro strips prevented the foot from slipping.
Three, 20-min dorsal and plantarflexion mobilization sessions were administered by means of the device, at a frequency of 1.5 Hz. The child was invited to sit quietly, relax, avoid any voluntary movement, and let the therapist move their foot. The child was asked to focus attention on the ankle, they were also allowed to talk with parents (or relatives) or browse/read a book.
The therapist induced a joint excursion from 20° of dorsiflexion to 20° of plantarflexion. The intervention was individually administered for one week, every other day, face-to-face in paediatric settings, by trained physiotherapists.

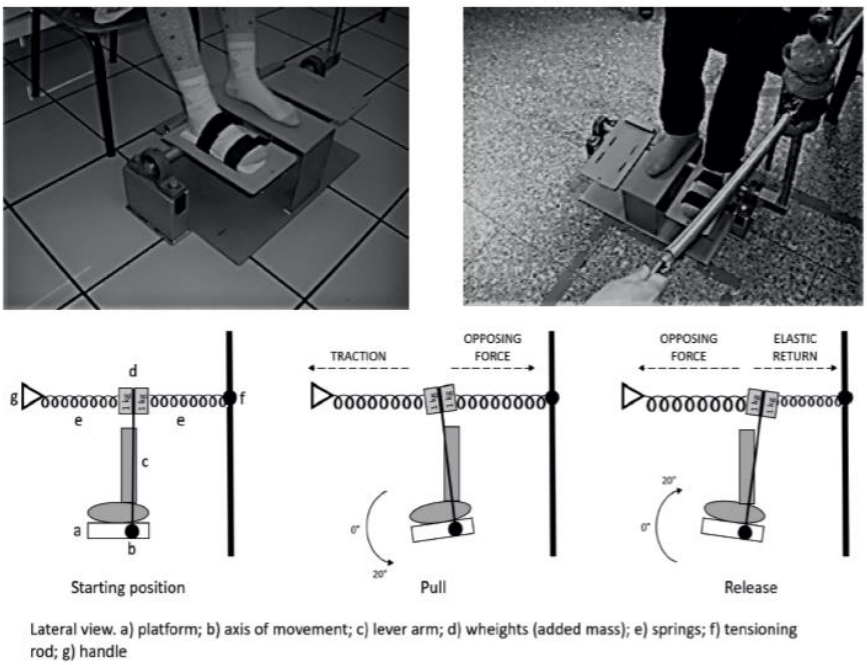

Figure 2.1.1. Mechanical set-up of the device. Alternating pull and release induce oscillations of the platform, producing relative muscle lengthening followed by sudden shortening of ankle dors iand plantar-flexor muscles. The fast accelerations are applied while the ankle is subjected to a force acting in the opposite direction (tensile stress).

2.1.1.3 Outcome measures

Muscle strength, passive and active range of motion (PROM and AROM) were assessed before the first treatment session (baseline, T0), at the end of the 1st, 2nd, and 3rd sessions (T1, T2, and T3, respectively), and one week after the 3rd session (follow-up, T4). The strength of the ankle dorsal and plantar flexor muscles was measured with a digital handheld dynamometer (in kg) (Weiheng Portable Electronic Scale; Guangzhou Weiheng Electronics Co., Ltd, Guangdong, China). Three joint angles were considered (neutral ankle position 0°, plantarflexion 20° and 40°). Three tests per-angle were performed, for the assessment that was considered the best result. Ankle excursion was measured with a manual goniometer, computing from maximum dorsiflexion to maximum plantarflexion and vice versa. The AROM was evaluated by applying minimal manual resistance.
The minimal detectable change (MDC95) has been estimated in children with CP for plantar flexors strength (0.211 kg) and dorsiflexion excursion (7.94°) (Willemse et al., 2013; Kim et al., 2018). The Selective Motor Control scale (SMC) (Boyd and Graham, 1999) and the modified Physician Rating Scale (PRS) (Koman et al., 1994) were administered at T0 and T3. The SMC was designed to assess the ability to voluntarily control the dorsiflexors; it ranges from 0 (no intentional movement) to 4 (intentional movement throughout the available range of motion) (Boyd and Graham, 1999). The PRS is an observational gait assessment tool; the score ranges from –2 (poor) to 22 (normal) per limb (Koman et al., 1994). Children were videotaped according to a protocol; the recordings were analysed offline. The intervention progression and assessment procedure are shown in Table 2.1.1.

Table 2.1.1. Intervention progression and assessment procedure

Intervention				
Day 1		Day 2	Day 3	Day 4
T0	T1	T2	T3	T4
Start	Queued at T0	2 days after T1	2 days after T2	7 days after T3, end
Parents' written informed consent and children informed oral assent	Administration of the intervention, session 1	Administration of the intervention, session 2	Administration of the intervention, session 3	Follow-up
Assessment				
Baseline	End of session	End of session	End of the intervention	Follow-up
Demographic characteristics	Muscle strength	Muscle strength	SMC scale	Muscle strength
SMC scale	Passive ROM	Passive ROM	Muscle strength	Passive ROM
Muscle strength	Active ROM	Active ROM	Passive ROM	Active ROM
Passive ROM			Active ROM	
Active ROM			Gait videotaping*	
Gait videotaping*				

*Offline analysis, modified Physician Rating Scale. ROM: range of motion; SMC: selective motor control.

2.1.1.4 Statistical analysis

Descriptive statistics were performed to analyse demographic, clinical, and outcome data. Friedman's test was used to analyse variation in muscle strength and range of motion. In case of significant results, post hoc tests were performed (Dunn's test). The Hodges-Lehmann estimator was used to estimate the 95% confidence intervals (95% CIs) of the median differences. Data on plantar flexors strength and dorsiflexion excursion were further analysed by plotting the median of the differences (95% CI) and the range of random measurement error (i.e. the interval between the ±MDC95 values); MDC95 proportions representing the children showing an improvement in performance (i.e. equal to or greater than the absolute values of the MDC95) were also calculated. Fisher's exact test was used to investigate variation in SMC score. Change in PRS scores was examined using the Wilcoxon signed-rank test. IBM SPSS Statistics for Windows (version 20.0; IBM Corp, Armonk, NY, USA) was utilized for calculations. The significance level was set at $p < 0.05$.

2.1.2 Results

Demographic, clinical, and outcome data are shown in Table 2.1.2. Friedman's tests showed significant differences between the assessments (Table 2.1.3). The median increase in muscle strength, PROM, and AROM are shown in Fig. 2.1.2 and Fig. 2.1.3. Dunn's post hoc tests showed significant improvements at T2, T3 and T4 (Table 2.1.3). For plantar flexors strength, analysis based on MDC95 showed partial overlapping of the 95% CIs at T1 and, in one case, at T4 (Fig. 2.1.2). The proportion of children showing an improvement in performance were 44–67–44% at T1, 100– 89–78% at T2, 100–100–89% at T3, and 100–100–67% at T4 (Fig. 2.1.2). In PROM and AROM analysis overlapping of the 95% CIs was observed across assessments (Fig. 2.1.3); the proportions of children showing improvements were 56–89% (PROM) and 56–78% (AROM) (Fig. 2.1.3).
No differences were observed between SMC scores at T0 and T3 (Fisher's exact test = 9.579, $p = 0.071$). Improvement in PRS scores was observed at T3 ($Z = 2.536$, $p = 0.011$; Hodges-Lehmann estimator 4.0, 95% CI 2.0/6.0).

Table 2.1.2. Demographic, clinical, and outcome data

Child ID	Sex	Age, years	Affected side		SMC	PRS	DF-S[a] np 0°	DF-S[a] pf 20°	DF-S[a] pf 40°	PF-S[a] np 0°	PF-S[a] pf 20°	PF-S[a] pf 40°	PROM[b]	AROM[b]
1	M	8	Right	T0	1	27	0.78	1.02	0.80	0.78	0.62	0.68	40	20
				T1			1.26	1.18	1.04	0.86	0.82	0.74	45	35
				T2			1.68	2.26	2.30	2.16	1.66	1.84	55	45
				T3	2	30	2.52	2.10	2.14	2.46	1.96	1.92	55	45
				T4			2.38	2.02	2.14	2.12	1.78	1.94	55	45
2	F	8	Left	T0	1	26	0.98	1.14	1.26	0.98	0.82	0.96	35	25
				T1			1.08	1.24	1.54	1.18	1.18	1.16	45	25
				T2			1.18	1.22	1.38	1.98	1.72	1.26	50	30
				T3	2	28	1.28	1.70	1.48	2.20	1.86	1.26	50	30
				T4			1.16	1.50	1.28	2.06	1.74	1.16	50	30
3	F	8	Right	T0	0	17	0.40	0.42	0.34	0.30	0.42	0.36	45	40
				T1			0.62	0.62	0.48	0.38	0.50	0.46	55	40
				T2			0.54	0.48	0.48	0.70	0.68	0.44	55	40
				T3	1	17	0.56	0.50	0.52	0.73	0.76	0.55	55	40
				T4			0.54	0.48	0.46	0.70	0.68	0.44	55	40
4	F	8	Right	T0	1	30	0.40	0.54	0.34	0.68	0.48	0.52	25	15
				T1			0.64	1.02	0.74	1.16	1.16	1.16	35	20
				T2			1.48	1.48	1.86	1.82	1.44	1.44	50	30
				T3	2	32	1.46	1.50	1.84	1.82	1.52	1.42	50	35
				T4			1.36	1.32	1.68	1.38	1.26	1.30	50	35
5	M	10	Right	T0	2	24	0.92	1.12	1.25	1.02	0.90	1.08	40	25
				T1			1.30	1.32	1.50	1.78	1.42	1.46	50	40
				T2			1.36	1.52	1.48	1.38	1.26	1.44	50	40
				T3	2	26	1.28	1.70	1.56	1.46	1.68	1.74	50	40
				T4			1.26	1.52	1.50	1.38	1.64	1.63	50	40
6	F	8	Left	T0	1	18	0.68	0.48	0.52	0.84	0.60	0.84	40	25
				T1			0.86	0.96	1.26	0.92	1.18	1.04	50	40
				T2			1.02	1.12	1.60	1.16	1.40	1.18	55	40
				T3	2	26	1.32	1.16	1.28	1.14	1.26	1.32	55	40
				T4			1.30	1.20	1.28	1.16	1.28	1.30	55	40
7	F	12	Right	T0	2	15	0.90	1.02	1.16	0.64	0.54	0.61	40	15
				T1			1.20	1.48	1.60	1.18	0.92	0.88	40	25
				T2			1.44	1.86	1.78	1.28	1.12	1.08	50	40
				T3	3	24	1.98	1.86	1.78	1.64	1.12	1.14	50	45
				T4			1.90	1.86	1.80	1.60	1.20	1.18	50	45
8	M	12	Left	T0	2	23	1.08	0.94	1.06	0.94	0.96	1.14	30	0
				T1			1.08	1.06	1.06	1.26	1.14	1.24	30	15
				T2			1.50	1.20	1.18	1.44	1.24	1.26	30	20
				T3	3	26	1.51	1.78	1.34	1.82	1.60	1.52	30	30
				T4			1.50	1.68	1.12	1.44	1.66	1.26	30	30
9	M	8	Right	T0	3	20	0.80	0.96	0.88	1.04	0.98	0.97	50	35
				T1			1.14	1.14	1.04	1.18	1.34	1.26	55	30
				T2			1.20	1.22	1.36	1.36	1.78	1.60	55	35
				T3	2	27	1.70	1.25	1.46	2.26	2.30	2.44	60	45
				T4			2.14	2.04	2.36	2.04	1.98	2.40	60	45
Summary measures[c]	F 55%	8 (8, 12)	Right 66%	T0	1 (0–3)	23 (15–30)	0.80 (0.40–1.08)	0.96 (0.42–1.14)	0.88 (0.30–1.30)	0.84 (0.30–1.04)	0.62 (0.42–0.98)	0.84 (0.36–1.14)	40 (25–50)	25 (0–40)
				T1			1.08 (0.62–1.30)	1.14 (0.62–1.48)	1.06 (0.48–1.60)	1.18 (0.38–1.78)	1.16 (0.50–1.42)	1.16 (0.46–1.46)	45 (30–55)	30 (15–40)
				T2			1.36 (0.54–1.68)	1.22 (0.48–2.26)	1.48 (0.50–2.30)	1.38 (0.70–2.16)	1.40 (0.68–1.78)	1.26 (0.44–1.84)	50 (30–55)	40 (20–45)
				T3	2 (1–3)	26 (17–32)	1.46 (0.56–2.52)	1.70 (0.50–2.10)	1.48 (0.52–2.14)	1.82 (0.76–2.46)	1.66 (0.76–2.30)	1.42 (0.55–2.44)	50 (30–60)	40 (30–45)
				T4			1.36 (0.54–2.38)	1.52 (0.48–2.04)	1.50 (0.46–2.36)	1.44 (0.70–2.12)	1.64 (0.68–1.98)	1.30 (0.44–2.40)	50 (3–60)	40 (30–45)

[a]kg; [b]degrees; c% or median (minimum–maximum). AROM: active range of motion; DF-S: dorsiflexors' strength; F: female; M: male; np: neutral position; pf: plantar flexion; PF-S: plantar flexors' strength; PROM: passive range of motion; PRS: Physician Rating Scale; SMC: Selective Motor Control scale.

Table 2.1.3. Friedman's tests and post hoc analysis results

			T1		T2 vs T0			T3 vs T0			T4 vs T0		
Variable	Friedman test	*p*-value	Dunn test	*p*-value[a]	Dunn test	H-L estimator	*p*-value[a]	Dunn test	H-L estimator	*p*-value[a]	Dunn test	H-L estimator	*p*-value[a]
DF-Sb np 0°	24.249	>0.001*	1.444	>0.30	2.500	0.440 (0.270/0.750)	0.008*	3.389	0.690 (0.330/1.085)	>0.001*	2.389	0.710 (0.280/1.170)	0.014**
DF-Sb pf 20°	26.483	>0.001*	1.444	>0.30	2.333	0.510 (0.170/0.890)	0.017**	3.444	0.685 (0.380/0.900)	>0.001*	2.778	0.720 (0.390/0.920)	0.002*
DF-Sb pf 40°	22.529	>0.001*	1.556	>0.30	2.722	0.610 (0.140/1.080)	0.003*	3.111	0.580 (0.250/1.050)	>0.001*	2.333	0.530 (0.060/1.050)	0.017**
PF-Sb np 0°	28.137	>0.001*	1.333	>0.30	2.500	0.660 (0.360/1.010)	0.008*	3.611	0.940 (0.460/1.280)	>0.001*	2.556	0.720 (0.400/1.040)	0.006*
PF-Sb pf 20°	30.463	>0.001*	1.111	>0.30	2.333	0.650 (0.360/0.920)	0.017**	3.556	0.850 (0.580/1.180)	>0.001*	3.000	0.760 (0.520/0.960)	0.001*
PF-Sb pf 40°	27.864	>0.001*	1.389	>0.30	2.278	0.465 (0.210/0.775)	0.022**	3.611	0.640 (0.340/1.065)	>0.001*	2.722	0.560 (0.200/1.000)	0.003*
PROM[C]	27.897	>0.001*	1.167	>0.30	2.333	12.5 (7.5/17.5)	0.017**	2.556	12.5 (7.5/17.5)	0.006*	2.556	12.5 (7.5/17.5)	0.006*
AROM[C]	26.045	>0.001*	0.611	>0.30	1.778		0.171	2.556	17.5 (7.5/25.0)	0.006*	2.556	17.5 (7.5/25.0)	0.006*

*$p > 0.010$, **$p > 0.050$. [a]After Bonferroni adjustments; [b]kg; [c]degrees.
AROM: active range of motion; DF-S: dorsiflexors' strength; F: female; H-L: Hodges-Lehmann, values are median of the score differences (95% confidence intervals; 95% CI); M: male; np: neutral position; pf: plantar flexion; PF-S: plantar flexors' strength; PROM: passive range of motion.

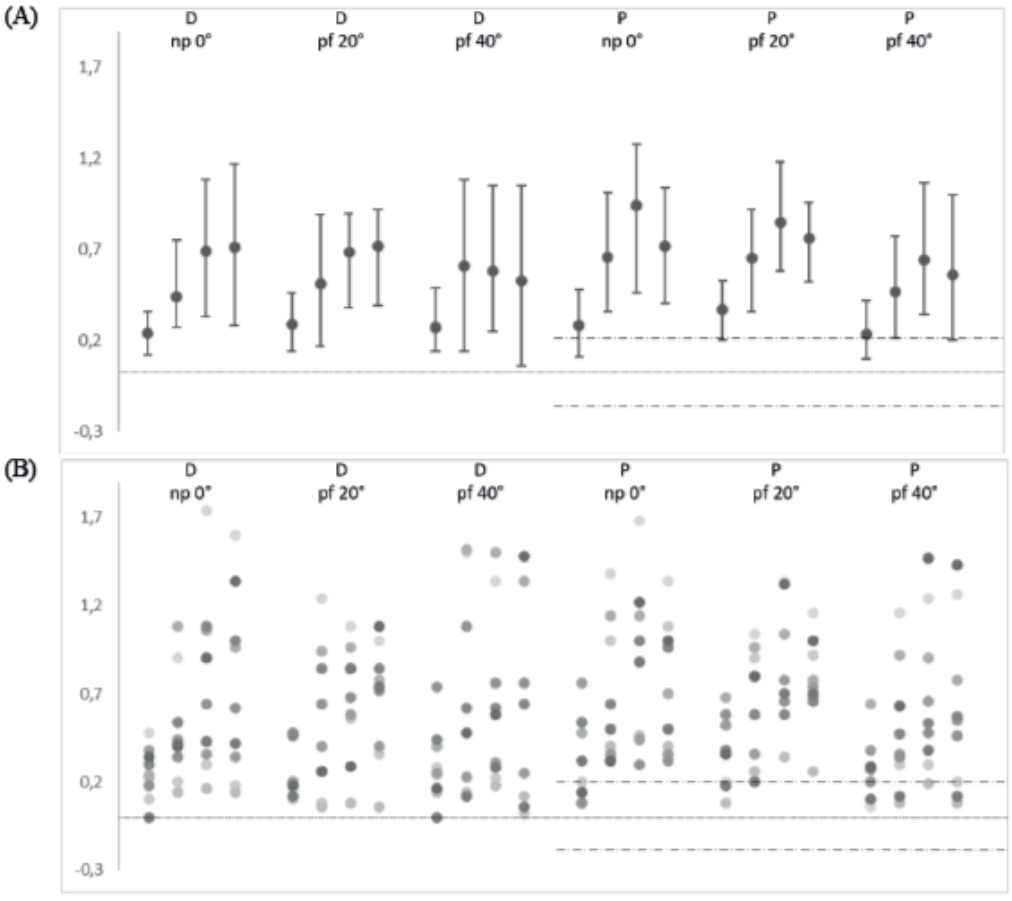

Figure 2.1.2. Change in muscle strength. (A) From left to right: median of the differences (kilograms) between T0 and T1, T0 and T2, T0 and T3, and T0 and T4 for each of the joint angle tested, respectively. The error bars represent the 95% confidence interval. (B) From left to right: individual differences (kilograms) between T0 and T1, T0 and T2, T0 and T3, and T0 and T4 for each of the joint angle tested, respectively. The horizontal lines indicate a difference of 0 and, only for plantar flexor strength, the ±MDC95 values. D: Dorsiflexor; np: neutral position; P: plantar flexor; pf: plantarflexion.

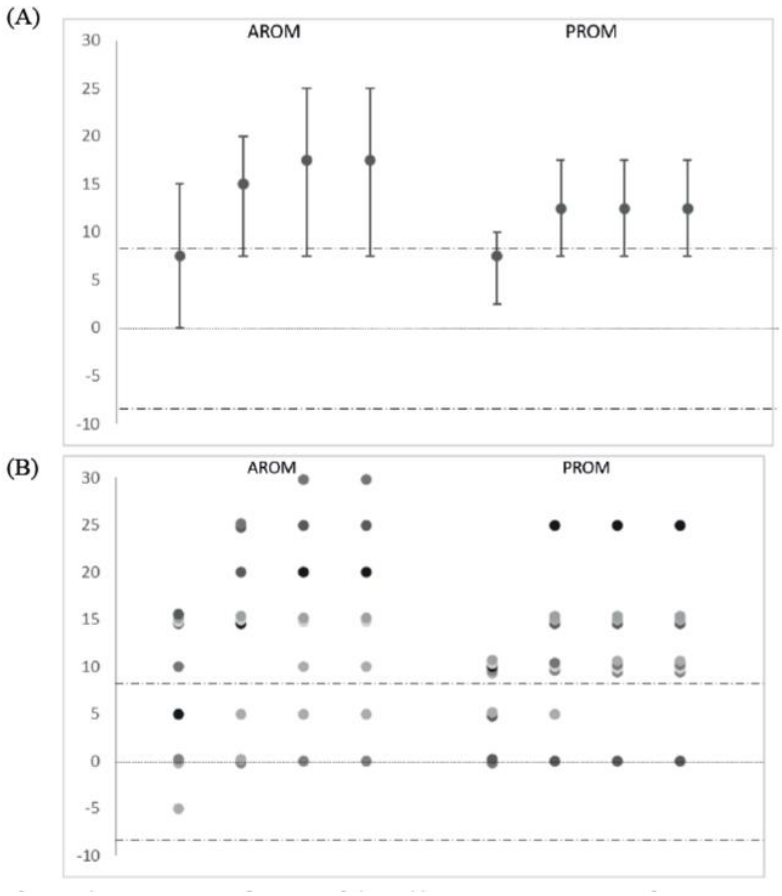

Figure 2.1.3. Change in range of motion of the ankle. AROM: active range of motion; PROM: passive range of motion. (A) From left to right: median of the differences (degrees) between T0 and T1, T0 and T2, T0 and T3, and T0 and T4. The error bars represent the 95% confidence interval. (B) From left to right: individual differences (degrees) between T0 and T1, T0 and T2, T0 and T3, and T0 and T4. The horizontal lines indicate a difference of 0 and the ±MDC95 values. AROM: active range of motion; PROM: passive range of motion.

2.1.3 Discussion

This is the first report to describe the applicability of the MSM in children affected by CP. The intervention was administered in accordance with the study protocol and no adverse events were observed. Children experienced an immediate increase in muscle strength and joint excursion of the ankle; the improvements were still present at follow-up after 7 days. Interesting observations can be drawn from the analysis based on MDC95; it is derived from the standard error of the mean (SEM) and a 95% degree of confidence, and can be regarded as the minimum amount of change due to a real modification in performance rather than to the random measurement errors. Apart from T1, analysis

of individual data showed a remarkable proportion of children (67–100%) with improvements in performance equal to or greater than the absolute values of the MDC95, for plantar flexors strength and ankle joint excursion (Table 2.1.2, Fig. 2.1.2 and Fig. 2.1.3). The quality of gait pattern was also enhanced, probably due to the ability to perform a better push-off and swing phase; although an MDC95 value is not available for the PRS. Despite the variations observed in the children's ability to move their ankles, change scores in the SMC were not significant.

This study has some limitations. An electro-goniometer would have given more accurate measurements of the ankle joint angles; a mean score of the 3 strength tests performed per-angle would have probably been more reliable. Moreover, assessing spasticity was not considered as it interferes with muscle strength and joint mobility, the use of an outcome measure such as the Tardieu Scale (Glinsky, 2016) or an objective, neurophysiological assessment, such as the TSRT measurement (Blanchette et al., 2016) would have provided additional data. In the current investigation, the dosing of the intervention (i.e. 3 × 20-min sessions) has been chosen with reference to a previous study (Crippa et al., 2004); due to the exploratory nature of the research, alternative dosages (e.g. greater frequency and duration) could have been considered. Finally, children should have been monitored for a longer time.

The effect of the MSM was previously investigated in individuals with multiple sclerosis (Crippa et al., 2004), spinal cord injury (Longo et al., 2017), and shoulder impingement (Melchiorre et al., 2014, 2018). The current findings regarding strength and joint excursion are in agreement with previous studies (Crippa et al., 2004; Longo et al., 2017; Melchiorre et al. 2014, 2018). In the children in the current study, impairment of the ankle was due to muscle weakness and unbalanced muscle action. According to Feldman's model, the modulation of TSRTs allows interaction with the environment by mean of a fluent control of muscular forces and joint angle. Regulation of thresholds, and positional and velocity gains of the stretch reflex are consequences of supraspinal action and may have implications in motor control disorders related to diseases of the nervous system (Feldman and Levin, 1995). The positive effect could be explained by the proprioceptive feedback due to the MSM, inducing a neuromuscular review; novel muscle tonic SRTs and configurations of the joint, within different body frames of reference (Latash et al., 2010, Feldman, 2006) may have produced a stronger and more balanced agonist-antagonist muscular action. It's known that the findings are related to body structure, and not to activity and participation domains; moreover, in management of CP, upstream therapeutic effects (e.g. on other ICF domains) are not supported by substantial evidence (Novak et al., 2020). However, in the context of multiple limiting factors, an eventual positive effect of MSM may allow better engagement in goal-directed and motor learning-based interventions (Novak et al., 2020).

In conclusion, the MSM is suitable for use in children affected by hemiplegia due to CP. Well-designed preclinical and clinical studies are needed to investigate its neurophysiological effect, relationship with human motor control and learning, and efficacy. Considerations should be made regarding the potential impact of the stimulation on spasticity; should a positive effect result, the minimal burden of the intervention would make it attractive compared with surgical or pharmacological interventions.

Should the effectiveness be confirmed, further research may address how the MSM could help in minimizing activity limitations and encouraging participation.

2.2 The effects of the Muscle Shortening Manoeuvre on motor control in chronic stroke survivors: a pilot study.

Physiotherapy plays a key role in stroke rehabilitation, with an array of approaches and techniques (Pollock et al., 2014). The growing body of knowledge on the physical and neurophysiological principles underlying movement control has led to the development of a variety of treatment interventions such as neurodevelopmental approach, motor learning, constraint induced movement therapy, functional electrical stimulation, or robotics, just to name a few (Langhorne et al., 2011). Debate about the relative effectiveness of treatment strategies is ongoing. There is evidence that some physiotherapy interventions (e.g., intensive high repetitive task-oriented and task-specific training) promote recovery after stroke (Langhorne et al., 2011; Veerbeek et al., 2014); however, none demonstrated greater efficiency than any others in the recovery of function and mobility after stroke (Pollock et al., 2014).

A pilot trial has therefore been designed to assess a) the potential mechanisms of action of the technique, thus investigating the hypothesis that MSM could influence the modulation of the TSRTs, and b) the implementation of a protocol exploring the MSM as a rehabilitation technique to improve body functions and activities in individuals with limitations due to chronic stroke, particularly its safety, usefulness of the outcome measures, and variation in participants' responses.

2.2.1 Methods

2.2.1.1 Participants

Being the present a stage 1 clinical rehabilitation pilot study (Dobkin, 2009), a convenience sample of 10 participants was enrolled by a physical therapist investigator blinded to baseline assessments. The recruiter randomly assigned participants to MSM or comparison groups. A numbered sequence of opaque and sealed envelopes containing the assignment number has been set by a health professional not involved in the recruitment.

Individuals affected by chronic stroke and admitted to the outpatient rehabilitation clinics Turati Foundation (Pistoia, Italy), MAiC Foundation (Pistoia, Italy), and Longo Physiotherapy Studio (Florence, Italy) were invited to participate. To be included individuals had to be 18 years or older, affected by chronic (> 1 year from event) ischemic stroke, with ankle plantaflexor spasticity (Modified Ashworth Scale – MAS score, 1-3) (Waninge et al., 2011), and able to reach the facilities involved in the study. Exclusion criteria were the presence of severe cognitive deficits (Mini-mental state examination ≤ 18), bone deformity and/or pain in the affected ankle joint, pregnancy, botulinum toxin therapy within the previous 5 months, and any comorbidity or disability that would preclude participation in the treatment program. The eventual use of an ankle-foot orthosis (AFO) was discontinued during the study.

2.2.1.2 Intervention

MSM treatment

In the MSM session, the individual lay supine on a physiotherapy bed, with the foot protruding from the edge; layers of foam rubber were placed below the knee to reduce tension in the calf muscles. A bandage was applied to the distal third of the leg and the whole foot. A flexible rod (harmonic steel rod covered with foam and neoprene; length, cm 60; width, cm 6; thickness, cm 0.5) was fixed with adhesive tape to the plantar surface along the transverse axis of the patient's foot, protruding about 5 cm from the rear edge of the heel. Small iron parallelepiped weights (weight, kg 1.2 or 3; width, cm 6; thickness, cm 0.5 or 1) could be applied to increase the elastic return of the harmonic steel (e.g., in case of reduced joint excursion of the ankle due to spasticity). The therapist, sitting by the bed, performed the MSM by pulling and releasing with his hand the end of the rod; thus, dorsal and plantar flexion movements were rhythmically performed (Hertz, 2) for 15 minutes. The participant was

requested to relax, avoid any voluntary movement, and let the therapist move his/her foot. The rod and the bandage were then removed.

The MSM treatment was administered by a trained physiotherapy undergraduate student under supervision. Training and supervision were provided by the first author, a physiotherapist with 10 years of clinical experience in neurological rehabilitation and expertise in MSM administration. Three sessions of one hour specific MSM training were provided by the senior physiotherapist. The treatment was administered individually, face-to-face, once a week for four consecutive weeks in an outpatient clinic; each session had a duration of 40 minutes, including time to apply/remove the bandage and intervention administration.

Comparator treatment, conventional physical therapy

The conventional physical therapy (CPT) was chosen as comparator treatment. The content of CPT was a combination of functional training in basic activities of daily living, balance and postural exercises, task training, mobilization and stretching, and individual and family/caregiver education. It represents the current standard of outpatient physiotherapy care for individuals with stroke provided by the local health authority. A common equipment was utilized. CPT was provided by two senior physiotherapists with more than 10 years of clinical experience in neurological rehabilitation and expertise in stroke recovery. The intervention was tailored accordingly to clinical condition and was administered individually, face-to-face. Ten sessions were provided in four weeks (three sessions in week 1 and 2, two sessions in week 3 and 4) in an outpatient clinic; each session had a duration of 60 minutes.

2.2.1.3 Outcome Measures

Data were extracted using a standard data recording spreadsheet, including characteristics of the participants and stroke-related issues (age, gender, side affected, year of the event, comorbidities); adherence rate, and adverse events were recorded.

To investigate variation of SRTs values and sensitivity of the threshold to the stretching speed (μ), the Montreal Spasticity Measure device (MSMD) measure (Levin et al., 2013) has been used. The measure involves the use of a surface EMG recorder and an electro-goniometer which provide data to a computer; a software computes the TSRTs in real time (Levin et al., 2013; Calota et al., 2008; Blanchette et al., 2016). The evaluation procedure was consistent with that used in previous studies (Blanchette et al., 2016; Calota et al., 2008). Briefly, a series of 20 passive stretches of the plantaflexor

muscles of the ankle were performed by the assessor, at various speeds. The data points obtained represented the dynamic SRTs angles at the different speeds, the software then performed offline linear regression to find the reflexotonic threshold angle from stretch at 0 speed. The same software computed the μ value, intended as the slope of the linear regression line.

To explore the eventual impact of the treatments on body functions and activity levels in individuals with limitations due to stroke, a selection of clinical and instrumental outcome measures was taken with exploratory aims. Strength of the dorsiflexor (ankle dorsiflexion item of the Motricity Index (MI) (Fayazi et al., 2012); electronic hand-held dynamometry, newtons) and passive and active range of motion (PROM and AROM; electronic goniometry, from maximum dorsiflexion to maximum plantarflexion and vice versa, AROM applying a minimal manual resistance) of the affected ankle were recorded. Spasticity was measured by means of the MSRT and the MAS (Waninge et al., 2011). The Barthel Index (BI) (Mahoney and Barthel, 1965) was used to assess the level of independency in basic activities of daily living; the Minimal Detectable Change (MDC) estimated in individuals with chronic stroke is 4.02 points (Hsieh et al., 2007). Finally, the Timed Up and Go test (TUG) was used as measure of functional mobility (Chan et al., 2017); the MDC estimated in individuals with chronic stroke is 2.9 seconds (Flansbjer et al., 2005).

Data were collected at baseline (T0), at the end of the treatment (T1), and one month after the end of treatment (T2).

2.2.1.4 Statistical Analysis

Data were analyzed by an independent investigator. Sample characteristics were analyzed using descriptive statistics. The $\chi 2$ test was used to detect differences in categorical variables. Given the sample size, nonparametric tests were selected; ordinal variables (i.e., MAS and MI) were treated as continuous. Differences between groups in continuous outcome measures were examined using the Mann-Whitney U test; score variations were calculated subtracting pretraining values from the corresponding posttraining values. Effect size was computed according to the formula $\eta^2 = Z^2/n$. The Friedman test was utilized to assess within-group variations across the assessments; in case of significant results, post-hoc analysis was conducted by the Dunn test, with Bonferroni correction. In case of significant differences in between- or within- comparisons, the Hodges-Lehmann estimator was used to estimate the 95% confidence intervals (CI) of the median of the differences. Data on TUG and BI were further analyzed by plotting change scores and the range of random measurement error (i.e., the interval spanning between the ±MDC95 values) and computing the proportions (95%

Confidence Interval-CI) of individuals showing an improvement in performance equal to or greater than the absolute MDC95 value.

The significant level was set at $p \leq 0.05$. Analyses were performed with IBM SPSS Statistics software for Windows (version 20.0; IBM Corp, Armonk, NY).

2.2.2 Results

The participants (male, 6) were 24-78 years old (median, 52 year); of them, seven had the left side affected and all scored >18 at the MMSE. One subject in each group used an AFO before enrollment. The treatment was administered 4-32 years after the event (median, 7). Demographic, clinical, and baseline data are presented in the Table 2.2.1. No significant difference between groups was found at baseline for any variable. All participants completed the study and had complete data; no adverse events were detected.

Table 2.2.1. Demographic, clinical and baseline data of participants. Legend: TSRT=Tonic Stretch Reflex Threshold; MAS=Modified Ashworth Scale; TAS= Tibialis Anterior Strenght; MI=Motricity Index; BI=Barthel Index; TUG= TImed Up and Go test; AROM DF= Active Range of Motion DorsiFlexion; PROM DF= Passive Range of Motion DorsiFlexion.

ID	Group	Sex	Age	Affected side	Stroke event	TSRT	μ	MAS	TAS	MI	BI	TUG	AROM DF	PROM DF
1	MSM	M	49	Left	1989	67,75	-0,0200	3	77	14	95	12,74	-16,5	10
2	MSM	M	46	Left	2016	95,16	0,0500	3	18	14	100	13,31	4,0	7
3	MSM	M	24	Right	2013	90,66	0,0900	3	68	14	95	13,02	-10,0	-5
4	MSM	F	55	Left	2016	99,34	0,1700	3	52	14	60	28,94	-17,0	-15
5	MSM	M	78	Right	1992	83,95	0,0700	3	25	14	70	30,72	-36,0	-20
6	CPT	F	46	Right	2016	113,26	0,1200	1	9	14	80	29,05	-10,0	0
7	CPT	F	58	Left	2013	80,36	0,0500	2	38	14	95	14,06	-16,0	-4
8	CPT	F	66	Left	2011	99,09	0,1800	3	23	14	75	16,50	-12,0	6
9	CPT	M	39	Left	2015	75,31	0,0800	2	75	14	100	12,90	1,0	8
10	CPT	M	60	Left	2017	77,56	0,1900	3	33	14	80	28,08	-30,0	-28

In post-treatment between-group comparisons there were differences based on change scores. In both T1 and T2 assessments, compared to the CPT, the MSM group showed decrease of the TSRTs and of the time needed to perform the TUG test, and increase in strength of the dorsiflexor (dynamometry) and AROM (Table 2.2.2). The estimate of the 95% CI of the median of the differences is presented in Figure 2.2.1. One participant per group (20%, 95%CI 4-62) showed improvement in the BI score

greater than the MDC95 value at T1 and T2. Three and four out of five participants in the MSM group (60%,95% CI 23-88 and 80%,95% CI 38-96, respectively) showed an improvement in the TUG performance greater than the MDC95 value at T1 and T2, respectively (Table 2.2.2, Figure 2.2.3).

Table 2.2.2. Post- treatment between group comparisons. Legend: TSRT=Tonic Stretch Reflex Threshold; MAS=Modified Ashworth Scale; TAS= Tibialis Anterior Strenght; MI=Motricity Index; BI=Barthel Index; TUG= TImed Up and Go test; AROM = Active Range of Motion; PROM= Passive Range of Motion.

	T0-T1				**T0-T2**			
Variable	**CPT (*n*=5)**	**MSM (*n*=5)**	η^2	*p*	**CPT (*n*=5)**	**MSM (*n*=5)**	η^2	*p*
TSRT, deg	-0.73 (-2.21; 0.71)	-12.12 (-13.58; -3.94)	0.682	0.009	-0.23 (-1.49; 1.24)	-11. 08 (-15.39; -4.01)	0.682	0.009
μ	0 (-0.01; 0.02)	-0.03 (-0.08; 0.07)	0.028	0.599	0 (-0.01; 0.03)	-0.03 (-0.12; 0.04)	0.054	0.463
MAS	0 (0; 0)	0 (-2; 0)	0.225	0.134	0 (0; 0)	0 (-2; 0)	0.225	0.134
TAS, N	2 (-2; 5)	27 (5; 53)	0.632	0.012	5 (0; 6)	29 (14; 66)	0.686	0.009
MI	0 (0; 0)	5 (0; 11)	0.375	0.053	0 (0; 0)	5 (0; 11)	0.375	0.053
BI	0 (0; 5)	0 (0; 15)	0.002	0.881	0 (0; 20)	0 (0; 15)	0.002	0.881
TUG, s	-0.45 (-1.10; 1.8)	-3.38 (-4.94; -1.82)	0.682	0.009	0.97 (0.71; 1.26)	-3.94 (-13.62; -1.72)	0.682	0.009
AROM, deg	4 (1; 5)	18 (6; 20)	0.686	0.009	4 (-12; 6)	20.5 (7; 27)	0.682	0.009
PROM, deg	4 (1; 8)	14 (1; 29)	0.323	0.072	4 (1; 8)	15 (2; 30)	0.317	0.075

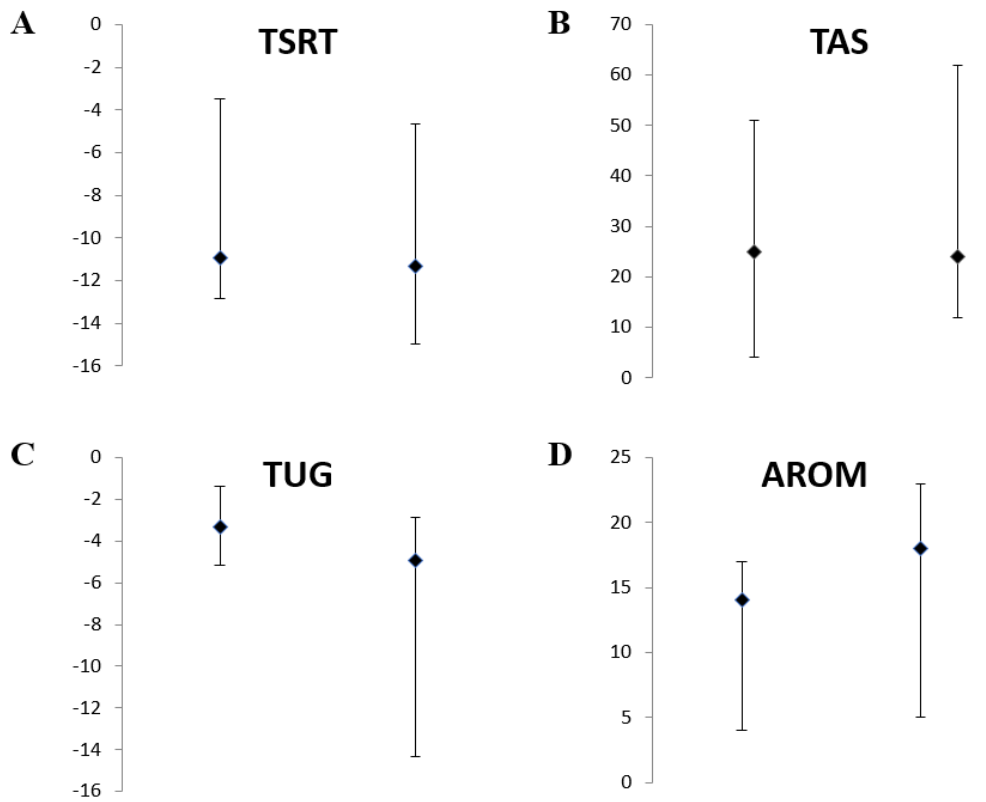

Figure 2.2.1. Between group T1 and T2 post-hoc comparisons. Hodges-Lehmann estimate and 95% confidence intervals. Legend: TSRT=Tonic Stretch Reflex Threshold; TAS= Tibialis Anterior Strenght; TUG= TImed Up and Go test; AROM = Active Range of Motion.

In within-group comparisons, the Friedman tests showed some differences between the assessments. In particular, changes in TSRTs, TUG, strength of the dorsiflexor (MI and dynamometry), AROM and PROM reached statistical significance in the MSM group, and PROM in the CPT group (Table 2.2.3). Post-hoc pairwise analysis indicated that T2 TSRT (p= 0.013), TUG (p= 0.013), dorsiflexor dynamometry (p= 0.005), AROM (p= 0.005) and PROM (p= 0.008) scores were significantly different from those of T0, whereas no differences were detected by for MI in the MSM group and PROM in the CPT group. The estimate of the 95% CI of the median of the differences is presented in Figure 2.2.2.

Table 2.2.3. Post- treatment within group comparisons. Legend: TSRT=Tonic Stretch Reflex Threshold; MAS=Modified Ashworth Scale; TAS= Tibialis Anterior Strenght; MI=Motricity Index; BI=Barthel Index; TUG= TImed Up and Go test; AROM = Active Range of Motion; PROM= Passive Range of Motion.

Variable	**CPT Group (*n*=5)**				**MSM Group (*n*=5)**			
	T0	**T1**	**T2**	***p***	**T0**	**T1**	**T2**	***p***
TSRT	80.36 (75.31; 113.26)	79.92 (76.02; 111.05)	78.94 (75.98; 114.50)	0.819	90.66 (67.75; 99.34)	78.14 (63.81; 88.48)	75.27 (63.74; 88.26)	0.015
μ	0.12 (0.05; 0.19)	0.11 (0.05; 0.21)	0.12 (0.06; 0.22)	0.607	0.07 (-0.02; 0.17)	0.06 (0.002; 0.140)	0.03 (0.004; 0.110)	0.692
MAS	2 (1; 3)	2 (1; 3)	2 (1; 3)	1	3 (3;3)	3 (1;3)	3 (1;3)	0.135
TAS, N	33 (9; 75)	31(11; 80)	34 (15; 81)	0.076	52 (18;77)	73 (37;104)	84 (43;115)	0.007
MI	14 (14; 14)	14 (14; 14)	14 (14; 14)	1	14 (14;14)	19 (14;25)	19 (14;25)	0.050
BI	80 (75; 100)	80 (80; 100)	95 (80; 100)	0.368	95 (60;100)	95 (70;100)	95 (70;100)	0.368
TUG	16.50 (12.90; 29.05)	18.30 (11.80; 29.30)	17.47 (13.63; 30.31)	0.247	13.31 (12.74; 30.72)	10.92 (9.25; 27.34)	11.02 (9.10; 26.78)	0.015
AROM	-12 (-30; 1)	-9 (-25; 3)	-11 (-24; 3)	0.069	-16.5 (-36.5; 4)	3 (-18; 10)	7 (-9; 11)	0.007
PROM	0 (-28; 8)	1 (-20; 13)	1 (-20; 11)	0.012	-5 (-20; 10)	9 (7; 17)	10 (9; 17)	0.008

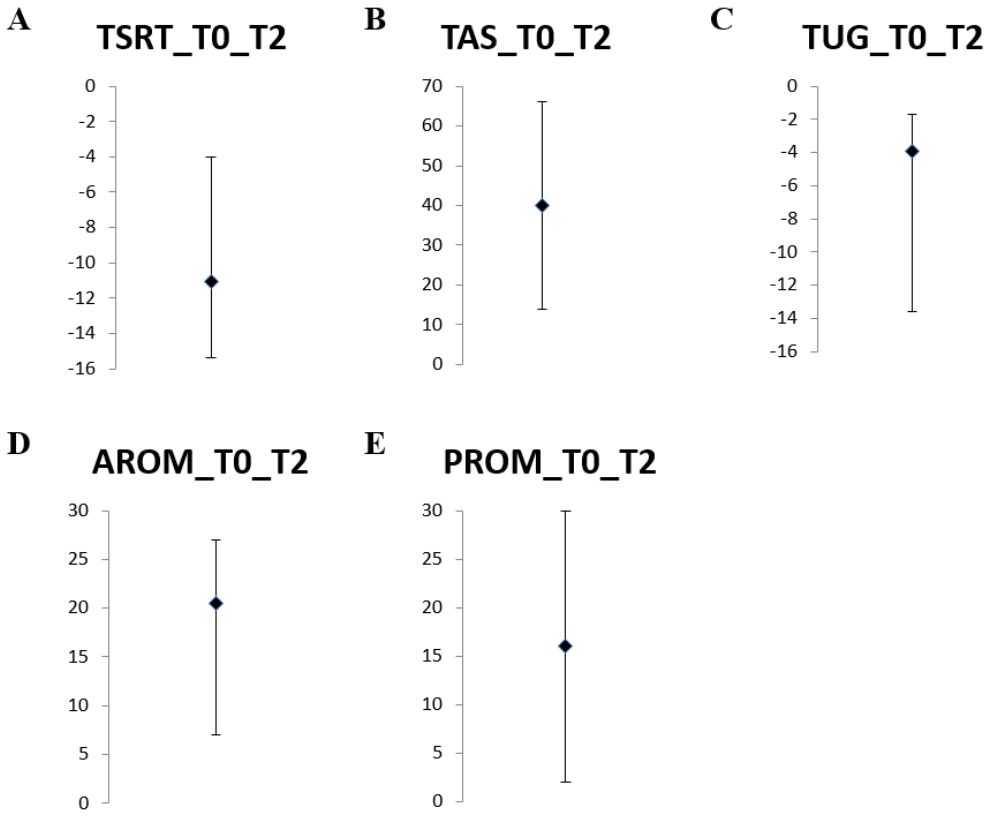

Figure 2.2.2. MSM within post-hoc comparisons. Hodges-Lehmann estimate and 95% confidence intervals. TSRT=Tonic Stretch Reflex Threshold; TAS= Tibialis Anterior Strenght; TUG= TImed Up and Go test; AROM = Active Range of Motion; PROM= Passive Range of Motion.

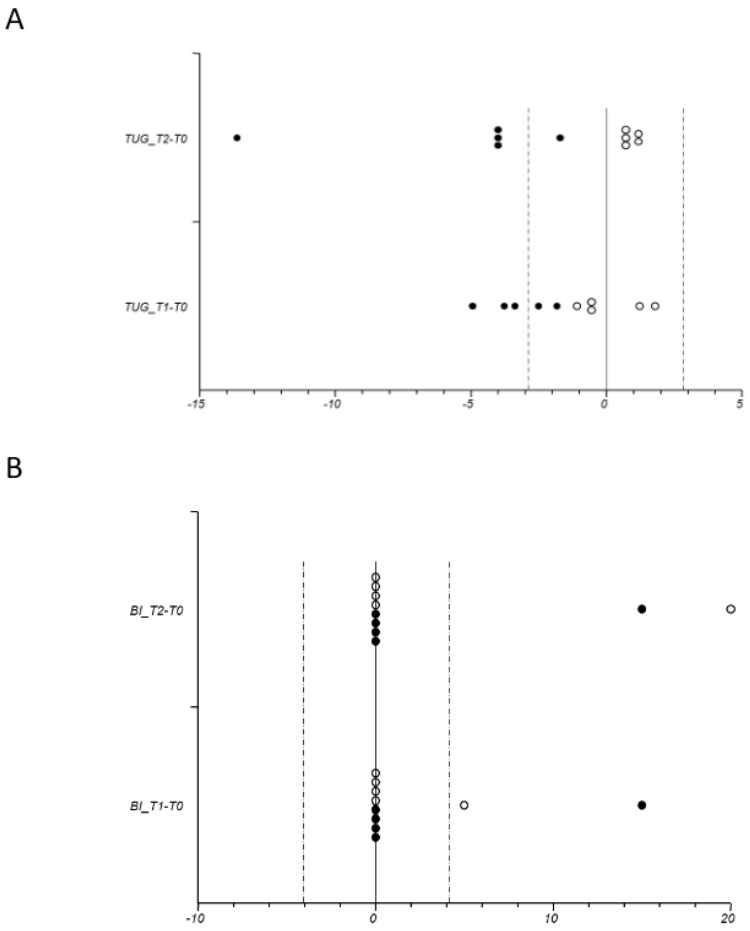

Figure 2.2.3. Individual TUG and BI change scores. A white dot represents a participant in the conventional physical therapy group; a black dot represents a participant in the muscle shortening maneuver group; the vertical lines indicate a difference of 0 and the ±MDC95 values. BI= Barthel Index; TUG= Timed Up and Go test.

2.2.3 Discussion

Being the base of well-designed randomized controlled trials, pilot studies are important for the research process aimed to develop interventions for individuals with disability (Dobkin, 2009); the pilot design was appropriate for the set objectives, and that is to assess the potential mechanisms of action of an intervention and the implementation of a protocol exploring a rehabilitation technique (Moore et al., 2011).

The MSMD is recognised as a reliable tool to measure TSRTs (Frenkel-Toledo et al., 2021) (Figure 2.2.4). According to the results, TSRTs values decreased in the MSM group, whereas the sensitivity of the threshold to stretching speed (i.e. the μ value) was unchanged. The variation of the TSRTs values observed by the MSMD measure is consistent with the hypothesised mechanisms of action of MSM, a modulation of the TSRTs (Grimaldi et al., 1986); it is plausible that the observed clinical variations in joint range of motion and muscle strength are linked to the decrease of the TSRTs, thus suggesting a potential effect of MSM on the neuromuscular spindles of the plantar flexor muscles of the affected ankle and related motor control. The MSM is oriented to body structure level and the observed effect (i.e., a more balanced agonist- antagonist- muscular action), if confirmed, would suggest behavioural restitution rather than compensation (Bernhardt et al., 2017).

TSRTs' characteristics discriminate between neurological deficits of muscle tone. In this sample hypersensitivity to velocity of plantar flexor muscle stretch has been observed with μ values almost similar to those detected in elbow muscles of individuals with chronic stroke by Mullick et al. (2013) (mean, 0.10 deg/s). One subject in the MSM group presented negative or very close to 0 μ values, which usually characterize Parkinson's disease rigidity; as he was the participant with the longest disease duration (over 30 years), fibrosis and small retractions could have interfered with the

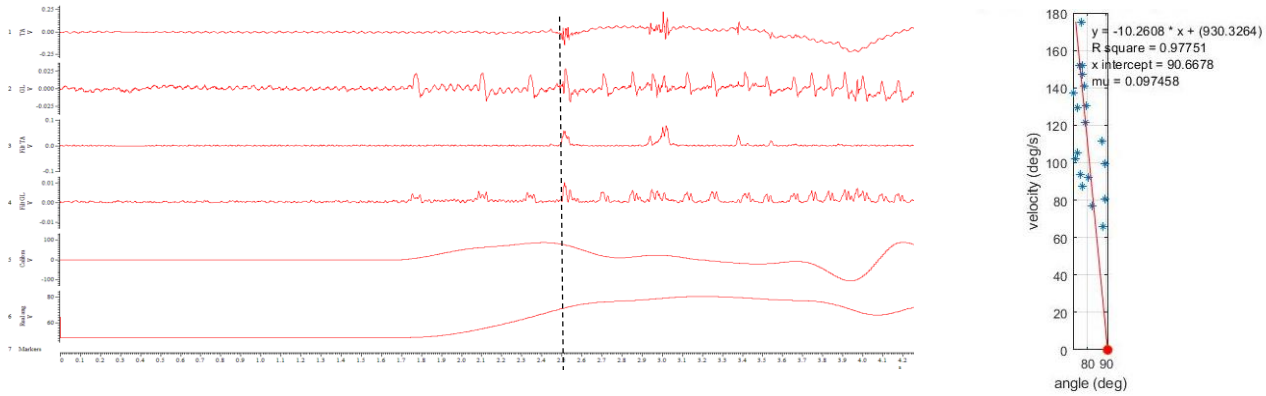

Figure 2.2.4. DSRT and TSRT. The right panel shows a dynamic stretch reflex threshold (DSRT) detection of one participant. The left panel shows the linear regression of multiple detections (blue asterisks) leading to the tonic stretch reflex threshold (TSRT) detection.

sensitivity to stretch. It would be recommendable consider the MSMD parameters (TSRT and μ) when planning and analyzing trials of stroke rehabilitation interventions including participants with spasticity.

The choice of quantitative instrumental outcome measures was satisfactory. The TSRT could be considered a quantitative motor control based spasticity measure (Frenkel-Toledo et al., 2021), therefore very suitable to investigate the eventual effect of the MSM in future studies; well trained assessors can lower the burden for the participant. Electronic goniometers, hand-held dynamometers, and chronometers are reliable and easy to use. Clinical measures such as the BI, MAS and MI should be used as independent variables, to select and characterize the sample. As recommended, demographic and stroke information and core measures (i.e., National Institute of Health Stroke Scale, Fugl–Meyer, 10-m walk test, EuroQOL-5D and simplified modified Rankin Scale) have to be considered in future developments (Kwakkel et al., 2017).

In the contest of this study, statistical testing was not intended demonstrate that one treatment would be more effective than the other, and was conducted as part of the pilot evaluation of participant responses. As already mentioned, CPT represents the routine therapy that would have been eventually administered. Despite the difference in the amount of attention provided (i.e., 2 h vs 10 h) and the physically inactive treatment (i.e., the participant laying on the bed), this small sample between group analysis showed a decrease of TSRTs and time needed to perform the TUG test, and amelioration of strength and AROM in the MSM group. The improvements were observed many years after the event, when the condition is considered almost unchangeable. Due to the MSM characteristics, reconditioning, a factor that may get involved with results in trials recruiting individuals at the chronic stage (Dobkin, 2009; Stinear et al., 2020), cannot be called into question. Effect size were large (Ferguson, 2009) and the medians of the differences, although consistent, have to be interpreted with caution, due to wide 95%CIs. Nowadays, the TSRT MDC95 has been reported for elbow flexor of individuals with sub-acute stroke (Frenkel-Toledo et al., 2021), thus it's not possible to compare these findings. Increments in strength of the dorsiflexor and ankle range of motion positively affect mobility in individual affected by stroke (Dorsch et al., 2012; Lin et al., 2006), and this is reflected in improving the TUG test performance. Participant in the MSM group mostly had an improvement in the TUG test greater than the absolute MDC95 value (Table 2.2.3, Figure 2.2.3), whereas one individual per group achieved a similar result at the BI.

Within- group analysis shows significant variations in TSRTs, TUG, strength of the dorsiflexor (MI and dynamometry), AROM and PROM in the MSM group, and PROM in the CPT group; however, in post hoc analysis variations of MI in MSM group and PROM in CPT group were not confirmed.

Post hoc analysis also shows that the improvements were significant one month after the end of treatment, at T2 follow up. These finding are in contrast to those reported in previous studies on the MSM; although they were conducted in a variety of clinical conditions and had various endpoints, outcomes were significantly favorable at the end-of-the-intervention assessment (Crippa et al., 2004; Longo et al., 2017, 2021, 2022; Melchiorre et al., 2014, 2018). It should be noted that, in the present study, the variables showing improvement were measured by reliable quantitative instrumental measures.

These findings encourage the progression toward a stage 2 trial. Keeping in mind a next study, and to appropriately register the trial, it's needed to reconsider methodological issues such as recruitment strategy, eventual participant stratification, blinding, exhaustive standardised intervention protocols and training programs for therapist and assessors, and many other (Walker et al., 2017; Stinear et al., 2020). Particularly challenging are decisions on MSM dosing and control intervention. In previous studies reporting on MSM, no harm or adverse events were evident; as the aim was exploratory and safety was the first concern, the low dosing has been chosen as a starting point. The used comparator treatment, although easy available and adequate for a pilot, would not be acceptable for an effectiveness study (Dobkin, 2009; Stinear et al., 2020). An interesting control intervention could be the Transcutaneous Electrical Nerve Stimulation (TENS); it has been recognized effective in reducing spasticity in participants with chronic stroke (Mahmood et al., 2019), with the underlying hypothesis that the treatment may have an effect on TSRTs modulation (Levin and Hui-Chan, 1992). Meta-analyses published on the topic rely on findings prevalently based on the MAS measure (Mahmood et al., 2019; Lin et al., 2018; Kwong et al., 2018); it would be interesting to compare MSM and TENS by the MSMD measure. Both interventions could be delivered in the existing health care settings, with a relatively low burden (i.e., twice a week, 45 minute sessions) for participants. Involving eligible individuals in study design could increase the relevance of the trial and its outcomes (Stinear et al., 2020).

2.3 The Muscle Shortening Maneuver: a new non-invasive approach to the treatment of peroneal nerve injury. A case report

After a peripheral nerve injury, cortical plasticity and nerve regeneration cause pathophysiological changes and reorganization of somatosensory and motor regions (Li et al., 2021). The treatment of peripheral nerve injuries is a debated topic. Many techniques aimed to facilitate the reinnervation process have been developed and researched. Most of them are related to surgical or pharmacological interventions (Hussain et al., 2020; Mu et al., 2011; Romeo-Guitart and Casas, 2011). Several rehabilitative interventions have been reported (Zink and Philip, 2020; Hussain et al., 2020; Armada da Silva et al., 2013); however, due to heterogeneity, low methodological quality, and controversial results of the studies, questions arose about the best approach to induce functional recovery.
The focus of this report is to describe the effects of the MSM combined with walking retraining in a patient with incomplete injury of the peroneal nerve.

2.3.1 Methods

2.3.1.1 Participant

The participant, which was of age when the report started to be drawn up, provided written informed consent for data extraction from chart review as needed, and eventual dissemination through publication. The male patient underwent osteotomy surgery of the proximal 2/3 of the fibula at the age of 15 years, due to an Ewing sarcoma. He completed four cycles of preoperative chemotherapy; the postoperative course was uneventful. Four chemotherapy cycles were administered after the surgical procedure. The main consequence of the osteotomy was a partial injury of the peroneal nerve, leading to a deficit of active dorsiflexion and eversion of the left ankle. The patient was then monitored by rehabilitation services; he underwent 40 sessions of outpatient conventional physiotherapy (i.e., range of motion -ROM- and progressive resistive exercises, plus walking retraining), twice a week. The individual accessed the physiotherapy service more than 18 months after surgery, at the age of 17 years; he did not undergo to other rehabilitative interventions in the previous eight months. The timeline is reported in Table 2.3.1.
The individual was independent in basic- and instrumental- activities of daily living.
He presented shortening of the Achilles tendon and limited passive- and active- Range of Motion (ROM) in dorsiflexion of the left ankle; the evertor muscles were elicitable, with no visible movement.

The individual walked without aids, with foot drop; caution was needed on uneven terrain. He was able to climb stairs using a greater hip flexion and right pelvis lifting.

According to the clinical presentation, the primary treatment goals was the improving of passive- and active ROM and muscle strength of the affected ankle, followed by the performance of a better and safe gait pattern. The assessment plan was developed accordingly. As some of the desired objectives of the therapeutic intervention coincided with the outcome observed in previous clinical experiences (Longo et al., 2017, 2021; Melchiorre et al., 2014, 2018) and given the absence of known side effects, the MSM has been included in the intervention plan. Considering the time elapsed since the onset of the disease, and narrative reports on the application of the technique in individuals with second motor neuron injury, some improvement, or no change in the clinical picture were expected.

Table 2.3.1. Timeline of events from chart review

	Event
August, 2017	early symptoms
September, 2017	diagnosis
September 25, 2017	preoperative chemotherapy, start
December 9, 2017	preoperative chemotherapy, end
December 29, 2017	osteotomy surgery
January 18, 2018	postoperative chemotherapy, start
May 4, 2018	postoperative chemotherapy, end
October 16, 2018	conventional physiotherapy, start
January 3, 2019	conventional physiotherapy, end
September 9, 2019	baseline assessment; first MSM session
September 19, 2019	follow up, end of the fourth MSM session
October 3, 2019	follow up, end of the last MSM session
November 11, 2019	follow up, one month (39 days) after the end of the last MSM session

2.3.1.2 Intervention

In the MSM session, the patient lay supine on a physiotherapy bed, with the foot protruding from the edge; layers of foam rubber were placed below the knee to reduce tension in the calf muscles. A bandage was applied to the distal third of the leg and the whole foot. A flexible rod (harmonic steel rod covered with foam and neoprene; length, cm 60; width, cm 6; thickness, cm 0.5) was fixed with adhesive tape to the plantar surface along the transverse axis of the patient's foot, protruding about 5

cm from the rear edge of the heel. The therapist, sitting by the bed, performed the MSM by pulling and releasing with his hand the end of the rod; thus, dorsal and plantar flexion movements were rhythmically performed (Hertz, 2) for 15 minutes (Fig. 2.3.1). The rod and the bandage were then removed.

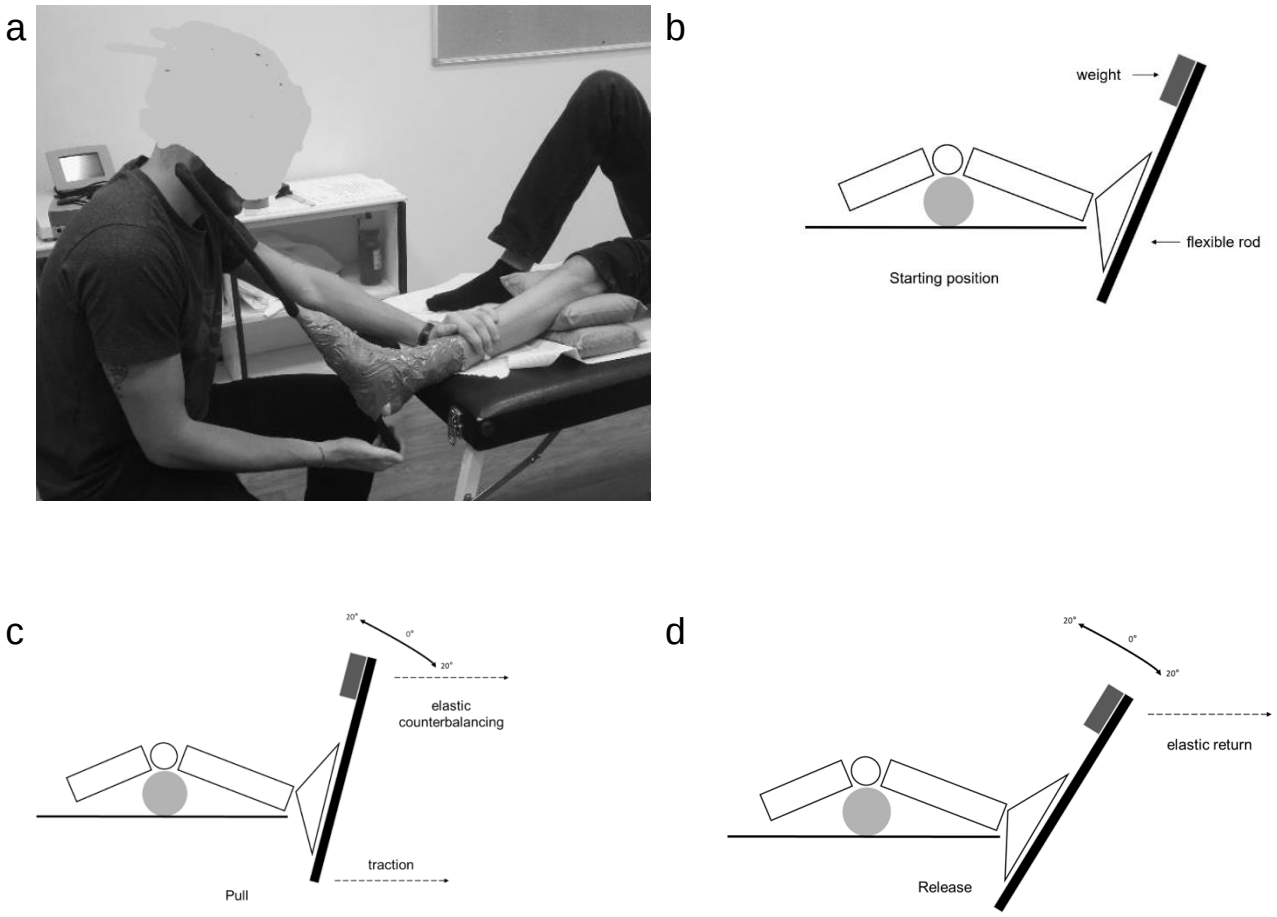

Fig. 2.3.1. Picture (a) and scheme (b-d) of the Muscle Shortening Maneuver

The components of walking retraining were: warm-up, stretching of the calf muscles, proprioception and balance exercises, muscle strengthening, and treadmill training. The session began with a 10-minute warm-up phase (cyclette, 25 Watt). The calf stretch was performed in the standing position. After placing the hands on a wall, the patient was requested to step back with the injured leg in a mini lunge (front leg bent, rear leg straight), then pressing the rear heel down until the stretch was achieved. The same exercise was performed with the rear knee slightly flexed (10 degrees). Heel drop stretch was also performed; the patient standing with the balls of injured foot on the edge of a step was requested to drop the heel towards the floor, until the stretch was achieved. Three repetitions were

performed for each exercise, progressing the stretch duration from 30 sec to 1 min. To elicit proprioception and balance, the subject was requested to hold the one-leg stand position (injured leg) up to 30 seconds; as ability improved, the task of reaching various targets with the contralateral hand or foot was added. Further training was performed by means of a rocker board, in the antero-posterior and latero-lateral directions (load on both feet). Ten repetitions were performed for each exercise, progressing up to 30 seconds of balance maintaining. The static glute bridge, side-lying leg abduction, hamstring curls, and seated leg raises were performed to improve muscle strength. The patient was requested to hold the active position for about 5-10 seconds; exercises progressed from 1 to 2 sets of 10 to 15 repetitions. The session ended with 15-minute of uphill treadmill training. Treadmill speed was set at 3.5 km/h; the incline varied from 0% to 3% (duration, both 2m 30 sec) to 5% (duration, 5 min) to 3% and 0% (duration, both 2m 30 sec).

The MSM treatment was administered by a trained physiotherapy undergraduate student under supervision. Training and supervision were provided by a physiotherapist with 10 years of clinical experience in neurological rehabilitation and expertise in MSM administration. Three sessions of 1 -h specific MSM training were provided by the senior physiotherapist.

Walking retraining was administered by another physiotherapist with 15 years of clinical experience in paediatric neurological rehabilitation field, the same one that had taken care of the patient after the postoperative chemotherapy.

The intervention was scheduled on a 4-week period, every week including two 30-minute (including time to apply/remove the bandage and intervention administration) MSM sessions on Monday and Thursday and a single 60-minute walking retraining sessions on Wednesday.

2.3.1.3 Outcome measures

The assessment plan of the left ankle movement ability comprised passive- and active- ROM and muscle strength of the dorsiflexor, plantar flexor, invertor, and evertor muscles (isometric task; seconds, 30); for this purpose electronic goniometer and hand-held dynamometer (J Tech Commander ECHO) have been used. In order to detect a direct effect of the treatment on motor units and quantity of electromiographic activity, surface electromyography (EMG) was recorded for the tibialis anterior, peroneus longus, peroneus brevis, and gastrocnemius lateralis muscles (Enraf-NoniusMyoMed X); the integrated EMG value (area under the voltage curve of the rectified EMG signal; processing software, MathWorks- MATLAB r2019) has been considered. Gait analysis was conducted using the iPhone application *Gait analysis Pro* (YTA, K.K., © 2014 Wataru Yasuda). https://apps.apple.com/us/app/gaitanalysispro/id915232074); walking speed, step length, step

cadence and bilateral symmetry were recorded while the individual performed a 5-meter walk test. Assessments were performed at baseline (T0), after the fourth session (T1), at the end of the intervention (T2), and one month after the end of the intervention (T3).

2.3.2 Results

The intervention was administered in accordance with the planned agenda and no adverse events were observed.

The dorsiflexion ROM substantially improved (≥175%), whereas plantar flexion ROM slightly decreased (≤13%) (Table 2.3.2). A part for the tibialis anterior, an increase in muscle strength was detected (Table 2.3.2). Surface EMG showed an increased activation, particularly in the peroneus longus; decreased activation was observed for the gastrocnemius lateralis (Table 2.3.2). A decrease in gait speed and step length was recorded from the gait analysis, with a better bilateral symmetry (Table 2.3.2).

Table 2.3.2. Observed measures and percentage variations from baseline. Legenda. µV/sec= microvolts/seconds; T0= baseline; T1= after the fourth session; T2= the end of the intervention; T3= one month after the end of the intervention.

	T0	T1	T2	T3	T1-T0	T2-T0	T3-T0
ROM, degrees							
Plantar flexion, passive	62	60	52	54	-3%	-16%	-13%
Plantar flexion, active	50	45	45	45	-10%	-10%	-10%
Dorsiflexion, passive	4	8	11	11	100%	175%	175%
Dorsiflexion, active	-9	6	8	7	167%	189%	178%
STRENGHT, newtons							
Dorsiflexors	50	50	53	47	0%	6%	-6%
Invertors	39	77	59	70	97%	51%	79%
Evertors	15	30	27	39	100%	80%	160%
Plantar flexors	113	119	96	120	5%	-15%	6%
SURFACE EMG, µV/sec							
Tibialis anterior	1.74E+08	1.99E+08	2.23E+08	2.49E+08	14%	28%	43%
Gastrocnemius lateralis	2.64E+08	2.80E+08	2.65E+08	1.83E+08	6%	0%	-31%
Peroneus longus	3.83E+07	5.43E+07	7.78E+07	1.01E+08	42%	103%	165%
Peroneus brevis	1.21E+08	1.22E+08	1.30E+08	1.46E+08	1%	7%	21%
GAIT ANALYSIS							
Gait speed (m/min)	26.1	30	25.7	20	15%	-2%	-23%
Step length (cm)	20.5	26	23.1	17.5	27%	13%	-15%
Cadence (steps/min)	127.5	115.2	111	114.8	-10%	-13%	-10%
Bilateral symmetry index	0.77	1	0.99	0.99	23%	22%	22%

2.3.3 Discussion

Clear improvement of the clinical picture has been observed. The most interesting data are those related to EMG, with an increased activation of the peroneus brevis and tibialis anterior, and a particularly consistent increment of the electromyographic activity of the peroneus longus; the improvement would be in line with the increase of active dorsiflexion ROM and muscle strength.

The integrated EMG value of gastrocnemius lateralis decreased over time; probably, due to an altered pattern, the subject activated the lateral gastrocnemius in order to compensate for the activation deficit of the tibialis anterior and evertor muscles. According to this hypothesis, the muscles activation pattern may have normalized because of the intervention.

The tendency towards a better motor control is also reflected in the gait pattern, indeed the gait parameters changed across assessments. At baseline the pattern was characterized by the foot drop and a shorter left stance phase, with compensatory and substitutive movements. At the follow-up assessment the individual showed a moderate decrease of gait speed, step length and cadence, and a symmetric gait pattern. It is probably due to the increase of active movements, walking retraining, and the awareness that a better gait pattern is possible.

The improvement was evident shortly after at the beginning of the intervention, with a subsequent increase; the outcome persisted one month after the last treatment session. This agrees with what has been observed in previous studies on MSM, which is characterized by an immediate effect, and outcomes lasting in the short term (Longo et al., 2017, 2021; Melchiorre et al., 2014, 2018).

This is the first report describing a possible association between the MSM and variations in EMG activity; positive correlation, even if weak, have been reported between EMG and motor change after peripheral nerve injury (Adiguzel et al., 2016). Positive effects have been reported on muscle strength and joint excursion when MSM was administered to individuals with central nervous system or orthopaedic conditions (Longo et al., 2017, 2021; Melchiorre et al., 2014, 2018). In this case, improvements were observed more than 18 months after a peripheral neural lesion, when the condition is generally considered chronic. MSM was the element which differentiate previous administered physiotherapy interventions from the present one. The positive effect could be explained by the proprioceptive feedback due to MSM, inducing a neuromuscular review; novel muscle tonic SRTs and configurations of the joint may have produced a stronger and more balanced muscular action. The increase of activation observed with EMG suggests a greater recruitment of motor units in the partially innervated muscles.

The components of the walk retraining may have played a role in the observed improvements. Research on animal models suggested a therapeutic potential of passive mobilization and physical exercise (e.g., treadmill training) in the treatment of traumatic peripheral nerve injuries; however, the same finding were not confirmed in clinical research (Armada da Silva et al., 2013). Other factors such as exercise intensity, duration, and timing for initiating the exercise, could impact the efficacy of physical exercise programs (Armada da Silva et al., 2013); the walk retraining, a 60-minute weekly session administered more than 20 month after surgery, did not have the potential for use as a stand-alone intervention.

In conclusion, the procedure was well tolerated; compared to other therapeutic approach to peripheral nerve injuries, MSM seem to be at very low risk of adverse event (Hussain et al., 2020). The intervention could be relevant to important aspects of functioning such as the walking ability. Studies should be designed to explore the feasibility of trials investigating the application of MSM in individuals affected by peripheral nerve injuries.

2.4 Shoulder impingement syndrome in waterpolo players: muscle shortening manoeuvre controls pain intensity, recovers function and normalises sonographic parameters

In practice, it's known that SIS, which is a multifactorial condition, is the most common cause of shoulder pain (Juel and Natvig, 2014). Usually, its etiology is due to the modification of intrinsic and extrinsic mechanisms of the rotator cuff eliciting eventually a damage of the shoulder structures (Michener et al., 2003; Seitz et al., 2011). External mechanical compression of the anatomical structures within the sub-acromial space is involved in SIS generation (Seitz et al., 2011). In SIS, the bone alterations of the acromion and the acromio-clavicular joint (ACJ) and the thickness of the coracoacromial ligament may be considered extrinsic factors involved SIS. In addition, the unbalanced action of the shoulder muscles with loss of central position of the humeral head may be biomechanical factors related to SIS (Van der Windt et al., 1995; Brox, 2003; Beltran et al., 2012; Haahr et al., 2005; Papadonikolakis et al., 2011) eliciting deficit in the muscle performance of the rotator cuff and of the scapular muscles. (Michener et al., 2003; Seitz et al., 2011; Ludewig and Braman, 2011). It is today suggested that muscle unbalance may be approached by muscle shortening manoeuvre (MSM) (Grimaldi et al., 1986; Crippa et al., 2004) which has been previously shown to be an effective therapeutic application in SIS (Melchiorre et al., 2014, 2018). In fact, it has been evidenced that the increase of muscle strength is the main outcome obtained with MSM. This

manoeuvre may increase serratus anterior muscle strength, stabilizing and balancing the joint and inducing pain relief (Melchiorre et al., 2014, 2018; Longo et al., 2017). Several sport activities can provoke a SIS by prolonged and intense activities. Waterpolo is an "open skill" and "overhead" sport, where the shoulder works continuously over 90° of elevation with repeated and frequent rotational movements. These movements may provoke pain, injury of glenoid labrum and SIS reducing the performance in the activity (Hams et al, 2019 a, b, c; Miller et al., 2019; Stromberg, 2017). Waterpolo is characterized by cyclic movements and complex coordination with frequent changes in direction, position and intensity of contraction of the upper and the lower limb. These complex activities, with a specific shot dynamic, are essentially characterized by five functional steps and the continuous repetitivity of the activity progressively determines chronic shoulder microtrauma evolving thus to SIS.

The aim of this work was to evaluate, in professional waterpolo players affected by SIS, either the effects of the MSM on shoulder pain and muscle strength and also to compare the shoulder modifications obtained with MSM to US parameters.

2.4.1 Methods

2.4.1.1 Participants

Out of 68 professional waterpolo players, 24 players of the Florence water polo team ("Firenze Pallanuoto") [14 male and 10 female; mean age:22.13 ± 3.34 (range 17-30)], affected by SIS, were enrolled in the study. Subjects were included in the study if they fulfilled the following diagnostic criteria: players currently active with chronic shoulder pain, pain provoked by abduction of shoulder with painful arc, positive Neer's impingement sign (Beltran et al., 2012; Neer, 1983), and Yocum and Hawkins tests (Yocum, 1983; Hawkins and Kennedy, 1980) positive. Exclusion criteria were:ex-players for at least 1 year, recent history of acute trauma (<2 months), treatment with physiotherapy for at least 1 month, taking NSAIDs two days before inclusion in this study. The study was approved from the local ethic committee (CEA 14900_spe) and all players signed the informed consent.

Enrolled players were consecutively and randomly assigned to one of 2 different treatment interventions. The first group of 14 players was treated with MSM: the manoeuvre is characterized by a series of fast accelerations in the upward direction applied to the upper limb connected to a spring through a metal plate with a ring. The ring is linked to a pulley which is submitted to forces acting in the opposite direction (added mass). The second control group of 10 players, was treated with a

simple traction only: in the simple traction the series of fast accelerations were performed without the added mass.

Table 2.4.1 Characteristics of the patients

	Group 1	**Group 2**
Age	21.71±2.99	22.7±3.86
Female	6	4
Male	8	6
Shoulder R	13	10
Shoulder L	1	0
IS	14	10

2.4.1.2 Intervention

Muscle Shortening Manoeuvre

MSM targeted the muscles responsible for shoulder protraction and retraction. It was performed on each player of the first group.

Participants were positioned in a supine position with the shoulder joint flexed to 90 °, the elbow in extension and with a clenched fist.

A first bandage was applied to a patient to protect the skin (using simple absorbent paper) starting from the proximal third of the shoulder, covering the hand. An eyelet plate was then placed on the proximal phalanges (second to fifth finger). The plate was anchored through a carabiner hook to the elastic elements, from one to three springs, depending on the weight of the limb. The springs, 50 cm long and 2 cm in diameter, were in turn connected to a pulley through a rope. The whole set was fixed with adhesive tape. In correspondence of the gleno-humeral joint, a spring with a parallelepiped weight (of 4 kg) was positioned, to increase the elastic return of the spring.

The physiotherapist, acting on the rope, applied manually stresses by moving the scapula in the direction of protraction, in a rhythmic way, with a frequency of about 2 Hz for a duration of 10 minutes. In each subject, the manoeuvre was performed only once.

Simple traction

The simple traction was performed on each player of the second group. It consisted of a simulation of MSM, offering all its characteristics, excluding the presence of the elastic elements (springs). In this way, the experimenters set out to perform a solicitation quite comparable to passive mobilization of the shoulder in protraction. As with MSM, the treatment duration was set at 10 minutes and each participant was treated only once.

2.4.1.3 Outcome measures

Pain intensity, Yocum and Hawkins tests, Neer's impingement sign, range of motion and muscle strength (Jtech Company dynamometer) were evaluated. The examination was performed before, immediately after and 30 days after each treatment. Pain intensity was assessed by a numerical rating scale (NRS) in a range of 0-10 points; range of motion (ROM) was evaluated in passive (PROM) and active (AROM) manner during intra and extra rotation (IR, ER), flexion and abduction of the shoulder (FS, AS) with the patient lying by a digital goniometer (Jtech Commander Echo). The value of ROM was considered reduced when < 90° during intra ed extra rotation; < 180° during flexion and abduction. Muscle strength was measured in the movement of flexion (MS FS), abduction (MS AS) with sitting subject, intra and extra rotation (MS IR, MS ER) with prone subject, by digital dynamometer (Jtech Commander Echo). The mean values were expressed in Newton. Sonography (US) was performed by a sonographer (DM) blinded to the results of clinical evaluation.

US was performed, as reported in earlier studies (Melchiorre et al., 2014, 2018; Farin et al., 1990; Galluccio et al., 2017) in all players before, immediately after and 30 days after each treatment with equipment ESAOTE MyLab 70 X-Vision with linear probe 8-16 MHz. The interobserver (κ=0.88) and intraobserver (κ=0.98) agreement was assessed. The following sonographic features were evaluated: 1) width of the subacromial-subdeltoid bursa (SSB); 2) thickness of supraspinatus (ST) and long biceps tendons (LBT); 3) hypoechoic halo surrounding the long biceps (LBH) and subscapularis tendons (STH); 3) width of acromioclavicular joint (ACJ) capsule and the distance between bone heads (ACD). Impingement (IS) was studied by dynamic examination with evaluation of coracoacromial ligament position. The glenoid labrum was also examined (Middleton et al., 1986; Crass et al., 1987).

2.4.1.4 Statistical analysis

IBM SPSS Statistics version 26 software was used for the statistical analysis.
In order to verify the normality of the data distribution, a Kolmogorov-Smirnov test was adopted.
The paired samples t-test was used to check the statistical significance of the differences within the groups for normally distributed variables. The independent samples t-test was adopted to verify the statistical significance of the differences between groups for the same kind of variables.
The Wilcoxon test and the Mann-Whitney test were used for the same purposes, for variables not distributed according to the normal.
For dichotomous variables, the Chi-squared test was used for differences within the groups while the McNemar test for those between groups.

2.4.2 Results

Results are shown in Table 2.4.2, Table 2.4.3 and Table 2.4.4.
In group 1 MSM induced an improvement of the pain at T1 (p=0.006) and T2 (p=0.02), of the Yocum test at T1 (p=0.063) and T2 (p=0.008), of the Hawkins test at T1 (p =0.125) and T2 (p=0.031), of the passive ROM at T1 (flexion p=0.030; abduction p=0.013, internal rotation p=0.463) and T2 (flexion p 0.001; abduction p 0.035, internal rotation 0.002), of the active ROM at T1 (flexion p=0.085, abduction p=0.028, internal rotation p=0.925) and T2 (flexion p 0.002; abduction p 0.016, internal rotation 0.001) (Table 2.4.2). US findings showed in group 1, after MSM, a decrease of thickness of SSB at T1 (p=0.01), and T2 (p=0.001), of LBT at T1 (p=0.635) and T2 (p=0.014); a decrease of LBH at T1 (p=0.008) and T2 (p=0.014), of STH at T1 (p=0.08) and T2 (p=0.002); a decrease in width of ACJ at T1 (p=0.005) and T2 (p=0.004); a reduction of bone heads ACD at T1 (p=0.002) and T2 (p=0.001). IS was absent in 12 out of 14 subjects, (Table 2.4.3)
In group 2 the simple traction did not show a significant change in all subjects.
Comparison between the groups shows better efficacy of MSM than simulated traction of NRS at T2 (p = 0.001), the Yocum test at T1 (p = 0.040) and T2 (p = 0.003), the Hawkins test at T2 (p = 0.013), passive ROM at T2 (flexion p = 0.002; abduction p = 0.036; internal rotation p = 0.004), active ROM at T2 (flexion p = 0.006; internal rotation p 0.002) and strength muscle at T2 (flexion p = 0.038) (Table 2.4.4). Comparison of US results between groups also showed some statistically significant differences about SSB thickness at T1 ($p < 0.0001$) and T2 ($p < 0.0001$), LBT thickness at T2 (p =

0.046), LBH at T2 (p = 0.000), SSH at T1 (p = 0.003) and T2 (p < 0.0001) and IS at T1 (p < 0.0001) and T2 (p < 0.0001) (Table 2.4.5).

Table 2.4.2. Mean values± SD and p of pain severity, clinical tests scores,passive and active range of motion (ROM), muscle strength scores before (T0), after the treatment (T1) and at the follow up (T2) in the group 1 and group 2. p<0.05

Group 1	Baseline (T0)	Post-treatment (T1)	PT1/T0	Follow-up (T2)	P	Group 2	Baseline (T0)	Post-treatment (T1)	P	Follow-up (T2)	P
NRS	5	3	**0.006**	0	**0.002**	**NRS**	4	4	**0.084**	5	**0.739**
Neer's T	5	2	**0.250**	2	**0.250**	**Neer's T**	4	5	**1**	5	**1**
Yokum T	12	7	**0.063**	4	**0.008**	**Yokum T**	10	9	**1**	9	**1**
Hawkins T	9	6	**0.125**	4	**0.031**	**Hawkins T**	8	8	**1**	8	**1**
PROM FS	160.42±23.36	164.29±21.38	**0.030**	178.25±2.50	**0.001**	**PROM FS**	170.50±5.68	170.70±5.88	**0.726**	172.50±4.84	**0.066**
PROM AS	165.29±28.05	174±28.58	**0.013**	182.37±5.72	**0.035**	**PROM AS**	173.50±16.2	174.30±14.24	**0.437**	174.83±10.68	**0.674**
PROM ER	88.36±14.73	92.50±10.81	**0.032**	93.37±3.59	**0.258**	**PROM ER**	91.30±8.15	91.90±5.72	**0.674**	90.83±4.67	**0.326**
PROM IR	59.79±15.49	61±10.16	**0.463**	79.87±8.74	**0.003**	**PROM IR**	64.80±.57	62.50±8.59	**0.721**	67.33±9.79	**0.308**
AROM FS	163.21±15.72	166.43±20.04	**0.085**	176.75±3.89	**0.002**	**AROM FS**	170.10±5.54	172±4.42	**0.062**	172.16±4.50	**0.036**
AROM AS	163.43±31	178±30.08	**0.028**	182.37±9.20	**0.016**	**AROM AS**	177.10±15.40	176.10±15.95	**0.368**	178.83±10.13	**0.878**
AROM ER	92.86±18.59	93.71±13.83	**0.937**	92.25±3.00	**0.3**	**AROM ER**	93.50±11.91	93.40±9.05	**0.514**	93.16±5.50	**0.721**
AROM IR	60.93±15.93	60.29±13.61	**0.925**	79±6.74	**0.001**	**AROM IR**	65.70±10.66	63.90±11.10	**0.385**	67.16±8.92	**0.635**
MS FS	74.64±16.19	75.93±22.93	**0.414**	80.87±8.24	**0.432**	**MS FS**	73.70±10.17	72.80±6.10	**0.505**	75.83±3.44	**0.445**
MS AS	69.21±16.44	70.79±21.32	**0.721**	73±10.08	**0.473**	**MS AS**	69.20±13.44	66.10±9.57	**0.115**	67.16±7.56	**0.453**
MS ER	66.64±14.85	69.93±17.96	**0.432**	72.62±13.83	**0.433**	**MS ER**	70.60±9.14	69±4.27	**0.608**	70.66±3.22	**0.799**
MS IR	84.07±19.44	82.93±17.57	**0.385**	84.71±10.62	**0.893**	**MS IR**	81.90±10.86	82.10±10.31	**0.917**	82.60±11.48	**0.795**

Table 2.4.3. US findings. Mean values ± SD and p of ultrasound report data,before (T0), after the treatment (T1) and at the follow up (T2) in the group 1 and group 2. p<0.05

Group 1	Baseline (T0)	Post-treatment (T1)	P	Follow-up (T2)	P	Group 2	Baseline (T0)	Post-treatment (T1)	P	Follow-up (T2)	P
SSB	3.10±0.59	1.85±0.51	**0.001**	1.85±0.29	**0.001**	**SSB**	3.09±0.43	3.13±0.46	**0.798**	2.80±0.38	**0.075**
ST	7.74±1.34	7.70±1.12	**0.925**	7.53±0.85	**0.638**	**ST**	7.89±1.44	7.95±1.41	**0.294**	7.63±0.48	**1**
LBT	3.45±0.93	3.28±0.55	**0.635**	2.90±0.31	**0.014**	**LBT**	3.32±0.39	3.27±0.44	**0.680**	3.14±0.32	**0.116**
LBH	1.33±0.85	0.65±0.79	**0.008**	0.21±0.44	**0.014**	**LBH**	1.17±0.82	1.27±0.94	**0.336**	1.63±0.37	**0.068**
STH	2.22±1.05	0.92±1.39	**0.008**	0.25±0.51	**0.002**	**SSH**	2.33±0.87	2.37±0.93	**0.336**	2.10±0.79	**0.115**
ACJ	3.44±1.33	2.59±0.64	**0.005**	2.48±0.39	**0.004**	**ACJ**	3.53±1.03	3.54±1.01	**0.305**	3.14±0.48	**0.593**
ACD	6.95±1.77	5.76±1.23	**0.002**	5.08±0.74	**0.001**	**ACD**	6.47±2.22	6.12±1.97	**0.055**	6.25±1.69	**0.944**
IS	14	2	**0.001**	2	**0.001**	**IS**	10	10	**1.**	10	**1**

Table 2.4.4. Groups Comparison p values of mean/median comparison of pain severity, clinical tests scores,passive and active range of motion (ROM), muscle strength scores before (T0), after the treatment (T1) and at the follow up (T2) between groups. p<0.05

Group 1/ Group 2	Baseline (T0)	Post-treatment (T1)	Follow-up (T2)
NRS	0.690	0.572	0.001
Neer's T	0.831	0.058	0.058
Yokum T	0.212	0.040	0.003
Hawkins T	0.633	0.069	0.013
PROM FS	0.277	0.618	0.002
PROM AS	0.482	0.558	0.036
PROM ER	0.659	0.680	0.212
PROM IR	0.100	0.860	0.004
AROM FS	0.216	0.977	0.006
AROM AS	0.363	0.240	0.054
AROM ER	0.638	0.791	0.512
AROM IR	0.617	0.481	0.002
MS FS	0.517	0.725	0.038
MS AS	0.998	0.525	0.137
MS ER	0.596	0.618	0.274
MS IR	0.753	0.895	0.647

Table 2.4.5 Groups Comparison p values of ultrasound report data,before (T0), after the treatment (T1) and at the follow up (T2) between groups. $p<0.05$

Group 1 / Group 2	Baseline (T0)	Post-treatment (T1)	Follow-up (T2)
SSB	0.680	0.000	0.000
ST	0.883	0.660	0.301
LBT	0.792	0.702	0.046
LBH	0.906	0.079	0.000
STH	0.596	0.003	0.000
ACJ	0.639	0.017	0.005
ACD	0.538	0.747	0.067
IS	0.388	0.000	0.000

2.4.3 Discussion

The main difficulty in the sport of water polo is finding the ideal position to make an effective shot. Therefore, the importance of a stable shoulder is obvious. In fact, during the preparation phase, the shoulder is maintained in an abducted position due to the activation of the medial and anterior part of the deltoid, of the supraspinatus and of the clavicular part of the pectoralis major. In the loading phase, an excessive articular excursion is determined, which involves an over distension of the capsular-ligamentous component and a consequent relative instability of the glenohumeral joint (Matzkin et al., 2016). MSM plays, as demonstrated in earlier studies, an important function in shoulder stabilization, as it results, in rapid self-centering of the head of the humerus (Melchiorre et al., 2014, 2018). These results showed that MSM is able to remove impingement, even in water polo players, as confirmed by US measurements (Table 2.4.3). Moreover, the data of this study showed other improvements in group 1: a significant difference of pain both at T1 ($p=0.006$) and at T2 ($p=0.02$) and of the passive and the active ROM at T1 and at T2 as reported in Table 2.4.2. Results were also confirmed by the comparison between the two groups (Table 2.4.4, Table 2.4.5). No athlete had symptoms consistent with a glenoid labrum injury and this was confirmed with US at time T0. In all athletes in group 1, US detected a marked improvement in the considered ultrasound parameters with a significant difference in both T1 and T2, as reported in Table 2.4.3. In SIS, the thickness of SSB

appears increased. US findings confirm this at T0 (Figure 2.4.1). It is important to point out that in water polo players of the first group, US, immediately after MSM, showed reduction of the bursa with a significant difference at T1 (p=0.01) and at T2 (p=0.001) (Table 2.4.3). A similar result was obtained when comparing the two groups (Table 2.4.5). In these results, an unexpected finding related to the distance between the bony heads of the ACD has been found (Figure 2.4.1). In fact, this distance appeared markedly and significantly reduced at T1 (p=0.002) and T2 (p=0.001) if compared to T0 in water polo players in group 1. In conclusion, these results showed the efficacy of MSM with a persistent amelioration at T2 and the improvement of water polo players performance during the follow-up period. It should be noted that the effectiveness of MSM is improved when comparing the two groups with simple traction.

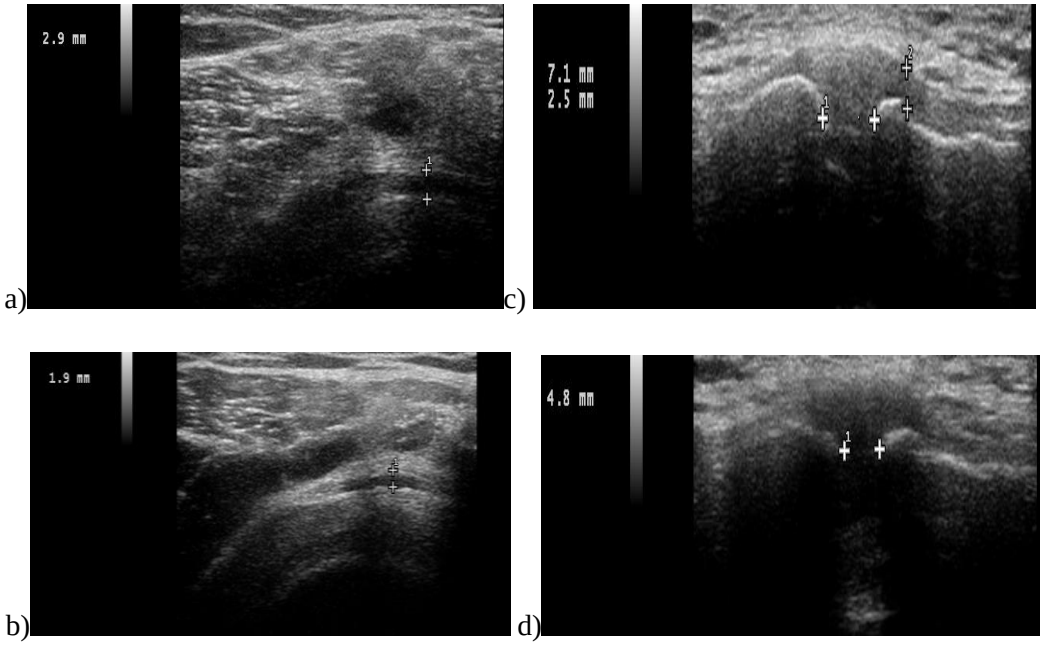

Figure 2.4.1 a) SSB thickness before MSM (T0); b)SSB thickness after MSM (T1); c)the distance between the bony heads of the ACD before MSM; d) the distance between the bony heads of the ACD after MSM.

Chapter 3. General discussion and conclusion

The use of objective and reliable measuring instruments is necessary for the investigation of the physiological functioning mechanisms of a physiotherapy technique studied on humans. For this reason, the data from this research, albeit with some limitations, represent a new starting point for understanding the effects of MSM.

In fact, in all the experiments performed, changes in the body structure can be highlighted which result in improvements in functional outcomes. It has been observed that nine children with CP, after MSM, experienced an immediate increase in muscle strength and joint excursion of the ankle and those improvements were still present after 7 days. These results proved to be equal or greater than the absolute values of the MDC95 for plantar flexors strenght and joint excursion in a remarkable proportion of subjects (67-100%) (Longo et al., 2021).

Another physiological parameter, EMG activity, improved clearly in a subject with a peroneal nerve injury. An increased activation of the peroneus brevis and tibialis anterioris, and a particularly consistent increment of EMG activity of the peroneus longus were found; the improvement would be in line with the increase of active dorsiflexion ROM and muscle strenght in the same subject. At the same time the integrated value of gastrocnemius lateralis decreased over time probably improving a compensation of an active deficit of the tibialis anterior and evertor muscles.

In the pilot study, as well as in the randomized clinical trial that will follow, for the first time, a reliable tool was used for measuring the TSRTs on patients with chronic stroke, which were chosen as measures of primary outcome to evaluate the MSM treatment applied on the spasticity of the plantaflexors of the ankle. According to the results, TSRTs values decreased in the MSM group and their values' variation is consistent with the hypothesised mechanism of action of MSM, a modulation of the TSRTs (Grimaldi et al., 1986). Also in this study there was an increase in the strength of the tibialis anterior and in the active and passive ROM of the ankle within the group treated with MSM.

Morphostructural changes in the shoulder joint were highlighted by the clinical trial conducted on a sample of water polo players. In particular, through the use of US, it was found that MSM is able to remove impingement with a consequent increase in active and passive ROM and with a marked reduction in the SAD bursa and in the distance between the boney heads of the ACD immediately after the application of the maneuver and at the follow up (Longo et al., 2022).

It is plausible that all the observed variations in joint passive and active ROM and muscle strength are linked to the decrease of TSRTs, thus suggesting a potential effect of MSM on the neuromuscolar spindles of the involved muscles and related motor control (Grimaldi et al., 1986). According to

Feldman's model, the modulation of SRTs allows interaction with the environment by mean of a fluent control of muscular forces and joint angle. Regulation of thresholds, and positional and velocity gains of the stretch reflex are consequences of supraspinal action and may have implications in motor control disorders related to diseases of the nervous system (Feldman, 2010, 2016). The positive effect could be explained by the proprioceptive feedback due to the MSM, inducing a neuromuscular review; novel muscle TSRTs and configurations of the joint, within different body frames of reference may have produced a stronger and more balanced agonist-antagonist muscular action (Grimaldi et al., 1986).

These assumptions may be behind the improvements in functional outcomes found in these studies. In fact, it was possible to find an improvement in the quality of the walking pattern both in children with CP (Longo et al., 2021) and in the single case of the subject with peripheral lesion of the peroneal nerve. In the first case, analyzing the gait by the means of gait videotaping and consequent offline modified Physician Rating Scale, it was found the ability to perform a better push-off and swing phase. In the single case it was found that the gait parameters, analyzed through an iPhone app that used the inertial sensor, changed across assessments. At baseline, the pattern was characterized by the foot drop and a shorter left stance phase, with compensatory and substitutive movements. At the follow-up assessment, the individual showed a moderate decrease of gait speed, step length and cadence, and a symmetric gait pattern.

Statistically significant improvements in walking speed were also highlighted in the pilot study on patients affected by chronic stroke, as shown by the performance values of the TUG test. In fact, participants in the MSM group mostly had an improvement in the TUG test greater than the absolute MDC95 value.

In the case of water polo players with SIS (Longo et al., 2022), on the other hand, the reduction of the SAD bursa and the disappearance of shoulder impingement led to a significant decrease in the pain perceived by the participants, assessed by means of the NRS scale, which resulted in a qualitative improvement of the athletic performance in the period between the two moments of observation.

These results seem to confirm some peculiarities of MSM already found in previous studies and in common clinical practice (Crippa et al., 2004; Longo et al., 2017; Melchiorre et al. 2014, 2018). For example, its supposed ability to affect the tonic stretch reflex and, consequently, the motor control makes it suitable not only for neurological injuries but also on pathologies with different etiopathogenesis, as evidenced by the study conducted on shoulder impingement. in water polo players.

In all the experiments conducted, MSM appears to have no adverse events and appears to be well tolerated by patients compared to other therapeutic approaches used for their respective pathologies.

The possibility of performing MSM even in the presence of pain, as assessed in the clinical trial on shoulder impingement, or functional limitations, such as, for example, the joint ROM evaluated in all the studies reported, seems to be confirmed.

In this research, MSM was performed on two muscle groups (ankle plantaflexors and shoulder adductors) in dissimilar districts. The resulting changes in physiological and functional parameters would seem to confirm the possibility of performing MSM on many different muscle groups in different kinematic contexts.

The contraindication of including muscle-tendon retractions and joint ankyloses in the inclusion criteria of the MSM studies seems to be confirmed by the results of a subject selected in the pilot study. It has been noticed that this subject in the MSM group presented negative or very close to 0 μ values, which usually characterize Parkinson's disease rigidity (Mullick et al., 2013); as he was the participant with the longest disease duration (over 30 years), fibrosis and small retractions could have interfered the sensitivity to stretch. These impairments, albeit minimal, could have influenced the result of the stimulation and, despite the presence of an improvement in the investigated outcomes, could create a source of error in the analysis of the results.

Particularly challenging are the considerations on dosing of the MSM. In all the tests carried out, in fact, the subjects' burden was very low. The stimulations lasted from 10 to 20 minutes with an oscillation frequency between 1 and 3 Hz and were performed once or twice a week for a period of between 1 and 4 weeks. Only in the case of peroneal nerve injury was the subject receiving MSM also given another treatment, thus increasing his weekly commitment. On the other hand, in the clinical trial on water polo players, the MSM was performed only once, after which the morphostructural and instrumental results were immediately detectable.

This latter assumption was re-identified in all studies conducted on MSM with the exception of the pilot study on subjects with chronic stroke who presented spasticity of the ankle plantaflexors. In that study, post hoc analysis showed that the improvements were significant one month after the end of treatment, at T2 follow up. It should be noted that, in that study, the variables showing improvement were measured by reliable quantitative instrumental measures.

Almost all the conducted studies show limitations from a methodological point of view, although they are referable to specific guidelines for the report of their own study designs. To truly demonstrate the effectiveness of this type of treatment, it would be necessary to carry out a randomized and controlled clinical trial based on the indications emerging from the pilot study on patients with chronic stroke. Keeping in mind this next study, and to appropriately register the trial, it's needed to reconsider issues such as recruitment strategy, participant stratification, blinding, exhaustive standardised intervention protocols and training programs for therapist and assessors, and many other

(Dobkin, 2009; Stinear et al., 2020). Furthermore, the comparator treatment that was used, although easy available and adequate for a pilot, would not be acceptable for an effectiveness study. An interesting control intervention could be the Transcutaneous Electrical Nerve Stimulation (TENS) and it would be interesting to compare MSM and TENS by the MSMD measure (Mahmood et al., 2019; Levin and Hui-Chan, 1992).

In conclusion, the results of these studies seem to highlight a real effect of MSM on motor control understood as modulation of TSRT, in the perspective of Feldman's threshold referent control theory. Obviously, higher methodological level studies need to be performed in order to test the real efficacy of the treatment and better explore the cause/effect relationships. However, this study indicates that MSM can be used in different muscle districts and for different diseases, which will allow researchers to greatly expand the possibilities of future investigation on this topic.

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