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STROKE REHABILITATION (GE FRANCISCO, SECTION EDITOR)

Peripheral Mechanisms Contributing to Spasticity and Implications for Treatment

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Abstract Histolopathological studies have demonstrated a generalized increase in extracellular connective tissue in spastic muscles. It is known that increased connective tissue in an immobilized and contracted muscle reduces its compliance and could reduce the threshold for stimulation of spindle receptors in the muscle. Various authors have investigated how increased stretch-induced stimulation of spindles in muscles with stiffer connective tissue can contribute to spasticity. In this review, we compile evidence for the idea that the primary injury to the central nervous system that leads to muscle paresis also triggers changes in the viscosity of the extracellular matrix due to abnormal turnover of hyaluronic acid. Hyaluronic acid is a complex molecule that exhibits non-Newtonian behavior at higher concentrations, leading to altered connective tissue viscosity, which begins a vicious circle that exacerbates spasticity through reduced tissue compliance and potentiation of reflex mechanisms and fibrosis, and contributes to abnormal limb posturing, pain symptoms, and decreases in activities of daily living. The rationale for emerging treatments to break this vicious circle are discussed.

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Introduction

Spasticity is defined as a motor disorder characterized by a velocity-dependent increase in muscle tone with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex as one component of the upper motor neuron syndrome [1]. The incidence of spasticity in patients with spinal cord injury is 65–78 % [2]. In contrast, only around 35 % of the patients with persistent hemiplegia after stroke manifest spasticity [3]. More specifically, the prevalence of spasticity is about 19 % within 3 months after stroke, but rises to 39 % after 12 months [4]. Spasticity commonly presents as muscle overactivity, reduction in the ability to relax, hypertonia, paresis, muscle spasms, and loss of fine motor control, which are attributed to neural mechanisms [5]. However, less understood symptoms include increased stiffness in the soft tissue, muscle fatigue, and postural changes in the limbs, which may be explained by non-neural contributions having secondary effects on skeletal muscles [6, 7]. Lundstrom et al. [8] postulate that spasticity cannot be considered an immediate consequence of CNS injury because it progresses during the weeks and months after the injury.

Several studies have demonstrated that muscular changes in spasticity cannot be explained by classic interpretations of the effects of neural changes alone [9, 10]. For example, Crone et al. [11] found that there is no correlation between the degree of spasticity (assessed by the Ashworth scale) and the degree of reduced "reciprocal inhibition." Gracies et al. [12, 13] proposed that muscular changes in spasticity cannot be fully explained by hyperreflexia or alterations in the central processing of sensory input in the

spinal cord alone. Studies show that individuals presenting with spasticity after spinal cord injury on clinical examination turn out not to have any signs of hyperreflexia [14, 15]. In addition, it was shown that reflex stiffness did not differ significantly between the impaired spastic and the less impaired contralateral limb in individuals with spastic hemiparesis [16]. It has therefore been suggested that structural and functional changes in and around skeletal muscles may account for the late presentation of disabling spasticity after CNS injury. These changes range from rounding of the muscle fibers, to an increase in the inter-fiber space in hypertrophic fibers, to fiber atrophy, which are all associated with deposition of excessive connective tissue in the muscle [17–20]. The purpose of this current report is to summarize the literature supporting the peripheral mechanisms contributing to spasticity after CNS injury. This article does not contain any studies with human or animal subjects performed by any of the authors.

Peripheral Alterations in Spasticity

Several studies support the involvement of peripheral tissues, such as muscle fibers and connective tissue, in spasticity. Mirbagheri et al. [21] found that intrinsic muscle stiffness was increased in patients with spasticity. Wood et al. [22] describe the complex interactions between muscle cells and the extracellular matrix that affect the contractile properties of skeletal muscle fibers relevant to changes that occur with spasticity. Lieber et al. [23] showed that spastic muscle bundles are stiffer than isolated single spastic fibers; only about 40 % of spastic muscle bundles were occupied by muscle fibers in contrast to 95 % in normal muscle bundles, suggesting increased intramuscular connective tissue deposition in spastic muscle bundles. Three different mechanisms have been proposed to explain the 'increased resistance to stretch' or intrinsic muscle stiffness [9]: (1) active muscle stiffness where increased stiffness is caused by an increase in the number of cross-bridges attached during muscle contraction; (2) neurally mediated reflex stiffness caused by descending influences on the monosynaptic reflex between muscle spindle afferents and the alpha motor neurons; (3) passive muscle stiffness caused by fibrosis within the muscle tissue or a change in the properties of the muscle fibers.

Active Muscle Stiffness: Alterations in the Extracellular Matrix

The extracellular matrix is composed of adipose cells, glycosaminoglycans, and hyaluronic acid. Hyaluronic acid is however the chief component [24]. Immobilization or paresis decreases the normal turnover of the extracellular matrix, increasing its concentration within and between the muscular compartments. It is known that hyaluronic acid behaves like a non-Newtonian fluid at high concentrations and becomes more viscous [25]. The increased viscosity of the loose connective tissue may cause decreased gliding between the layers of collagen fibers, which may be perceived by patients as stiffness [26]. In a longitudinal study examining the effects of immobilization in rat soleus muscle, hyaluronic acid concentrations were increased, and sarcomere length was shortened by as early as 1 week [27]. These changes can lead to an increase in the number of cross bridges attached during contraction [28, 29], producing active muscle stiffness. Note that at this stage the arrangement of collagen fibrils in the endomysium is still longitudinal, but becomes more circumferential by 4 weeks [27]. It is known that under homeostatic conditions hyaluronic acid has important roles in tissue's structural integrity. However, a series of events that leads to muscle contracture may begin with subtle changes in the turnover of hyaluronic acid [30, 31] and the properties of the extracellular matrix very early on after CNS injury (Fig. 1).

Neurally Mediated Muscle Stiffness: The Role of Muscle Spindles

The muscle spindles are enclosed in a capsule and have both sensory and motor components. The motor component consists of several small specialized muscle fibers known as intrafusal fibers, localized at either end of the muscle spindle. The sensory component is localized in the central area of the spindles, where specialized nerve endings termed annulospiral and flower-spray endings are present. The annulospiral endings (Ia afferents) provide information about the length and velocity of muscle contraction, whereas the flower spray endings (group II afferents) only provide information on muscle length, but these sensory fibers respond even when the muscle is at rest. When the muscle lengthens and the muscle spindle is stretched, mechanically gated ion channels in the sensory dendrites are opened. This leads to a receptor potential that triggers action potentials in the muscle spindle afferents; the firing of the spindle Ia afferents stimulates the alpha motor neurons in the spinal cord causing reflex contraction of the extrafusal muscle fibers. At the same time Ia spindle afferents synapse in the posterior horn of the cord and stimulate inhibitory interneurons, which then depress alpha motor activity to the antagonistic muscles. Thus, the simple myotatic/stretch reflex acts as a servo-mechanism to maintain correct muscle tone. Muscle tone (residual muscle tension or tonus) is the continuous and partial contraction of the muscles or the muscle's resistance to passive stretch during rest. If the muscle spindles cannot be activated or

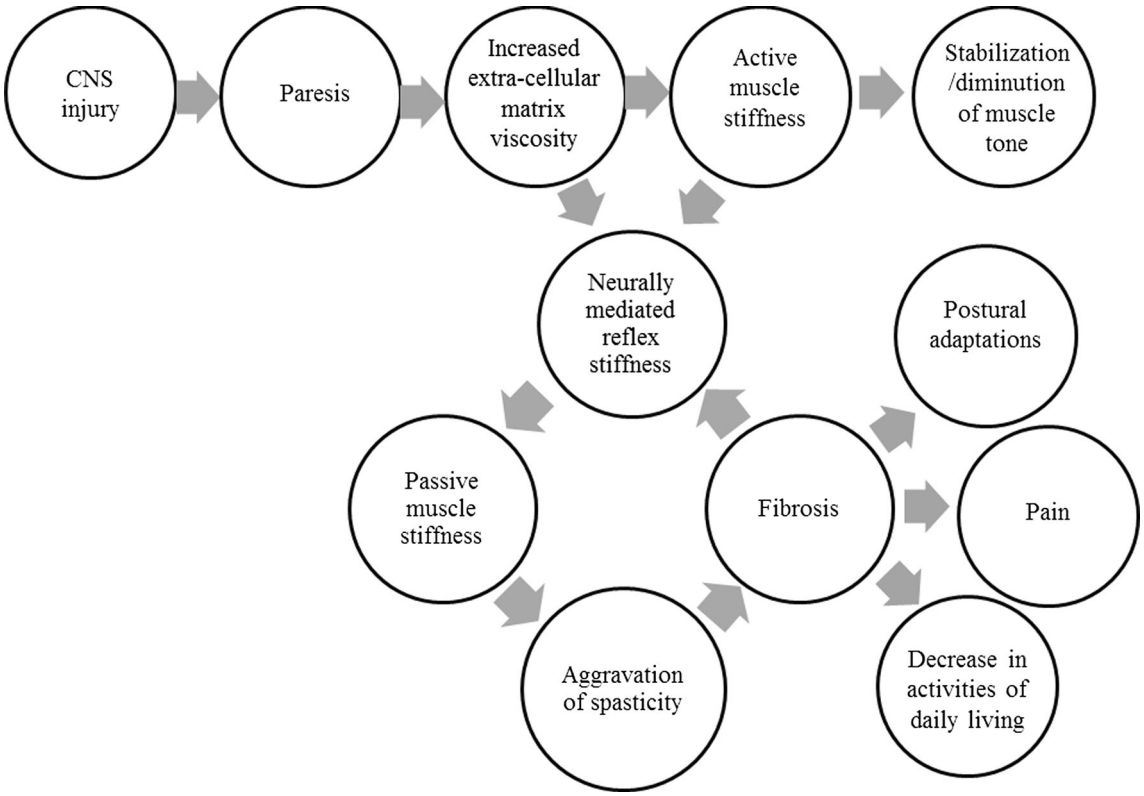

Fig. 1 Proposed model of the evolution of the spastic process

are activated too easily, the regulation of muscle tone will be compromised [5, 32, 33].

When the relationship between muscle spindles and the intramuscular connective tissue is considered, the role of the muscle spindles in peripheral motor coordination becomes evident. The muscle spindles are localized in the perimysium, and their capsule is connected to the epimysium and fascial septae [34, 35]. Strasmann et al. [36] analyzed the septum of the supinator muscle and found that many muscle spindles are inserted directly into the connective tissue of the septum. Studies have demonstrated that the extra- and intrafusal muscle fibers possess complex biophysical properties that contribute to muscle stiffness and/or laxity [37, 38]. Increased stiffness of connective tissue in an immobilized muscle reduces its compliance. This in turn increases spindle stimulation to a given stretch, as the pull is transmitted more efficiently to the spindles in a less extensible muscle [39]. Such an increase in spindle responses has been demonstrated after immobilization in a shortened position, which augments stretch reflexes and eventually contributes to the stretch-sensitive forms of muscle overactivity [40–42]. Thus, Gracies proposed that the etiology of spasticity involves increased stretch-induced stimulation of spindles in muscles with stiffer connective tissue (endomysium, perimysium and epimysium), which contributes to abnormal feedback and feed-forward control of the extrafusal muscle fibers [43]. However, the relative contribution of intrinsic muscle stiffness versus neurally mediated spindle responses may vary by body region affected [44].

It is commonly noted that voluntary movements that stretch a spastic muscle produce a reflex in the antagonistic muscle opposing the initiating movement [45]. Constant overuse of spastic antagonist muscles can augment the production [46•] and retention [47] of hyaluronic acid in the connective tissue. The increased concentration of hyaluronic acid on the spread surface can lead to its further self-association, leading to dramatically increased viscoelasticity [48]. The higher viscosity extracellular matrix can alter the perimysium as well the muscle spindle capsule, leading to hyperstretching of the annulospiral ring, and further decrease the threshold of activation of the spindle afferents and the alpha motoneuron, with increasing spasticity in the corresponding motor unit. In fact, Beres-Jones [49] has demonstrated that repetitive clonic muscle contractions are more likely to be associated with impaired interaction of central and peripheral mechanisms than with recurrent stretch reflex activity. Elderly individuals however often show a decrease in basal tone and reflex activity, perhaps because of sarcopenia and consequent alterations in muscle tone and muscle spindle activation [50]. Disabling spasticity occurs more commonly in young survivors (<65 years) or after a first stroke [51], further

necessitating that we understand the mechanisms and initiate appropriate treatment early.

Passive Muscle Stiffness: Deposition of Collagen and Fibrosis

In the chronic phase, histolopathological studies show a generalized increase in extracellular connective tissue in spastic muscles, specifically an increase in the concentration of collagen [18, 19]. Stecco et al. [52] reported similar findings in patients after 10 months of immobilization that could simulate the period of flaccid paralysis after CNS injury. The authors dissected several recently amputated legs of patients that had been immobilized with a tibiofemoral external fixator because of severe trauma to the knee region. They showed the existence of fibrotic zones in the subcutaneous tissue that created adherences between the skin and deep fascia in the ankle region, which had not been injured. The entire ankle region demonstrated alterations in the subcutaneous tissue, and the deep fascia showed a disorganized arrangement of the fibrous bundles. Histological study showed that the loose connective tissue separating the subcutaneous planes was absent and that all the structures were replaced by homogeneous fibrous tissue. Studies by Järvinen et al. [53] reveal that immobilization results in a marked increase in the endo- and perimysial connective tissue of the muscle, the majority of the increased endomysial collagen being deposited directly on the sarcolemma of the muscle cells. The connective tissue becomes very dense, and the number of irregularly oriented collagen fibers is markedly increased. Further, immobilization clearly disturbs the normal structure of the endomysium, making it impossible to distinguish the various networks of fibers from one another. One might hypothesize that similar findings would be seen in individuals with chronic stroke. In fact, the presence of dense connective tissue (fibrosis) has been recently confirmed through ultrasonography by Picelli et al. [54•]. The authors quantified the disruption of normal muscle architecture in spastic muscles by evaluating and grading muscle echo intensity. The hyper-echogenicity in the muscle in the chronic stage is due to an increase in collagen fiber both within and between the muscle bundles (Fig. 2). Excessive collagen deposition is thought to lead to the development of abnormal postures, and greater amounts of collagen predict a lower response to conventional treatments for spasticity such as botulinum toxin injections.

Although muscle fibers are the main tissues studied in spasticity, there is no agreement on the role of muscle fiber pathology and abnormal muscle activity in spasticity [9, 23]. Muscle biopsies from patients with spasticity show abnormalities such as increased variability in fiber size, increased numbers of 'rounded' fibers, and 'moth-eaten' fibers [17, 20, 55, 56]; these are however non-specific changes also noted in other disease states and may be directly attributed to the effect of immobilization. Morphometric and histochemical investigations show changes in mechanical muscle fiber properties [17, 28, 57] that might contribute to spastic muscle tone, indicating an increase in passive stiffness of a muscle to stretch in patients with stroke and spasticity due to subclinical contractures. Indeed, studies have found that functional alterations in patients with muscle hypertonia are associated with subclinical muscle contracture rather than with reflex hyper-excitability [6, 13, 16, 58–60]. Thus, the data are congruent with the idea that instead of spasticity causing contracture, contracture may actually potentiate spasticity in some patients [59]. Consequently, the Ashworth scale and modified Ashworth scale remain low-sensitivity instruments for distinguishing between soft tissue and neural contributions to hypertonia [61]. Electromyographic measurements can quantify the resistance to passive movement, but cannot determine how much resistance is produced by the tonic stretch reflex and how much is produced by soft tissue stiffness [5].

Role of Peripheral Mechanisms in Generating Pain

Post-stroke spasticity is often associated with secondary complications such as pain and limitation in mobility. Motor and sensory impairments are associated with an increased risk for stroke-related pain [8]. Patients with spasticity produce compensatory movements and postures because of changes in their muscles and soft tissues. Such compensations are also noted with common musculoskeletal dysfunction. Indeed, Stecco et al. [26] have documented alterations in the soft tissue and muscle in patients with chronic myofascial pain and have correlated the alteration in the loose connective tissue of the deep fascia with patients' stiffness and pain. The connective tissue is well innervated with free nerve endings and proprioceptors such as Pacini and Rufini corpuscles [62–64]. It has been shown that change in the visco-elasticity of the connective tissue shapes the dynamic response of the mechanoreceptors in the tissue, which may become the source of pain [65, 66]. Thus, there may be greater similarities between non-specific musculoskeletal pain and spastic muscle pain.

Implications for Treatment

In the early stages of immobilization from muscle paralysis, it is clear that the concentration of hyaluronic acid is altered, which triggers a cascade of changes leading to the

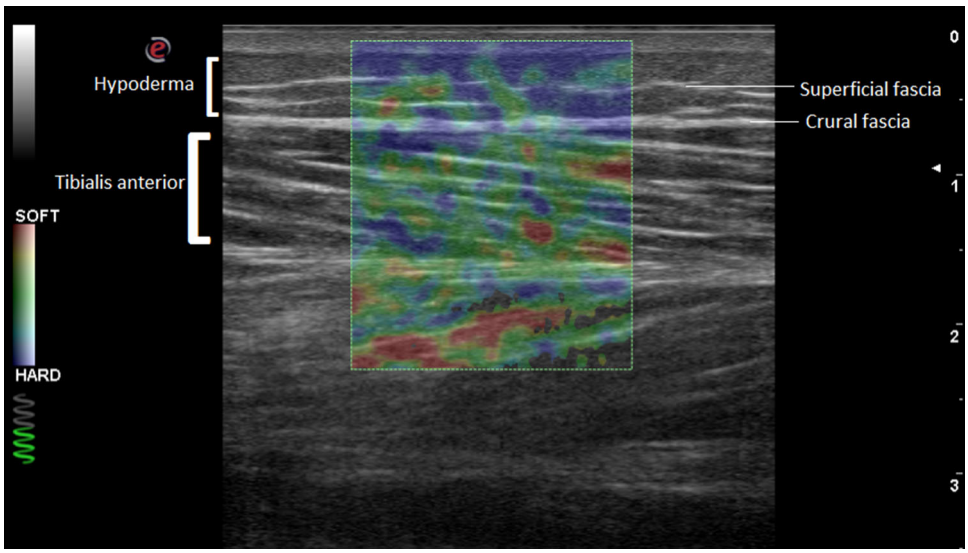

Fig. 2 Ultrasound elastosonography can be used to assess tissue stiffness as shown in the image of a spastic tibialis anterior muscle. In this method, the change in the radiofrequency pulses from a structure are assessed via ultrasound before and after manual compression and displayed as an elastogram, which overlaps with the B-mode tracing of the ultrasound. The various colors represent areas of scanned tissue with different elasticities, more elastic (*red*) or more stiff (*blue*)

deposition of collagen within and between muscle bundles later on. Hyaluronic acid at higher concentrations behaves like a non-Newtonian fluid and increases the viscosity of the connective tissue. We hypothesize that the non-Newtonian behavior of hyaluronic acid may be especially responsive to mechanical stress, particularly manual deep friction or vibration, earlier on. However, studies testing the effects of mechanical interventions early on are sparse and may be warranted. Furthermore, when subjected to mechanical stress, hyaluronic acid becomes depolymerized and lower molecular mass polymers are generated [30]. Stern et al. [31] found that small polymers of hyaluronic acid, smaller than 1,000 Da, may be able to catalyze specific inflammatory reactions; these polymers may be generated by the injection of hyaluronidase enzyme. Thus, mechanical and biochemical control of the properties of hyaluronic acid early on may help restore the quality of hyaluronic acid and re-establish normal tissue-sliding mechanisms involving the endomysium, perimysium, epimysium, and deep fascia.

In the middle and later stages, when subclinical or overt contractures are already present, can treatment reverse the changes? It is thought that connective tissue is organized according to the principle of tensegrity, where the tensional and compressive forces are distributed and balanced to stabilize the structure [67]. Based on this principle, an increase or decrease in tension on one part of the structure leads to re-balancing of the entire structure to maintain stability. This principle can perhaps explain why subtle contracture in one region, for example at the elbow or wrist, may increase spasticity in another more distant region, for example, in the fingers. The principles of tensegrity are highly relevant to remodeling of connective tissue as well [68]. Various forms of exercise such as yoga and tai chi, and manual therapy such as massage and manipulation, attempt to regulate the transduction of forces through the body [69•, 70]. Myofascial release and osteopathic manipulation have been shown to be promising for reducing muscle spasticity in children with cerebral palsy [71]. It is well known that sustained stretch, for example, through casting, can be an effective therapeutic modality in the treatment of spasticity and hypertonia [72–75], even though it is difficult to implement appropriately. Combination treatment involving motor training, stretch, and local partial nerve blocks have long been advocated [76], and when implemented early may yet be the most effective approach for remodeling of connective tissue. The importance of motor training cannot be overestimated, as the mechanical forces from performing the action(s) may play a key role in both neural and mechanical remodeling through plasticity. However, guidelines still need to be worked out for selection of the motor training task(s). Recently, the use of vibratory stimulation applied to the whole body [77] or the plantar fascia [78] has also shown promise. Further research is however needed on how various physical modalities and forms of exercise modify and re-balance the tensional and compressive forces to relieve contractures and spasticity.

Conclusion

The primary lesion leading to spasticity lies within the central nervous system, but the connective tissue in patients with spasticity is also dramatically altered because of paralysis and the ensuing immobilization. This review presents a comprehensive discussion of the pathophysiology of connective tissue within and around muscles and its contribution to the evolution

of spasticity and hypertonia after CNS injury. We argue that connective tissue alterations begin a vicious circle composed of three phases: (1) an increase in the viscosity of the extracellular matrix leading to active muscle stiffness; (2) exacerbation of neurally mediated reflex mechanisms due to subclinical contractures affecting the threshold of muscle spindle activation; (3) fibrosis due to collagen deposition and an increase in passive muscle stiffness. Fibrosis leads to a further increase in extracellular matrix viscosity in the surrounding areas re-starting the circle. These peripheral mechanisms contribute to abnormal postural adaptation, myofascial pain syndromes due to the dynamic response of the mechanoreceptors localized in altered connective tissue, and further disuse and disability. We provide a rationale for emerging therapies that may be helpful to restore normal connective tissue architecture and tissue gliding mechanisms.

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Compliance with Ethics Guidelines

Conflict of Interest A. Stecco declares no conflicts of interest. C. Stecco declares no conflicts of interest. P. Raghavan has a patent for rehabilitative training devices for use by stroke patients issued.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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