Chapter 1

Pathophysiology of post-stroke spasticity

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Introduction

Hemiparesis is the hallmark motor impairment after stroke. It includes positive signs (spasticity, hyperreflexia, abnormal motor synergy, etc.) and negative signs (weakness, loss of dexterity, etc.). Both positive and negative signs are easily recognized clinically. Spasticity is commonly described as a phenomenon of increased resistance to externally imposed muscle stretch. Spasticity is viewed to be associated with hyperreflexia of stretch reflexes. However, due to changes in mechanical properties of spastic muscles, stiffness

from spastic muscles contributes to the clinical finding of increased resistance (muscular hypertonia) when they are passively stretched. These peripheral contributions are not adequately distinguished from neurally-mediated spasticity in routine clinical examinations,[1] and in quantitative assessment in a laboratory setting as well.[2] Furthermore, these motor impairments (spasticity, weakness, abnormal synergy) interact with each other in a vicious cycle,[3-5] resulting in various motor deficits in stroke survivors, such as difficulty in standing, walking, reaching, grasping etc. Thus, it is more appropriate to describe the finding of increased resistance from spastic muscles as "spastic hypertonia", while spasticity is hyperreflexia-mediated increase in resistance.[6-9] This differentiation helps us better understand neurally-mediated (*i.e.*, spasticity) and non-neurally mediated (*i.e.*, muscle stiffness or mechanical change of muscle property) increase in spastic hypertonia.[10,11] Better understanding of underlying pathophysiology of each component can help us recognize and diagnose the clinical problems accurately and guide us select the appropriate treatment options.

Definitions of spasticity

James Lance proposed a first definition of spasticity as a consensus from a symposium in 1980.[6] Though it is not validated, this definition is still widely used as follows: *"Spasticity is a motor disorder characterized by velocity-dependent increase in tonic stretch reflexes ('muscle tone') with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome"*.

The definition of spasticity has been evolved overtime, as research evidence and understanding of spasticity has progressed. The Lance's definition has been challenged and alternative definitions have been proposed.[12, 13] For example, Pandyan *et al.*, proposed a different definition in 2005 as follows:[12] *"Spasticity is a disordered sensori-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles"*.

This definition expands spasticity as a disorder of sensori-motor control, rather than simply a motor disorder. In fact, with this definition, spasticity is used as a generic term to include all positive signs and symptoms of the upper motor neuron syndrome, but yet it is narrow enough to exclude peripheral biomechanical changes in the muscles and joints. However, this definition does emphasize spasticity is a neurally mediated phenomenon. Specifically, abnormal regulations of stretch reflex are considered to contribute to hyperreflexia

and spasticity, including supraspinal control pathways and changes in alpha motor neuron properties.

To reflect recent research advances in the underlying pathophysiology of post-stroke spasticity and its relations with other parallel motor impairments, as outlined in the following sections, Li and colleagues proposed a new definition of post-stroke spasticity in 2021 as follows:[7] *"Spasticity is manifested as velocity- and muscle length-dependent increase in resistance to externally imposed muscle stretch. It results from hyperexcitable descending excitatory brainstem pathways and from the resultant exaggerated stretch reflex responses. Other related motor impairments, including abnormal synergies, inappropriate muscle activation, and anomalous muscle co-activation, coexist with spasticity and share similar pathophysiological origins."*

A longitudinal view of motor recovery and post-stroke spasticity development

Muscle weakness in the arm and leg on the paretic side occurs at the stroke onset as a result of direct damage to the motor cortex and/or its descending corticospinal pathways. Recovery of muscle strength and motor function commences almost immediately. The severity of initial motor impairment can be used to predict the amount of recovery at 3 months after stroke, (*i.e.*, proportional recovery).[14-16] Motor recovery follows a relatively predictable pattern after a stroke regardless of type (ischemic or hemorrhagic) or location (cortical or subcortical),[17] (*i.e.*, Brunnstrom stages).[18, 19] In contrast, post-stroke spasticity emerges with a time delay and evolves over time (Figure 1.1). The median time to detect post-stroke spasticity, as measured by the modified Ashworth scale ≥1, is 34 days after stroke onset.[20] Spasticity is only seen in a small portion (19%) of stroke survivors with moderate to severe motor impairments by 3 months after stroke.[21] By 12 months, spasticity is present in 43.2% of stroke survivors.[22] As a stroke survivor progressively recovers in an orderly manner in the course of complete motor recovery, post-stroke spasticity emerges, evolves, decreases, and eventually disappears. However, if motor recovery is plateaued or arrested, (*i.e.*, partial recovery), post-stroke spasticity evolves and persists after its emergence.[17, 19] It often becomes more severe over time.[23] In chronic stroke survivors with moderate and severe motor impairments, the prevalence of spasticity is up to 97%.[24]

Different trajectories of motor recovery and spasticity in the course of recovery reflect different underlying mechanisms. Motor recovery is a process of neuroplasticity and spontaneous biological recovery from

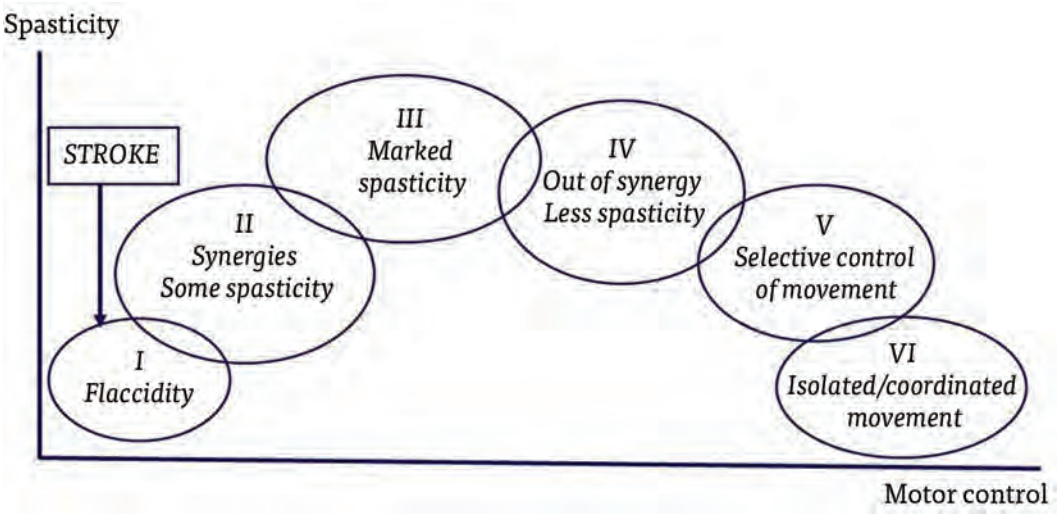

Figure 1.1.

Brunnstrom stages of stroke recovery and spasticity development. Spasticity emerges with a delay, and evolves as motor recovery progresses. Spasticity further decreases and disappears in the course of complete motor recovery. It persists and becomes worse over time in incomplete motor recovery (Li and Francisco).[31]

the damaged corticospinal system. The corticospinal tract is primarily involved in voluntary movement. Isolated lesions to this pathway in animal studies produce weakness, loss of dexterity, hypotonia and hyporeflexia, instead of spasticity. In a patient with a lacunar stroke causing an exclusive lesion of the pyramidal fibers at the medullary level, no spasticity was observed.[25] The observations of delayed onset and persistence / evolvement of spasticity during incomplete motor recovery imply that spasticity emerges as a reflection of abnormal plasticity. After an initial period of hypotonia after stroke, there is a gradual return of reflexes, but not a sudden progression to hyperreflexia. This process occurs usually between 1 to 6 weeks after the initial injury and is regarded as an attempt at restoration of function through emergence of novel neuronal circuitry.[26] Plastic rearrangement occurs within the brain and spinal cord.[3, 4, 9, 26-29] In particular, plastic rearrangement in the spinal cord is secondary and maladaptive as a result of disruption of descending supraspinal regulations of spinal reflexes.[3, 9, 27, 30] Sist *et al.*[30] demonstrated in an animal model that after a cortical sensorimotor stroke, there is a time-limited period of heightened structural plasticity in both brain and spinal cord. The plastic change correlates with the severity of cortical injury and promotes behavioral recovery. Elevated structural plasticity in the spinal cord is highest during the first two weeks and returns to baseline levels by 28 days post-stroke.

Abnormal regulations of spinal stretch reflex and spasticity development

As abnormal neuroplasticity develops, hyperreflexia occurs and spasticity starts to emerge.[3, 31] As mentioned above, abnormal intraspinal processing is secondary and maladaptive, hyperexcitability of stretch reflex in stroke survivors with spasticity is primarily mediated by abnormal descending regulations.[31-33]

In neurologically healthy people, excitability of the stretch reflex arc (afferent fibers, spinal motor neurons and efferent fibers) is predominantly regulated and maintained by a balanced descending regulation from the inhibitory dorsal reticulospinal tract and the facilitatory medial reticulospinal tract and vestibulospinal tract.[3, 13, 27, 28, 34] The dorsal reticulospinal tract originates from the dorsolateral reticular formation in the medulla. The dorsal reticulospinal tract and the lateral corticospinal tract descend adjacent to each other in the dorsolateral funiculus at the spinal level. The medial reticulospinal tract originates primarily from the pontine tegmentum of pontomedullary reticular formation. The vestibulospinal tract originates from the lateral vestibular nucleus. Both medial reticulospinal tract and vestibulospinal tract descend in the ventromedial cord.[13, 28, 32, 34]

In addition to distinctly different anatomical pathways, medial and lateral reticulospinal tracts differ in their cortical connections. Recent studies demonstrate that cortico-reticulo-spinal projections are bilateral, but have laterality dominance.[35-37] For the medial pontomedullary reticular formation, it receives inputs primarily from ipsilateral premotor and supplementary motor area, and descends ipsilaterally to the spinal cord. This medial cortico-reticulo-spinal tract provides excitatory descending inputs to spinal motor neurons. On the other hand, the dorsolateral pontomedullary reticular formation receives inputs primarily from the contralateral primary motor cortex via corticoreticular fibers. The corticospinal tract and corticoreticular tracts descend from the cortex in close anatomical proximity in the corona radiata and internal capsule. This dorsal cortico-reticulo-spinal tract provides inhibitory descending inputs to the spinal motor circuitry. Therefore, medial and lateral reticulospinal tracts provide balanced excitatory and inhibitory inputs to spinal motor neuron network.

In stroke affecting the motor cortex and its descending pathways, damages often happen to both corticospinal tract and corticoreticular tracts, resulting in loss of cortical facilitatory input to the medullary inhibitory center. This leaves the facilitatory medial reticulospinal tract unopposed and gradually hyperexcitable, since it receives inputs

predominantly from contralesional cortex. Consequently, abnormal intraspinal processing and spinal reflex hyperreflexia develops gradually, so spasticity emerges on the affected side as a result.[13, 31-33] Recent findings support this pathophysiological process of abnormal plasticity. For example, following focal cortical lesions in monkeys, there are reports of upregulation of contralesional supplementary motor area/premotor area-corticoreticular projections, continuing to medial reticulospinal tract, (*i.e.*, increased excitatory descending inputs).[35, 37, 38] In 3 to 6 weeks after stroke, there was greater disruption of corticoreticular tracts (lower fractional anisotropy) at the contralesional medulla level in those patients with spasticity as compared to those without,[39] suggesting decreased inhibitory descending inputs. This pathophysiological process of imbalanced excitatory and inhibitory descending inputs to spinal stretch reflex circuits is illustrated in Figure 1.2.[37, 40, 41]

Experimental findings from invasive lesional studies in animals in the last century,[28, 32, 34] support the important role of medial reticulospinal tract in spasticity development. For example, section of unilateral or bilateral vestibulospinal tract in the anterior cord only caused a transient reduction in the extensor tone in the lower limbs. With more extensive cordotomies that damage the medial reticulospinal tract, spasticity was drastically reduced, but tendon hyperreflexia, clonus and adductor spams, persisted. The reticulospinal tract hyperexcitability in humans has been assessed indirectly through acoustic startle reflex.[42-53] The human acoustic startle reflex circuit includes the cochlear nucleus, the caudal pontine reticular nuclei, the motor neurons of the brainstem and its descending medial reticulospinal tract.[54-56] In stroke survivors with cerebral infarcts, normal acoustic startle reflex motoric responses could be elicited in flaccid muscles in the acute phase, however no response from the same muscles to magnetic cortical stimulation of the primary motor cortex was elicited in these patients,[42] suggesting that the circuit of acoustic startle reflex remained intact in these patients in the acute phase. In a different study in chronic stroke, exaggerated acoustic startle reflex responses were observed in spastic muscles,[43] suggesting the reticulospinal tract hyperexcitability in these patients with spasticity. In a recent study,[51] acoustic startle reflex responses were compared in chronic stroke at different stages of motor recovery (Flaccid, Spastic, and Recovered). Acoustic startle reflex responses were exaggerated on the spastic side in spastic subjects, but were within normal limits in stroke survivors without spasticity (Flaccid or Recovered). These results suggest that reticulospinal tract hyperexcitability occurs in the Spastic stage, but not in the Flaccid or Recovered ones in chronic stroke. Furthermore, the disappearance of spasticity and reticulospinal tract hyperexcitability in fully-recovered stroke survivors suggests that

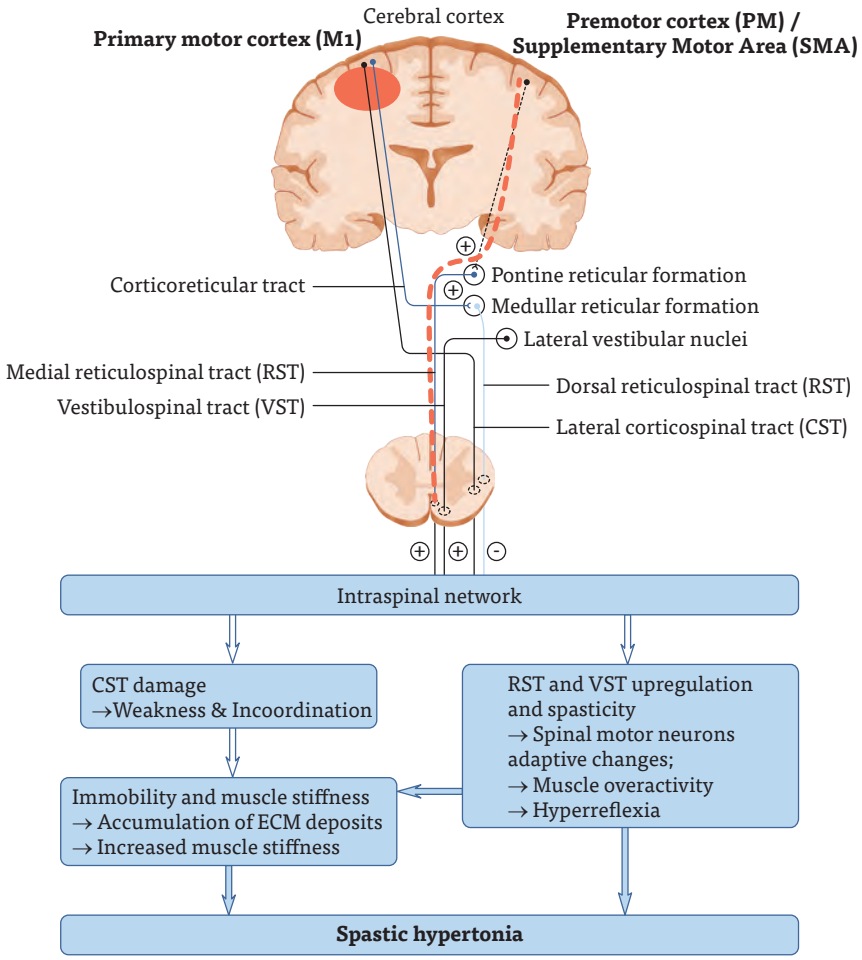

Figure 1.2.

Schematic illustration of pathophysiology of spastic hypertonia. A stroke often leads to damages to the motor cortex and its descending corticospinal tract (CST). Muscle weakness and incoordination occur immediately after CST damages, subsequently leading to joint immobilization. Due to its anatomical proximity to CST, corticoreticular pathways to medullary reticular formation are damaged as well, resulting in diminished inputs from the dorsolateral reticulospinal (RST) tracts into the spinal motor network. Since the dorsolateral RST provides inhibitory inputs, its impairment makes the descending excitatory inputs (medial RST and vestibulospinal tract [VST]) unopposed, and becomes hyperexcitable overtime (red dotted line). RST hyperexcitability appears to be the most likely mechanism related to post-stroke spasticity. RST hyperexcitability provides unopposed excitatory descending inputs to spinal stretch reflex circuits, resulting in elevated excitability of spinal motor neurons and spinal reflex circuits, thus spasticity and hyperreflexia. Clinical presentation of spasticity is confounded by concomitant changes in peripheral muscle properties, such as extracelluar matrix (ECM) deposition and macromolecular crowding of hyaluronan and increased muscle stiffness.

spasticity is a phenomenon of "disinhibition", or abnormal plasticity in the course of motor recovery.[42]

In another study that examined the potential role of vestibulospinal tract in post-stroke spasticity, vestibular evoked myogenic potentials in the sternocleidomastoid muscle in response to high-level acoustic stimuli (130dB) to the ears of stroke survivors were analyzed. The magnitudes of evoked potentials were greater on the affected side than the unaffected side, and had a strong positive relationship between the degree of asymmetry and the severity of spasticity in spastic-paretic stroke survivors, thus suggesting hyperexcitability of vestibulospinal tract.[57] Yet this level of acoustic stimuli is also likely to activate acoustic startle reflex via reticulospinal pathways.[55, 58] Furthermore, the vestibulospinal tract mediating the evoked myogenic potentials terminates in the cervical region,[59] thus not likely to be involved in lower limb spasticity. However, further studies are needed to investigate the role of this pathway in post-stroke spasticity.

Maladaptive changes in intraspinal processing

Abnormal intraspinal processing after stroke as a result of imbalanced excitatory and inhibitory descending inputs to the intraspinal network has been well documented in the literature.[3, 9, 27, 28] The reported adaptive changes could include: 1) increased afferent inputs. The gain of spindles (group Ia primary and group II secondary afferent fibers) is increased due to activation of the gamma fusimotor system and/or adaptive changes after immobilization; 2) altered processing of reflex circuits. The possible factors are reduction in presynaptic inhibition on Ia afferents, group Ib facilitation (instead of inhibition), group II facilitation, and reduced reciprocal inhibition. As a result, less inhibition from intraspinal reflex circuits results in hyperexcitable alpha motor neurons; and 3) altered intrinsic properties of alpha motor neurons. Disruption of descending inputs could cause alpha motor neurons to activate voltage-dependent persistent inward currents.[60] As such, a transient afferent input, such as a bout of passive stretch, could cause development of plateau potentials and self-sustained firing of alpha motor neurons. These changes in reflex circuits and intrinsic properties of spinal motor neurons can lead to alpha motor neuron hyperexcitability (*i.e.*, spontaneous motor unit firing or at subthreshold levels) and thus decreased reflex threshold.

Alpha motor neuron hyperexcitability has been considered as the primary intraspinal change in stroke survivors with spasticity.[10] It can manifest as at subthreshold or at spontaneous firing.[61-67] For example, spontaneous motor unit discharges were detected at rest