ACUTE EFFECTS OF WHOLE-BODY VIBRATION ON SPASTIC HYPERTONIA IN PATIENTS WITH CHRONIC STROKE

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CERTIFICATE OF ORIGINALITY

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it reproduces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

MEIZHEN HUANG (Name of student)

ABSTRACT

Whole-body vibration (WBV) may be a useful adjunct in the management of spastic hypertonia due to its reported effects on muscles and the nervous system. However, few studies have examined the possible physiological mechanism and therapeutic effects of WBV on spastic hypertonia in people with chronic stroke. Therefore, this thesis aimed to address the knowledge gap which was achieved through a series of five integrated studies.

Study 1 (Chapter 2) is a systematic review aimed to examine the effects of WBV on spasticity among people with central nervous system disorders. Based on extensive review of the literature, there was some evidence that WBV may be useful in reducing leg muscle spasticity in cerebral palsy, but the effect was uncertain in multiple sclerosis, stroke and spinocerebellar ataxia. Moreover, the Modified Ashworth Scale was extensively used in the reviewed studies, despite its low reliability, validity, and responsiveness. Studies in high methodological and reporting quality are warranted.

As spastic hypertonia has two components in chronic stroke patients, namely, the reflex component (e.g., hyperreflexia) and the non-reflex component (e.g., changes in the mechanical properties of the affected muscles). Study 2 (Chapter 3) aimed to investigate the mechanical properties of the medial gastrocnemius (MG) muscle in chronic stroke survivors using the Supersonic Shear imaging (SSI) technology. The results showed that SSI had good reliability for measuring passive muscle stiffness in people with chronic stroke. Alterations in the architectural properties and poor functional mobility were observed in chronic stroke patients with spastic hypertonia.

For WBV applications, both the efficacy and safety of the vibration application should be considered. Thus, Study 3 (Chapter 4) examined the transmission of WBV signals in the human body. The results indicated that vibration transmissibility and signal purity were influenced by the vibration amplitude, frequency, body postures, and their interaction for chronic stroke survivors. With the exception of bilateral ankles, increased vibration frequency, amplitude, or knee flexion angle led to lower the transmissibility. The transmissibility in the paretic side was comparable to the nonparetic sides, excepting that at the ankle during tip-toe standing. In a few conditions at the paretic ankle, knee, knee and hip, more-severe leg motor impairment was correlated with greater transmissibility. No significant association was observed between the leg muscle spasticity and WBV transmissibility.

Furthermore, Study 4 (Chapter 5) was conducted to investigate the effect of WBV on neuromuscular activation. The results showed that the addition of WBV to exercise led to a significant increase in muscle activation in the MG and the tibial anterior (TA) and medial hamstrings, but not the vastus medialis, on both paretic and nonparetic sides among individuals with chronic stroke. The effect of WBV was similar on the two sides except TA. Higher muscle activation was associated with larger attenuation of the signals at more proximal anatomical sites, which supports the muscle-tuning mechanism of WBV exercise.

In the final study of this thesis (Chapter 6), a randomized cross-over controlled study was conducted. A 5-minutes of WBV intervention was shown to inhibit the soleus H-reflex in the paretic leg by 14% and increase the vascular index of the MG muscle in the same leg by two-fold, and the effect was sustained for 3 or 4

minutes. However, no significant changes were seen in the shear modulus of the MG muscle in the paretic leg after the same WBV intervention.

Overall, for clinical application, the thesis indicates that WBV is a safe training modality for people with chronic stroke. WBV frequency, amplitude, body posture can influence the WBV transmissibility, signal purity and WBV-induced muscle activation. Muscle activation could damp the vibration during the WBV. Thus, specific WBV parameters should be carefully set to achieve the intended the therapeutic purpose.

WBV may have potential applications in the management of spasticity hypertonia dominated by hyperreflexia and may be a substitute method of exercise to increase peripheral circulation, particularly for frail stroke survivors who cannot participate in other forms of exercise training. However, these postulations will require further research.

PUBLICATIONS ARISING FROM THE THESIS

A. Peer review journal papers

1. **Huang M**, Ying M, Miller T, Pang MYC. Acute effect of whole-body vibration on neuromuscular excitability, muscle stiffness and muscle blood volume: A randomized within-patient cross-over study. Under review.

2. **Huang M**, Miller T, Fu SN, Pang MYC.Morphological and passive mechanical properties of the medial gastrocnemius muscle and their association with functional mobility in individuals with chronic stroke. Under review.

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5. **Huang M**, Liao L-R, Pang MY. Effects of whole body vibration on muscle spasticity for people with central nervous system disorders: a systematic review. *Clinical Rehabilitation.* 2017;31(1):23-33.

B. Conference papers

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patient cross-over study. *13th International Society of Physical and Rehabilitation Medicine, Japan, 2019.*

2. **Huang M**. Pang MYC. The influence of vibration frequency, amplitude, body posture on muscle activation and vibration transmissibility: application of whole body vibration in chronic stroke survivors. *11th Pan-Pacific Conference on Rehabilitation. Hong Kong, 2018.*
3. **Huang M**, Miller T, Fu SN, Pang MYC. Morphological and passive mechanical properties of the medial gastrocnemius muscle among individuals with chronic stroke. *The Hong Kong Physiotherapy Association 55th Anniversary Conference. Hong Kong, 2018.*
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5. **Huang M**, Fu SN, Kowk L, Pang MYC. Material properties of tibial anterior muscle among people with chronic stroke. *World Confederation for Physical Therapy Congress - Asia Western Pacific & Physical Therapy Association of Thailand 2017, Bangkok, Thailand, 2017.*
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LIST OF ABBREVIATIONS

%MVC	Percentage of the peak EMG amplitude
η_p^2	Partial eta squared
A	Amplitude
ANOVA	Analysis of variance
a_{peak}	Peak acceleration
C	Comparison
CMP	Continuous passive motion
CI	Confidence interval
CVA	Cerebrovascular accident
dCPD	Directional color power Doppler
df	Degrees of freedom,
DF	Dorsiflexors
DS	Deep squat
E	Young's modulus
EMG	Electromyography
EMG%	WBV-induced muscle activation
$EMG_{mvc\%}$	Normalization of electromyography to maximum voluntary contraction
EMG_{rms}	Root mean square electromyography
f	Frequency
FMA	Fugl-Meyer Motor Assessment
g	Gravitational constant of the earth
G	Shear elastic modulus
GABA	γ-aminobutyric acid

H/M ratio	Ratio of the Hoffmann reflex to the direct motor response
Hmax	Maximum Hoffmann reflex
H-reflex	Hoffmann reflex
HR	Heart rate
Hz	Hertz
I	Intervention
ICC	Intraclass correlation coefficient
IQR	Interquartile range
MAS	Modified Ashworth Scale
MDD	Minimal detectable difference
MG	Medial gastrocnemius
Mmax	Maximum direct motor response
M-wave	Direct motor response
min	Minute
mm	Millimeters
MAS	Modified Ashworth Scale
MH	Medial hamstring
ms	millisecond
MTS	Modified Tardieu Scale
MVC	Maximal voluntary contraction
NMES	Neuromuscular electrical stimulation
O	Outcomes
p	Significant level
P	Patients

PASE	Physical activity scale for individuals with physical disabilities
PEDro	Physiotherapy Evidence Database
R^2	coefficient of determination
rms	root mean square
rTMS	Repetitive transcranial magnetic stimulation
ROI	Region of interest
s	second
SES	Standardized effect size
SSI	Supersonic Shear Imaging
SCI	Spinal Cord Injury
SD	Standard deviation
TA	Tibialis anterior
tDCS	Transcranial direct current stimulation
TENS	Transcutaneous electrical nerve stimulation
TMS	Transcranial magnetic stimulation
T-reflex	Tendon reflex
TUG	Timed Up and Go test
UMN	Upper motor neuron
v	Shear wave speed
VAS	Visual analogue scale
VM	Vastus medialis
W	Watt
WBV	Whole body vibration
WHO	World Health Organization

1. Chapter 1: General Introduction

1.1 Epidemiology of stroke

Stroke, or cerebral vascular accident (CVA), is defined by World Health Organization (WHO) as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin" (Aho*, et al.*, 1980). There are two main categories of stroke: ischemic stroke, caused by a lack of blood flow (Hisham and Bayraktutan, 2013), and hemorrhagic stroke, caused by the rupture and leakage of blood vessels in the brain (Howard, 2016). The brain cells die as a result of insufficient supply of blood and oxygen (Hisham and Bayraktutan, 2013) and/or compression of tissue from an expanding hematoma(s) (Howard, 2016). Body functions (e.g., motor, verbal) are ultimately lost as a result of the damage to the corresponding functional brain areas.

Stroke is a devastating neurologic disease that leads to death and disability (Johnson*, et al.*, 2016, Mackay*, et al.*, 2004). In 2010, 16.9 million people worldwide had their first stroke (Feigin*, et al.*, 2014). The number of stroke survivors has been estimated at 33 million (Feigin*, et al.*, 2014). Advanced age is among the foremost risk factors for stroke (Feigin*, et al.*, 2009). In fact, 95% of strokes occur after 45 years of age, and two thirds of strokes occur after 65 years of age (Feigin*, et al.*, 2009). As the global population rapidly ages, the number of strokes is anticipated to increase for the foreseeable future. According to estimation of the WHO, there will be 23 million first-ever strokes and 7.8 million stroke-related deaths by 2030 (Strong*, et al.*, 2007). The WHO predicts that the number of disability-adjusted life years lost to stroke (a measure of the burden of

disease) will rise from 38 million in 1990 to 61 million in 2020 (Mackay*, et al.*, 2004).

In 2016 alone, Hong Kong had more than 25 000 episodes of inpatient discharge or death due to stroke in public and private hospitals (*HealthyHK*, 2018). Generally, the incidence of stroke increases sharply with age, from 12.2 per 100 000 population for people 24 years of age and younger to 1805 per 100 000 population for people 65 years of age and older (Mackay*, et al.*, 2004). Due to the aging population, it is estimated that the population of people 65 years of age and older in Hong Kong will surge from the current 1.1 million to 2.4 million by 2044 (Census and Statistics Department, 2015). Stroke will thus continue to be a critical health issue both locally and globally.

1.2 Muscle hypertonia after stroke

Lesions of the motor areas or pathways are common after a stroke and give rise to a cluster of signs and symptoms known as upper motor neuron syndrome (Arene and Hidler, 2009a). The clinical features of the movement disorders in upper motor neuron syndrome include muscle weakness, increased muscle tone (i.e., hypertonia), and loss of selective control of muscles and limb segments (Arene and Hidler, 2009a). These symptoms may severely undermine the performance of activities of daily living in stroke survivors (Arene and Hidler, 2009a). In the following section, the literature review focuses on topics surrounding spastic hypertonia, because they are highly related to the research work described in this thesis.

1.2.1 Pathophysiology of spastic hypertonia

Spasticity, a consequence of upper motor neuron lesions, is among the severe sequelae experienced after stroke (Zorowitz*, et al.*, 2013). Studies have shown that between 17% and 42.6% of stroke survivors suffered poststroke spasticity within 3 months of stroke onset (Wissel*, et al.*, 2013). Spastic hypertonia is common in leg extensors after stroke (Arene and Hidler, 2009b) and may have negative effects on transfer and balance functions, which in turn hamper daily activities and compromise health-related quality of life (Arene and Hidler, 2009b, Dietz and Sinkjaer, 2007). Lance described spasticity as "a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as one component of the upper motor neuron (UMN) syndrome" (Lance, 1980). However, the accumulated experimental evidence suggests that spastic hypertonia could be the result of changes in both neural pathways (i.e., reflex stiffness) and muscle properties (i.e., non–reflex stiffness) (Katz and Rymer, 1989).

1.2.1.1 Neural mechanics of muscle hypertonia

The Changes in the mechanical-elastic properties of muscular and connective tissues may also contribute to hypertonia (i.e., nonreflex stiffness) (Singer, 2001). The biomechanical and architectural properties of skeletal muscle fibers and connective tissues can be altered considerably after brain lesions (Carey and Burghardt, 1993, Friden and Lieber, 2003, Goldspink and Williams, 1979, Lieber*, et al.*, 2003, Tabary*, et al.*, 1972). Following an acquired brain injury, immobility caused by paresis leads muscles to remain in a shortened position, which may lead to an increase in actin-myosin cross bridge linkages (Carey and

Burghardt, 1993), loss of sarcomeres (Tabary*, et al.*, 1972), altered muscle fiber size (Friden and Lieber, 2003), increased stiffness of spastic muscle cells (Friden and Lieber, 2003), proliferation of extracellular matrix material (Lieber*, et al.*, 2003), and remodeling of muscle connective tissues (e.g., intramuscular connective tissues) (Goldspink and Williams, 1979). Evidence from biopsy studies has also shown atrophy of type II muscle fibers and hypertrophy of type I muscle fibers (Dietz*, et al.*, 1986). Moreover, fat infiltration was found in the spastic leg muscles (Ryan*, et al.*, 2002). Because skeletal muscle is highly adaptable, the mechanical changes in skeletal muscle after stroke are a complicated process (Katz and Rymer, 1989).

In summary, spastic hypertonia is a multifactorial problem that can be categorized into two components: hyperreflexia-mediated hypertonia, which has a neurologic origin (i.e., spasticity), and non-reflex hypertonia, which is due to changes in the mechanical properties of muscle tissues (i.e., intrinsic stiffness) (Dietz and Sinkjaer, 2007, Katz and Rymer, 1989, O'Dwyer*, et al.*, 1996, Trompetto*, et al.*, 2014). Therefore, it is important to consider and evaluate all possible underlying factors of hypertonia, which would enable researchers and clinicians to select appropriate assessment tools and intervention strategies and facilitate better treatment outcomes for people with spastic hypertonia (Singer, 2001).

1.2.1.2 Biomechanical factors of muscle hypertonia

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1.2.2 Measurement of spastic hypertonia

The assessment and treatment of spastic hypertonia are challenging and delicate (Katz and Rymer, 1989). Spasticity is a complex phenomenon, with a cluster of clinical manifestations complicated by the accompanying disorders of upper motor neuron syndrome (Burridge*, et al.*, 2005). Various methods have been proposed to evaluate spastic hypertonia. The following sections will discuss four approaches: clinical scales (Platz*, et al.*, 2005), biomechanical assessment (Wood*, et al.*, 2005), neurophysiologic assessment (Voerman*, et al.*, 2005), and muscle imaging.

1.2.2.1 Clinical scales for spastic hypertonia

The Modified Ashworth Scale (MAS) is one of the most widely used clinical measures of spasticity in clinical practice and research (Bohannon and Smith, 1987). It is a six-point (0 to 4) single-item ordinal scale used to rate the resistance encountered during passive movement of a limb through the range of motion to passively stretch a specific muscle group (e.g., ankle plantar flexors) (Bohannon and Smith, 1987). The concurrent validity of MAS is excellent, and it has moderate intra-rater reliability for measuring leg spasticity in stroke survivors (Platz*, et al.*, 2005). However, intrinsic joint stiffness and persistent muscle activity may limit the reliability and validity of MAS scores (Fleuren*, et al.*, 2010, Pandyan*, et al.*, 2003, Platz*, et al.*, 2005). The velocity of the passive limb movements is unspecified, which makes inter-rater comparison difficult (Platz*, et al.*, 2005).

In contrast to the MAS, the Modified Tardieu Scale (MTS) may be considered more clinically related to Lance's definition of spasticity for measuring spasticity, because it includes both the velocity of passive joint movement and the angle at

which muscle contraction occurs (Haugh*, et al.*, 2006). In the MTS, three components are used to assess the spasticity: velocity of stretch(i.e., slow, normal, fast), angle of muscle reaction, and quality of muscle reaction(Boyd and Graham, 1999). The slow speed is used to measure passive range of motion (i.e., recorded as R2) which is suggested as the muscle length at rest. The normal or the fast speed is used to measure the joint angle of a "catch" (i.e., recorded as R1) at which the assessor feels the onset of muscle contraction. The difference between R2 and R1 (R2–R1) could help to estimate the contributions of neural and mechanical restraints to the resistance of passive movement. A large difference between R1 and R2 is inferred as the spasticity, while a small difference is indicative of contracture of the soft tissue(Boyd and Graham, 1999). The quality of muscle reaction is rated by a six-point scale that 0 indicates 'no resistance through the course of the passive movement' and 5 indicates that 'the joint is immobile (Boyd and Graham, 1999). However, the inter and intra-rater reliability across all components of MTS is moderate to substantial in people with stroke(Ansari*, et al.*, 2013, Li*, et al.*, 2014). Inter-rater and intra-rater reliability for the dynamic component of spasticity (R2–R1) were moderate in the elbow flexors and ankle plantarflexors for stroke survivor(Ansari*, et al.*, 2013, Li*, et al.*, 2014). Moreover, the difference between the two raters for R2 was statistically significant (Ansari*, et al.*, 2013). Thus, the unreliability of the R2 due to the inaccuracy of the goniometric measures, fluctuated spastic condition may undermine the validity of the MTS (Ansari*, et al.*, 2013, Li*, et al.*, 2014). Similar as the MAS, the unspecified passive limb movements velocity, rater-depended subjective muscle qualitative rating, weaken the inter-rater reliability (Ansari*, et al.*, 2013, Li*, et al.*, 2014).

The main construct of clinical scales generally focuses on resistance to passive movement without distinction between reflex and non-reflex components (Burridge*, et al.*, 2005, Platz*, et al.*, 2005). Although the clinical scales are time-saving and easy-to-use tools (Burridge*, et al.*, 2005), they are relatively subjective measures (Katz and Rymer, 1989) and may not be sufficiently accurate to detect changes in muscle tone (Burridge*, et al.*, 2005). Thus, quantitative neurophysiologic and biomechanical measurement is warranted to provide a more accurate measure of spastic hypertonia (Burridge*, et al.*, 2005).

1.2.2.2 Neurologic assessment for spastic hypertonia

Spasticity-related neurologic assessment generally concentrates on the phasic stretch reflex (Voerman*, et al.*, 2005). Electromyography (EMG) is used to register the synaptic reflex, which can be classified into two subgroups: (1) EMG response to mechanical stimulation such as the tendon reflex (T-reflex) and (2) EMG response to electrical stimulation like the Hoffmann reflex (H-reflex).

1.2.2.2.1 Tendon reflex (T-reflex)

The T-reflex is a spinal reflex elicited by mechanical stimuli (e.g., tapping) on a distal tendon. The muscle spindle is stimulated by this stimulus, which activates afferent Ia fibers that excite the α-motoneuron to induce muscle contraction (Voerman*, et al.*, 2005). In the leg, the T-reflex is usually evoked at the ankle (Achilles reflex) and knee (patellar reflex) joints.

The major parameters derived from the T-reflex are the reflex's latency and amplitude. The latency is the time interval between the stimulus and the first deflection recorded in the EMG signal (Voerman*, et al.*, 2005). It is the sum of the

conduction time of the afferent impulses and the time for synapse transmission in the spinal cord, which may suggest the excitability of α-motoneurons of the spinal reflex arch (Voerman, *et al.*, 2005). In young, healthy adults, the latency of the Achilles T-reflex is about 30 to 40 ms (Frijns, *et al.*, 1997). A shorter T-reflex latency is revealed in people with spasticity due to the increased excitability of α-motoneurons (Voerman, *et al.*, 2005). The amplitude is the electrical voltage between the positive and negative peak (Voerman, *et al.*, 2005). For the Achilles T-reflex, the mean amplitude is 0.9 ± 1.1 mV in the healthy population (Buist, *et al.*, 1972), and an increase in the reflex amplitude is a common feature of upper motor neuron syndrome (Voerman, *et al.*, 2005).

With well-controlled tapping intensity and frequency, good intersession reliability has been reported for the reflex latency and amplitude of the biceps T-reflex after stroke (intraclass correlation coefficient [ICC], 0.914 and 0.882, respectively) (Min, *et al.*, 2012). A moderate correlation was reported with the MAS score in the elbow (Min, *et al.*, 2012) and ankle (Borromei, *et al.*, 1999, Min, *et al.*, 2012).

1.2.2.2.2 Hoffmann reflex (H-reflex)

a The Hoffmann reflex (H-reflex) is a monosynaptic reflex elicited by electrical stimulation of an Ia afferent excitatory volley (Voerman, *et al.*, 2005). Unlike the T-reflex, the H-reflex bypasses the muscle spindle (Voerman, *et al.*, 2005) and is theoretically less affected by the γ efferent system. Therefore, the H-reflex is a useful measure of the modulation of monosynaptic reflex activity in the spinal cord (Palmieri, *et al.*, 2004). The H-reflex is commonly studied in the soleus by stimulating the tibial nerve, but other arm and leg muscles such as the

quadriceps and flexor carpi radialis have also been investigated (Palmieri, *et al.*, 2004).

To evoke the H-reflex, a mixed peripheral nerve (i.e., containing both motor and sensory fibers) is activated with a low-intensity, short-duration electric stimulus, and the corresponding muscle response is recorded with an EMG set (Palmieri, *et al.*, 2004). The impulse caused by the electrical stimulus travels up to the Ia afferent fibers and stimulates the α-motoneuron, inducing a muscle response (i.e., the H-reflex) (Palmieri, *et al.*, 2004). Increasing the intensity of the electrical stimulus further evokes a short-latency muscle response: the M-wave (Palmieri, *et al.*, 2004). The M-wave, which has a higher evoking threshold than the H-reflex, is the direct response of the motor nerve fibers to electrical stimuli (Palmieri, *et al.*, 2004). When the electrical stimulus is increased, the M-wave continues to rise, whereas the H-reflex would first peak (i.e., H_{max}) and then fade away. The reason for the disappearance of H-reflex is the collision between the orthodromic and antidromic potential (Magladery and McDougal Jr, 1950). At the maximal stimulus intensity, the M-wave peaks (i.e., M_{max}), whereas the H-reflex is completely abolished (Magladery and McDougal Jr, 1950, Palmieri, *et al.*, 2004) (Figure 1-1).

The H-reflex is believed to be a manifestation of the α-motoneurons' excitability (Palmieri, *et al.*, 2004). The H_{max}, as the maximal response of the H-reflex, is an estimate of the degree of motoneuron pool that could be active in a given state α-motoneuron (Palmieri, *et al.*, 2004). The M_{max} represents the

maximum muscle activation and can be used to indicate the activation level of the entire motoneuron pool (Palmieri, *et al.*, 2004).

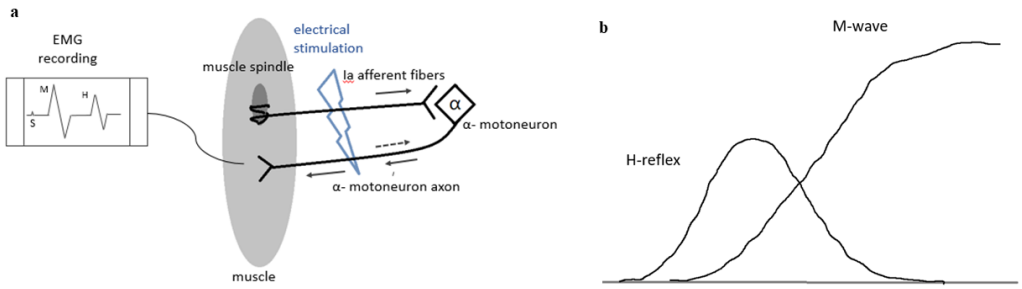

Figure 1-1 Illustration of H-reflex
(a) Pathway of H-reflex and M-wave and their EMG signal recording. (b) Recruitment curve of M-wave and H-reflex.

As with the T-reflex, the latency and amplitude are the typically measured parameters of the H-reflex (Palmieri, *et al.*, 2004). The normal latency of the soleus muscle M-wave is about 5 to 10 ms, and that of the H-reflex is about 30 ms in young, healthy adults (Palmieri, *et al.*, 2004). However, the reflex is influenced by the length of the limb (Voerman, *et al.*, 2005). The amplitude of the H-reflex is therefore a better expression of the α-motoneurons' excitability than the response to excitatory inputs (Ali and Sabbahi, 2000, Palmieri, *et al.*, 2004). In addition, normalization of the amplitude of the H-reflex with a constant M-wave of each individual, which indicates the percentage of activated motoneurons, can enable comparison among subjects (Voerman, *et al.*, 2005, Zehr, 2002). An elevated H/M ratio is associated with an increase in motoneuron excitability (Palmieri, *et al.*, 2004) and has been reported in stroke survivors with hemiplegia (Levin and Hui-Chan, 1993, Pisano, *et al.*, 2000). However, the H-reflex is influenced by several factors, including the subject's position, the limb's position, and the stimulus duration and frequency. Therefore, studies of the H-reflex should be designed,

conducted, and interpreted with care (Palmieri, *et al.*, 2004, Voerman, *et al.*, 2005, Zehr, 2002).

The soleus H/M shows high reliability (ICC=0.92) in stroke survivors (Levin and Hui-Chan, 1993), and the correlation between the Achilles reflex and the H-reflex amplitude was moderate (r=0.7) (Milanov, 1992). However, the correlation between the H-reflex parameters and the MAS score was poor to moderate (Levin and Hui-Chan, 1993, Milanov, 1992, Pisano, *et al.*, 2000). The poorer correlation may be related to the fact that reflex and nonreflex components are both involved in the MAS score, whereas only the reflex component is involved in measurement of the H-reflex.

1.2.2.3 Biomechanical assessment for spastic hypertonia

According to Lance's definition of spasticity, the biomechanical technique for measurement of spasticity is to quantify the abnormal resistance when mechanical perturbation is applied directly to a joint (Wood, *et al.*, 2005). Quantification can be made of (1) torque—the extent of force evoked by moving the limb across a specified angle, and (2) threshold—the particular angle at which the torque or EMG begins to increase notably (Katz and Rymer, 1989, Wood, *et al.*, 2005). The commonly used mechanical perturbation includes a controlled displacement method and a gravitational method (Wood, *et al.*, 2005).

1.2.2.3.1 Controlled displacement methods

In the controlled displacement method, the joint is passively rotated using servo-controlled motors at a predefined speed and/or amplitude so the torque of the joint and the EMG response of the muscle can be tracked (Wood, *et al.*, 2005).

A torque-velocity curve can thus be produced. The degree of spasticity can be determined as the angles and velocities at the outset of the considerable increase in torque or EMG (Wood*, et al.*, 2005). The elbow flexors, knee extensors, and ankle plantarflexors are frequently tested. The common angular velocity of passive movement is between 30°/s and 120°/s (Wood*, et al.*, 2005). However, this method of measurement may not be suitable for people with contractures and severe spasticity due to safety concerns (Wood*, et al.*, 2005). In addition, the resistance measured could involve both reflex and nonreflex components (Katz*, et al.*, 1992, Wood*, et al.*, 2005). The servomotor velocity or amplitude varies among different studies, which makes it difficult to compare and interpret the results (Katz and Rymer, 1989, Wood*, et al.*, 2005).

1.2.2.3.2 Gravitational methods (pendulum test)

The pendulum test of the knee joint is widely used to assess hypertonia of the knee extensors (Bohannon*, et al.*, 2009, Wartenberg, 1951, Wood*, et al.*, 2005). The subject rests in a supine position with both legs hanging over the plinth. When the subject is relaxed, the legs are lifted to the fully extended level and then released (Wartenberg, 1951). The movement of the legs is dampened or bracketed by the viscoelastic components of the limb (Katz and Rymer, 1989). Knee movement is captured by an electrogoniometer (Jamshidi and Smith, 1996), motion sensor (Bohannon*, et al.*, 2009), or videotape recorder (Jamshidi and Smith, 1996). The quantitative parameters include the (1) relaxation index, which is computed as the ratio of the amplitude of the first swing angle against the difference between the starting and resting angles; and (2) the first-swing excursion angle (Bohannon*, et al.*, 2009, Fowler*, et al.*, 2000, Jamshidi and Smith,

1996, Whelan, *et al.*, 2018). Good correlation (r = 0.8 to 0.9) has been reported between these parameters and the MAS score (Bohannon, *et al.*, 2009, Whelan, *et al.*, 2018). However, the parameters can be influenced by factors such as the joint structures and the muscle length. In addition, the pendulum method cannot distinguish between hyperreflexia and mechanical resistance (Wood, *et al.*, 2005).

1.2.2.4 Ultrasound technique

The use of ultrasound to examine hypertonic muscles has gained popularity in the past decade. B-mode ultrasound is generally used to assess changes in muscle architecture (e.g., muscle fascicle length, pennation angle) under passive movement (Gao, *et al.*, 2009, Hoang, *et al.*, 2009, Hoang, *et al.*, 2007, Kwah, *et al.*, 2012), and elastography is generally used to measure the mechanical properties of muscle tissue (Bilgici, *et al.*, 2018a, Bilgici, *et al.*, 2018b, Brandenburg, *et al.*, 2014, Brandenburg, *et al.*, 2015, Eby, *et al.*, 2013, Eby, *et al.*, 2017, Gao, *et al.*, 2018, Jakubowski, *et al.*, 2017, Lee, *et al.*, 2016, Lee, *et al.*, 2015, Wu, *et al.*, 2017).

1.2.2.4.1 B-mode ultrasound

Due to the approximate uniaxial properties of the ankle joint and the superficial location of the medial gastrocnemius (MG) muscle, the MG muscle and ankle joint are the most frequently investigated of the leg joints (Gao, *et al.*, 2009, Hoang, *et al.*, 2009, Hoang, *et al.*, 2007, Kwah, *et al.*, 2012). The ankle joint was moved passively with a servomotor, the torque of movement was recorded with a dynamometer, and the muscle structural changes (e.g., the length and pennation angle of the muscle fascicle) were captured by B-mode ultrasound (Gao, *et al.*, 2009, Hoang, *et al.*, 2009, Hoang, *et al.*, 2007, Kwah, *et al.*, 2012). The stiffness

of the muscle fascicle fibers could then be estimated by processing the changes in the fascicles' length and joint torque(Wood*, et al.*, 2005). However, inconsistent outcomes were reported. Gao et al. reported that stroke survivors had greater fascicular stiffness and a shorter fascicle length than healthy control subjects (Gao*, et al.*, 2009). However, Hoang et al. found that the maximal strains of the whole muscle–tendon units, muscle fascicles, or tendons of participants with ambulatory multiple sclerosis were comparable with those of healthy control participants (Hoang*, et al.*, 2009). Kwah et al. also reported that the mean stiffness and length of the muscle-tendon and its fascicles at low tension in stroke survivors did not differ from those in healthy subjects (Kwah*, et al.*, 2012). It should be noted the measured passive torque was assumed to be contributed only by the MG muscle, and the joint capsules, ligaments, and other synergistic muscles such as the soleus were ignored (Gao*, et al.*, 2009, Hoang*, et al.*, 2009, Hoang*, et al.*, 2007, Kwah*, et al.*, 2012). Thus, the estimation of stiffness is focused only on muscle fascicles rather than on muscle tissue per se.

1.2.2.4.2 Ultrasound elastography

Ultrasound elastography is an ultrasound-based technique used to qualify or quantify the material properties of tissue in a noninvasive manner. The general principle of the measurement is to assess the deformation of tissue caused by the applied mechanical force (e.g., compression or shear wave) (Brandenburg*, et al.*, 2014, Sigrist*, et al.*, 2017). Based on the methods to induce and measure the deformation, several ultrasound elastography techniques have been developed that can be classified into strain imaging methods and shear wave imaging methods (Sigrist*, et al.*, 2017). The strain imaging method uses internal or external

compression stimuli, including strain elastography and acoustic radiation force impulse, which provides semiquantitative measurements of elasticity (Brandenburg, *et al.*, 2014). In contrast, shear wave elastography quantifies tissue stiffness by estimating the ultrasound-generated traveling shear wave stimuli. This technique has evolved rapidly in recent decades (Brandenburg, *et al.*, 2014). Among shear wave elastography techniques, supersonic shear imaging (SSI) is one of the most advanced technologies and has gained increasing popularity in research and clinical practice (Sigrist, *et al.*, 2017).

Briefly, SSI involves an ultrasonic scanner that generates a remote acoustic radiation force via focused acoustic beams that can induce propagation of shear waves in the tissues (Bercoff, *et al.*, 2004). Ultrahigh frame rate ultrasonic imaging is generated to capture the propagation (Bercoff, *et al.*, 2004). The shear wave speed (v) is estimated at each pixel using a cross-correlation algorithm (Bercoff, *et al.*, 2004), and the shear elastic modulus can be calculated as follows:

$$E=3G=3\rho v^2$$

where E is Young's modulus, G is the shear elastic modulus, v is the shear wave speed, and ρ is the muscle mass density, which is assumed to be 1000 kg/m^3 (Gennisson, *et al.*, 2013).

The higher the shear wave speed, the higher Young's modulus or shear elastic modulus (higher stiffness). The elastogram of the region of interest is color-coded, and the image quality is considered satisfactory when a homogeneous color appears throughout the map.

SSI has shown promise in application for noninvasive assessment of the liver, breast cancer, prostate, kidney, and lymph node (Sigrist, *et al.*, 2017), and its application in the measurement of skeletal muscle is emerging (Brandenburg, *et*

al., 2014). The feature of real-time noninvasive direct measurement of individual muscles can advance our understanding of skeletal muscles (Brandenburg*, et al.*, 2014). It has been reported that SSI is a valid tool to evaluate the mechanical properties of skeletal muscles (Koo*, et al.*, 2013, Miyamoto*, et al.*, 2015). The shear modulus measured by SSI was strongly correlated with passive muscle tension in an ex vivo animal model (Koo*, et al.*, 2013). Good inter-rater and inter-day reliability (ICC, 0.8 to 0.9) was reported in the resting muscles, including the medial gastrocnemius, tibialis anterior, and biceps brachii muscles (Brandenburg*, et al.*, 2016, Lacourpaille*, et al.*, 2012).

It is proposed that SSI could quantify hypertonic muscle in patients with cerebral palsy (Brandenburg*, et al.*, 2016, Lee*, et al.*, 2016) and stroke (Jakubowski*, et al.*, 2017, Lee*, et al.*, 2015). A higher shear modulus or shear wave speed was found in the spastic gastrocnemius and biceps brachii muscles than on the unaffected side for both populations (Brandenburg*, et al.*, 2016, Jakubowski*, et al.*, 2017, Lee*, et al.*, 2016, Lee*, et al.*, 2015), but not in the tibial anterior muscle (Jakubowski*, et al.*, 2017). A significant negative correlation was reported between the shear wave speed of the biceps brachii and the Fugl-Meyer Assessment score for the arms after stroke (Lee*, et al.*, 2015), but no such correlation was found for the legs (Jakubowski*, et al.*, 2017). It should be noted that the measured shear modulus or shear wave speed is very sensitive to changes in the joint angle (Jakubowski*, et al.*, 2017, Koo*, et al.*, 2014). Stroke patients with various levels of motor impairment may have distinct mechanical properties of muscles (Lieber*, et al.*, 2017). In addition, Koo et al. (2014) used SSI to measure the elasticity of the tibial anterior muscle while passively stretching the muscle from dorsiflexion to plantarflexion, thereby developing an elasticity-angle curve (Koo*, et al.*, 2014).

The parameters derived from that elasticity-angle curve include the elasticity change rate and the muscle slack angle, which may provide meaningful information about the muscle's passive mechanical properties (Koo*, et al.*, 2014). Therefore, the elasticity-angle curve in stroke survivors would be worthy of investigation.

1.2.3 Treatment of spastic hypotonia

The techniques proposed to manage spastic hypertonia can be classified as pharmacologic and nonpharmacologic approaches. Although they differ in nature, the various treatment approaches aim to modify the neural circuits involved in hyperreflexia or alter the viscoelastic properties of the connective tissue (Chang*, et al.*, 2013). The methods commonly used in stroke patients are presented in the following sections.

1.2.3.1 Pharmacologic approach

Pharmacologic intervention acts on neurotransmitters and/or neuromodulators within the central nervous system (e.g., diazepam, tizanidine, baclofen) or at peripheral neuromuscular sites (e.g., dantrolene, botulinum toxin) (Chang*, et al.*, 2013). For example, diazepam, a long-acting benzodiazepine, is the classic medication for the management of spasticity. It can facilitate the affinity of γ-aminobutyric acid (GABA) for the $GABA_a$-receptor complex, resulting in an increase of presynaptic inhibition and a reduction in synaptic reflexes (Gallichio, 2004). Tizanidine, as an agonist on α_2-adrenergic receptors, can increase the presynaptic inhibition of motor neurons (Gallichio, 2004). Baclofen is capable of binding at the $GABA_b$ receptors of the spinal cord, thereby increasing inhibition

both presynaptically and postsynaptically (Gallichio, 2004). Dantrolene is a peripherally acting muscle relaxant that impedes the release of calcium from the sarcoplasmic reticulum, therefore suppressing excitation/contraction coupling and reducing spasticity (Gallichio, 2004). Oral medications act systemically in the body, but these drugs are generally associated with unwanted adverse effects, such as drowsiness, sedation, dizziness, or cognitive impairment (Gallichio, 2004). The condition of stroke survivors with cognitive deficits may be worsened by oral medications (e.g., impairment of memory) (Katz, 1991). In some conditions, antispasticity drugs could be contraindicated with other drugs commonly prescribed to stroke patients. For example, dantrolene sodium and statins may induce hepatotoxicity, and tizanidine and clonidine can lead to hypotension (Francisco and McGuire, 2012).

An alternative approach is administration via intramuscular injection. Botulinum toxin injection is common in the treatment of focalized hypertonic muscle (Gallichio, 2004) because it inhibits the release of acetylcholine at the neuromuscular junction so as to reduce muscle activity (Gallichio, 2004). An injection is often administered to reduce the tone of the adductors of the shoulder, the flexors of the elbow and wrist, and the plantarflexors of the ankle (Rosales and Chua-Yap, 2008). A significant reduction in the MAS score was observed after 4 to 6 weeks of botulinum toxin injections (Rosales and Chua-Yap, 2008); however, the high cost and transient nature of the treatment effect are major disadvantages (Ozcakir and Sivrioglu, 2007). Moreover, the high-dosage injection may lead to muscle weakness and muscle atrophy (Ozcakir and Sivrioglu, 2007). In addition to botulinum toxin injection, functional training is recommended as an adjunctive intervention to enhance motor function (Rosales and Chua-Yap, 2008).

In summary, several pharmacologic options are available for the treatment of spasticity after stroke, and each has potential benefits and disadvantages. The decision in terms of whether or how to choose these pharmacologic agents should consider the spasticity distribution, severity, and cause and the individual's concomitant medications and budget (Gallichio, 2004).

1.2.3.2 Nonpharmacologic approach

1.2.3.2.1 Stretching

Stretching is one of the most commonly used nonpharmacologic interventions for the management of spasticity (Bethoux, 2015), although the underlying mechanisms are still not entirely clear (Bovend'Eerdt*, et al.*, 2008). Stretching promotes "elongation of a muscle for varying lengths of time causing viscous deformation changes" (Synnot*, et al.*, 2017) and can be applied manually, mechanically (i.e., with a dynamometer or an intelligent feedback–controlled device) (Bovend'Eerdt*, et al.*, 2008), or with splinting, casting, or orthotic techniques (Nair and Marsden, 2014). Repeated stretching was reported to increase the passive joint range of motion and decrease stiffness of the ankle in stroke survivors (Gao*, et al.*, 2011, Nair and Marsden, 2014, Zhang*, et al.*, 2002). The Achilles T-reflex torque also decreased after stretching (Zhang*, et al.*, 2002). However, a systematic review of 21 clinical trials in patients with stroke and multiple sclerosis was inconclusive regarding the clinical benefit of stretching on spasticity (Bovend'Eerdt*, et al.*, 2008).

1.2.3.2.2 Transcutaneous electrical nerve stimulation (TENS)

Transcutaneous electrical nerve stimulation (TENS) is a form of electrical stimulation usually delivered as biphasic modified square wave pulses at a frequency of greater than 50 Hz or less than 10 Hz and low intensities in a repetitive manner to mainly excite sensory nerve afferents for pain relief (Naro*, et al.*, 2017, Sluka and Walsh, 2003, Wang*, et al.*, 2016). TENS may have the ability to reduce segmental hyperexcitability by inducing the release of ß-endorphins, which may decrease motoneuronal excitability (Ng and Hui-Chan, 2007, Wang*, et al.*, 2000), and by reshaping cortical synaptic plasticity via backward input from the spinal cord to sensory areas (Ng and Hui-Chan, 2007, Wang*, et al.*, 2000). TENS has been shown to have an acute effect on spasticity in stroke survivors, as measured by the MAS (Laddha*, et al.*, 2016, Ng and Hui-Chan, 2007, Oo, 2014, Wang*, et al.*, 2016). However, this improvement may not persist after TENS is discontinued (Ng and Hui-Chan, 2007) unless delivered as an adjunct to an active therapy (e.g., exercise and task-related training) (Mills and Dossa, 2016). A systematic review suggested that repeated applications of TENS as an adjunct to functional training could improve walking capacity and reduce spasticity in stroke survivors (Kwong*, et al.*, 2017).

1.2.3.2.3 Neuromuscular Electrical Stimulation (NMES)

Neuromuscular electrical stimulation (NMES) delivers small electrical impulses directly to the motor nerves to produce muscle contraction of paretic muscles (Chae*, et al.*, 2008). The possible neural mechanisms that underlie its effect on the reduction of spasticity include facilitating the antagonist reciprocal inhibition, Renshaw cell recurrent inhibition, and cutaneous sensory habituation; modulating muscle spindle activity; and enhancing Ib-fiber activation (Naro*, et al.*,

2017, Stein*, et al.*, 2015). A meta-analysis of 29 studies with 940 stroke survivors showed that NMES combined with other interventions could lead to a reduction in the MAS score and an increase in range of motion, whereas NMES alone had no treatment effect (Stein*, et al.*, 2015).

1.2.3.2.4 Noninvasive neuromodulation

Noninvasive brain stimulation techniques, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), that use magnetic stimulation or electrical current have the capacity to modulate cortical excitability and plasticity (To*, et al.*, 2018). Repetitive TMS (rTMS) uses a strong magnetic field generated by a powerful electrical coil that traverses the skull to the cerebral cortex and painlessly stimulates the targeted brain area (McIntyre*, et al.*, 2012). In general, the modulatory effect depends on the stimulation frequency. Low-frequency rTMS (≤1 Hz) usually suppresses motor cortex excitability, whereas higher frequencies (>5 Hz) lead to increased cortical excitability (McIntyre*, et al.*, 2017). In addition, cortical or subcortical areas that are connected functionally to the stimulation sites can also be influenced. Thus, the effects are not constrained to a single region. rTMS has been widely used to investigate neurologic processing in neurologic and psychological disorders including Parkinson's disease, stroke, and depression (Naro*, et al.*, 2017).

The therapeutic strategy for hemiplegic stroke involves the delivery of excitatory rTMS to the lesioned hemisphere cortex to facilitate cortical excitability, thus increasing intracortical facilitation, or the delivery of inhibitory stimulation to the nonlesioned hemisphere (McIntyre*, et al.*, 2017). The effects of rTMS have been widely investigated in poststroke spasticity, especially in the arm muscles

(McIntyre*, et al.*, 2012, Naro*, et al.*, 2017). A meta-analysis of uncontrolled pre-post studies found a significant reduction in MAS scores for the elbow, wrist, and finger flexors (McIntyre*, et al.*, 2017). A randomized control trial by Rastgoo et al. reported no improvement in the MAS score for the legs after rTMS (Rastgoo*, et al.*, 2016).

Transcranial direct current stimulation (tDCS) works by delivering a constant low-amplitude current (0.5 to 2 mA) between the positive (anodal) and negative (cathodal) electrodes placed on the scalp, passing through the brain to complete the circuit (Thair*, et al.*, 2017). The constant current may alter the resting membrane potential of neurons, resulting in the hyperpolarization or depolarization of a cell. The modulatory effect depends on the direction of the current. Cathodal tDCS decreases cortical excitability, whereas anodal tDCS increases it (Thair*, et al.*, 2017). The rationale for the application of tDCS is similar to that of rTMS in that it aims to facilitate the affected hemisphere and inhibit the unaffected hemisphere so as to modulate the cortical-spinal excitability (Naro*, et al.*, 2017). However, a meta-analysis of five randomized controlled trials found that tDCS had no effect on spasticity, as measured by the MAS (Elsner*, et al.*, 2016).

In summary, the results of research on noninvasive brain stimulation techniques in the management of spasticity are not consistent. Most studies used MAS as an outcome measurement, which may not adequately measure the neurologic component of spasticity (Katz and Rymer, 1989). In addition, the cortical motor area that represents the leg occupies a relatively deep location. Thus, the effects of stimulation may be modest (Madhavan and Stinear, 2010).

1.2.3.2.5 Thermotherapy and therapeutic ultrasound

Thermal and electrophysical agents have been used to modulate spasticity. One study reported that after being immersed in warm water at 41°C for 10 min, the F-wave of the tibial nerve on the affected side was decreased significantly in stroke survivors (Matsumoto, *et al.*, 2006). The authors also proposed that thermotherapy may have antispasticity effects in its ability to relax muscles and soft tissues and decreased γ-afferent fiber activity, leading to reduced sensitivity of muscle spindles (Matsumoto, *et al.*, 2006). Therapeutic ultrasound may also induce thermal and mechanical effects on soft tissues, bringing about increased extensibility of connective tissue and decreased α-motoneuron excitability (Nakhostin Ansari, *et al.*, 2009, Sahin, *et al.*, 2011). However, two randomized controlled studies found no significant therapeutic effect of therapeutic ultrasound on poststroke spasticity, as measured by the H-reflex and the MAS (Nakhostin Ansari, *et al.*, 2009, Sahin, *et al.*, 2011).

1.3 Whole-body vibration training

1.3.1 General characteristics of whole-body vibration training

Vibratory stimuli have long been investigated for their potential effects on neuromuscular function (Charcot, 2011, Hagbarth and Eklund, 1969). The history of vibratory therapy can be traced to the 1800s. Various methods of generating vibratory stimulation (e.g., vibratory chair and vibratory hamlet) were considered to be “sedatives” of the nervous system (Charcot, 2011) because patients showed a reduction in muscle stiffness or found it easier to fall asleep after vibration therapy (Charcot, 2011). Since the 1960s, muscle vibration has been proposed to treat rigidity and spasticity in patients with neurologic diseases (Hagbarth and

Eklund, 1969). A novel vibration technique called whole-body vibration (WBV) was developed in the late 1990s and has since gained increasing interest in sports training and rehabilitation (Rittweger, 2010).

In WBV, vibration stimuli (i.e., mechanical oscillation) are delivered to the body from the feet, which make contact with a vibration platform (Rittweger, 2010). There are two major types of WBV platform generation sinusoidal vibration signals: (1) vertical/synchronous vibration platforms on which the whole plate oscillates up and down simultaneously; and (2) side-alternating/reciprocal vibration platforms with reciprocating vertical displacements on the left and right sides of a fulcrum (Cardinale and Wakeling, 2005). The sinusoidal vibration signals can be described in the following physical terms (Figure 1-2): frequency (f) (i.e., the number of occurrences of a repeating oscillation per second [unit: Hz]); period duration (T) (i.e., the duration of one oscillation cycle [unit: s]); amplitude (A) (i.e., the maximum displacement from equilibrium [unit: mm]); and peak-to-peak displacement (D) (i.e., the displacement from the lowest to the highest point of the total vibration excursion [unit: mm]) (Rauch*, et al.*, 2010).

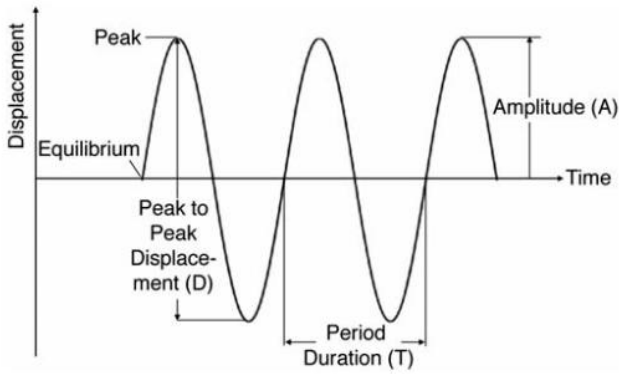

Figure 1-2 Illustration of sinusoidal WBV signal.

The peak acceleration (a_{peak}), which is often used to indicate the vibration intensity, is determined by the combination of frequency and amplitude, as shown in the following equation:

$$a_{peak} = (2\pi f)^2 A$$

where the peak acceleration is preferably presented as peak acceleration (a_{peak}) in multiples of Earth's gravity (symbol: g; 1 g = 9.81 m/s^2).

During vibration, the mechanical stimulus is transferred from the occurring source (i.e., the vibration platform) upward into the various body parts, which induces reactive forces within the body (Cochrane, 2011). The effect of the mechanical stimulus on the body depends on the vibration frequency and amplitude and on the body posture (Caryn*, et al.*, 2014, Cook*, et al.*, 2011, Friesenbichler*, et al.*, 2014, Kiiski*, et al.*, 2008, Muir*, et al.*, 2013, Munera*, et al.*, 2016, Ritzmann*, et al.*, 2013a, Tankisheva*, et al.*, 2013). It has been reported that WBV training had a significant effect on muscle flexibility in young healthy people (Houston*, et al.*, 2015); leg muscle strength (Lau*, et al.*, 2011), functional mobility (e.g., sit-to-stand and timed up-and-go test) (Lau*, et al.*, 2011, Orr, 2015), and balance (Lam*, et al.*, 2012, Orr, 2015) in the older population; and bone health in postmenopausal women (Ma*, et al.*, 2016). WBV has gained popularity in stroke survivors over the past decade for its potential effects in improving muscle strength, bone health, and mobility (Liao*, et al.*, 2015). Other potential advantages of WBV training include the requirement for only simple movements or static postures while standing on the platform, the minimal fall risk of patients, and the low level of supervision needed (Lam*, et al.*, 2018). These factors make WBV quite applicable in daily clinical practice.

1.3.2 Proposed mechanisms in the management of spastic hypertonia

Given that the spastic hypertonia has both neurologic and biomechanical origins, the potential mechanisms of WBV in the management of spastic hypertonia are related to its potential neurophysiologic and mechanical effects.

1.3.2.1 Potential neurophysiologic effects

High-frequency (>50 Hz) and low-amplitude (<1 mm) focal vibrations on a muscle belly or tendon can inhibit the H-reflex or T-reflex (Arcangel*, et al.*, 1971, Boxtel, 1986), which is known as vibration-induced reflex depression (Boxtel, 1986). It was thus postulated that WBV could reduce spinal reflex responses, and several studies have been conducted to investigate the potential mechanisms of WBV and its effects on reflex activity (Apple*, et al.*, 2010, Armstrong*, et al.*, 2008, Cakar*, et al.*, 2014, Chan*, et al.*, 2012, Cochrane*, et al.*, 2010a, Games and Sefton, 2013, Harwood*, et al.*, 2017, Hopkins*, et al.*, 2009, Hortobagyi*, et al.*, 2014, Karacan*, et al.*, 2016, Kipp*, et al.*, 2011, Kramer*, et al.*, 2013, Krause*, et al.*, 2016, McBride*, et al.*, 2010, Rittweger*, et al.*, 2003, Ritzmann*, et al.*, 2013b, Ritzmann*, et al.*, 2018, Sayenko*, et al.*, 2010, Yeung*, et al.*, 2014).

In line with the findings observed in studies of focal vibration applied locally to individual muscles and tendons, inhibition of the H-reflex or T-reflex was observed during and after WBV exposure (Apple*, et al.*, 2010, Armstrong*, et al.*, 2008, Cakar*, et al.*, 2014, Games and Sefton, 2013, Karacan*, et al.*, 2016, Kipp*, et al.*, 2011, Kramer*, et al.*, 2013, Krause*, et al.*, 2016, Ritzmann*, et al.*, 2013b, Ritzmann*, et al.*, 2018), but the diminishment of the H-reflex persisted for 30 s to 20 min in young healthy people (Apple*, et al.*, 2010, Armstrong*, et al.*, 2008, Games and Sefton, 2013, Harwood*, et al.*, 2017, Hortobagyi*, et al.*, 2014, Kipp*, et*

al., 2011, Krause*, et al.*, 2016, Ritzmann*, et al.*, 2013b). However, a few studies also reported no change in spinal reflex activity after an acute WBV exposure (Cochrane*, et al.*, 2010a, Hopkins*, et al.*, 2009, McBride*, et al.*, 2010, Yeung*, et al.*, 2014). The important methodological differences between studies in terms of the WBV platform setting, body posture, and exposure time make it difficult to compare the studies and determine the most effective protocol in inhibiting the reflex activity (Hortobagyi*, et al.*, 2014). For example, administration of vertical WBV for 1 min at 35 Hz and a 1-mm amplitude was reported to suppress the H-reflex by as much as 40% during WBV, and the H-reflex recovered to 60% of baseline 1 min later (Sayenko*, et al.*, 2010). In contrast, five 1-min exposures to side-alternating WBV at 26 Hz and a 3-mm amplitude induced no change in the patellar T-reflex (Hopkins*, et al.*, 2009) and only minimal changes in the H-reflex amplitude in young healthy people (Games and Sefton, 2013).

Possible mechanisms of this depression include postactivation depression (Kipp*, et al.*, 2011), presynaptic inhibition (Gillies*, et al.*, 1971), intracortical modulation (Mileva*, et al.*, 2009a), and reciprocal inhibition (Ritzmann*, et al.*, 2018). Repetitive excitations occur in the muscle during WBV as the muscle spindles are stretched repeatedly by the vibration stimulus (Ritzmann*, et al.*, 2010). The repetitive excitation causes depletion of the transmitter within the presynaptic terminals and thus a reduction in postsynaptic excitation (Hultborn*, et al.*, 1996, Kipp*, et al.*, 2011). However, postactivation depression was sustained for only about 10 s (Hultborn*, et al.*, 1996), so it cannot explain the inhibition of the H-reflex that persisted longer than 1 min after WBV exposure (Apple*, et al.*, 2010, Harwood*, et al.*, 2017, Hortobagyi*, et al.*, 2014, Kipp*, et al.*, 2011, Krause*, et al.*, 2016, Ritzmann*, et al.*, 2013b). Based on studies of the effects of local vibration

applied to muscle and tendon, presynaptic inhibition may be responsible for the monosynaptic reflex inhibition. The H-reflex and stretch reflex were suppressed during and after locally applied vibration (Arcangel, *et al.*, 1971, Boxtel, 1986) due to an increase in presynaptic inhibition elicited by GABAergic interneurons caused by vibration (Gillies, *et al.*, 1971). In addition, increased motor cortical excitability (Krause, *et al.*, 2016, Mileva, *et al.*, 2009b) and intracortical inhibition were observed in response to WBV (Mileva, *et al.*, 2009b), so WBV-induced monosynaptic inhibition may also be caused by intracortical inhibition. Finally, an increase in disynaptic reciprocal inhibition during submaximal isometric contraction was found after WBV (Ritzmann, *et al.*, 2018). These factors may account for the observed inhibition of the H-reflex induced by WBV exposure.

Research on the neurophysiologic effects of WBV in people with neurologic diseases is scarce. Only one study reported H-reflex modulation in people with spinal cord injury and found that WBV could suppress the H-reflex up to 40% of its baseline (35 Hz, 1 mm, 60 s) and sustain the inhibition for 60 s (Sayenko, *et al.*, 2010). Another study found that H_{max}/M_{max} decreased up to 53% after WBV (12 Hz, 4 mm, 20 min) on both paretic and nonparetic sides in stroke survivors (Chan, *et al.*, 2012). However, its description of the H-reflex measurement in the stroke study was very vague. For example, it is unclear how the researchers managed to measure both legs after a single WBV intervention (Chan, *et al.*, 2012).

1.3.2.2 Potential effects on skeletal muscle mechanical properties

Alterations in tissue temperature can induce changes in the tissue's mechanical properties (Bleakley and Costello, 2013, Noonan, *et al.*, 1993, Point, *et al.*, 2018). Heat has been shown to decrease the stiffness and increase the

extensibility of muscles and other collagenous tissues (Mutungi and Ranatunga, 1998, Noonan*, et al.*, 1993, Woods*, et al.*, 2007). Thus, warming up before exercise is widely recommended to increase flexibility and prevent injury (Cochrane, 2013, Woods*, et al.*, 2007). Thermal agents have also been used to reduce soft tissue stiffness in rehabilitation practice (Bleakley and Costello, 2013). Since the 2000s, WBV, which induces rapidly repeating concentric-eccentric muscle actions (Cardinale and Wakeling, 2005), has been suggested as a possible method to increase the metabolic rate, blood flow, and intramuscular temperature (Rittweger, 2010). WBV exercise has also been proposed as a method to warm up before exercise (Cochrane, 2013).

Indeed, WBV exercise can effectively increase intramuscular temperature (Cochrane*, et al.*, 2010b, Cochrane*, et al.*, 2008). Cochrane et al. (Cochrane*, et al.*, 2008) reported that 6 min of WBV (26 Hz, 3 mm) with a dynamic squatting posture could rapidly increase the intramuscular temperature of the vastus lateralis (0.30°C/min) compared to 10 min of 70-W cycling (0.15°C/min) and a hot bath (0.09°C/min). Several mechanisms could account for the temperature change: (1) shock-absorption mechanisms related to muscle tuning (Wakeling*, et al.*, 2002); (2) an elevated metabolic rate (Cardinale*, et al.*, 2007, Coza*, et al.*, 2011, Rittweger*, et al.*, 2010, Yamada*, et al.*, 2005, Yarar-Fisher*, et al.*, 2014); and (3) increased peripheral circulation and perfusion (Beijer*, et al.*, 2015, Hazell*, et al.*, 2008, Herrero*, et al.*, 2011b, Kerschan-Schindl*, et al.*, 2001, Lohman*, et al.*, 2007, Rittweger*, et al.*, 2000).

It is well known that the human body is a spring-mass system in which muscle and tendon act as spring-mass elements to store, release, and absorb mechanical energy (Prilutsky and Zatsiorsky, 1994, Rittweger, 2010). During

WBV, the muscular system dampens the vibration stimuli, which promotes muscle activity (i.e., muscle tuning) (Wakeling*, et al.*, 2002) and results in local heat production (Prilutsky and Zatsiorsky, 1994).

The enhanced muscle activation required greater consumption of adenosine triphosphate, shown as increased tissue oxygenation (Rittweger*, et al.*, 2010). Moreover, vibration may lead to an increase in shear stress of the vascular endothelium because of the blood's inertia (Mester*, et al.*, 2006), which promotes the release of endothelial-derived vasodilators such as nitric oxide (Sackner*, et al.*, 2005, Yue and Mester, 2007) and peripheral perfusion.

In healthy young people, Kerschan-Schindl et al. observed a two-fold increase in the mean blood velocity in the popliteal artery and two-fold increases in quadriceps and gastrocnemius muscle perfusion immediately after a 9-min WBV exercise (static squatting, 26 Hz, 3 mm) without a significant increase in heart rate or blood pressure (Kerschan-Schindl*, et al.*, 2001). Lythgo et al. reported a four-fold increase in mean blood velocity in the femoral artery after a brief period of WBV exposure (30 Hz, 4.5 mm, 1 min) (Lythgo*, et al.*, 2009). Yamada et al. used near-infrared spectroscopy to find a significant increase in oxygenation and in the total hemoglobin-to-myoglobin ratio in the vastus lateralis muscle after a 3-min squatting exercise with WBV (15 Hz, 13 mm). Games et al. also observed a significant increase in the total hemoglobin and deoxyhemoglobin levels after 5 min of WBV (50 Hz, 2 mm) (Games and Sefton, 2013). A few studies also investigated the vascular effects of WBV in patients with spinal cord injury (Herrero*, et al.*, 2011b, Yarar-Fisher*, et al.*, 2014) and Friedreich's ataxia (Herrero*, et al.*, 2011a) and consistently found an increase in the blood flow velocity in the femoral artery (Herrero*, et al.*, 2011a, Herrero*, et al.*, 2011b) and heme

concentration and oxymyoglobin concentration in the gastrocnemius muscle after WBV (Yarar-Fisher*, et al.*, 2014).

Several studies have revealed that WBV training could increase flexibility in young athletes, recreationally active individuals, and elderly people (Cardinale and Lim, 2003, Cochrane and Stannard, 2005, Dallas*, et al.*, 2014, Gerodimos*, et al.*, 2010, Gomez-Cabello*, et al.*, 2013, Jacobs and Burns, 2009, Sa-Caputo Dda*, et al.*, 2014). For example, static squatting on a side-alternating WBV platform for 5 min (26 Hz, 3 mm) led to a significant increase (8.2%) in the sit-and-reach flexibility score compared to no vibration or seated cycling at 50 W (5.3%) among elite female field hockey players (Cochrane and Stannard, 2005). Likewise, recreationally active young healthy people showed significant increases in sit-and-reach scores (16.2%) from 6 min of continuous vibration (26 Hz, amplitude unknown) compared to a 2.6% increase in the control group, which engaged in upright stationary cycling at an intensity of 50 W (Jacobs and Burns, 2009). An 11-week WBV training program with static squatting for ten 45-s bouts on a vertical WBV platform (40 Hz, 2 mm, 3 times per week) significantly increased the sit-and-reach performance (average change, 2.1 cm) compared with the control group that performed only static squats without WBV (average change, 0.7 cm) (Gomez-Cabello*, et al.*, 2013). However, it should be noted that performance on the sit-and-reach test, which involves movement of the whole body, is explained mainly by hamstring and lumbar extensibility (Mayorga-Vega*, et al.*, 2014), so the outcome of the sit-and-reach test is inadequate to reveal changes in muscle stiffness per se.

1.4 Knowledge gap and study rationale

Based a Based on the literature review, we can confirm that spastic hypertonia has both reflex and non-reflex components (Dietz and Sinkjaer, 2007, Katz and Rymer, 1989, O'Dwyer*, et al.*, 1996, Trompetto*, et al.*, 2014), and our review also revealed that WBV training has the potential to modulate spastic hypertonia because of its effects on neural activity and its skeletal muscle passive mechanical properties. Research into WBV intervention in patients with neurologic disorders has also increased dramatically. It is thus timely to examine the literature to determine the state of knowledge regarding WBV and spasticity management. A systematic review (Chapter 2 of this thesis) was thus conducted to consolidate the existing evidence of WBV training for spasticity in people with central nervous system disorders.

Our systematic review shows most studies used the MAS to measure hypertonia. As mentioned in Section 1.2.2.1, the MAS cannot distinguish the reflex and nonreflex components of spastic hypertonia and is not sensitive enough to reveal changes in hypertonia over time. To investigate reflex-related stiffness, the H-reflex has been widely used to quantify the spinal reflex. In contrast, the biomechanical assessment traditionally used to indirectly quantify the nonreflex stiffness is not ideal because the outcome is influenced by the joint's structure and because the procedures are time-consuming. Therefore, in Chapter 3, we introduce a state-of-art technique—SSI — and investigate its reliability and feasibility to measure muscle stiffness in the chronic stroke survivors.

Our systematic review also revealed inconsistent findings across studies regarding the effects of WBV on spasticity in people with central nervous system disorders. One reason for the inconsistent outcomes of the available WBV trials is the heterogeneity of the WBV protocols. During the WBV training, the vibration

is indirectly applied to the body (Rittweger, 2010). As mentioned in Section 1.3.1, the effects of the mechanical stimulus on the body depend on the vibration frequency and amplitude and on body posture. Attenuation, amplification, and distortion of the vibration signals may occur, with a substantial effect on treatment effectiveness. The safety of WBV application is of utmost importance, because prolonged occupational exposure to vibration has been deemed detrimental and can cause damage to the retina (Ishitake*, et al.*, 1998) and the inner ear (Bochnia*, et al.*, 2005). It is thus essential to ensure minimal transmission of the vibration stimuli to the head region. However, no studies have systematically investigated the influence of vibration frequency or amplitude or that of body posture on vibration transmissibility in long-term stroke survivors. To address this knowledge gap, the study described in Chapter 4 was designed to investigate WBV transmissibility and signal purity in various combinations of vibration frequency and amplitude and body posture.

Vibration can induce muscle activation, but the muscle's response depends on the WBV protocols, as mentioned in Section 1.3.2. No studies have yet investigated the influence of WBV frequency and amplitude and that of body posture on neuromuscular activation or the effects of muscle activation patterns on vibration transmissibility in stroke survivors. Thus, the study described in Chapter 5 aimed to determine how leg EMG responses were influenced by various combinations of WBV frequency and amplitude and body posture and how the EMG responses were related to vibration transmissibility at various anatomic landmarks in stroke survivors. And Chapter 4 and Chapter 5 would provide valuable reference to design a safe and effected protocol.

Finally, in Chapter 6, a randomized cross-over study was conducted to investigate the effects of WBV on spastic hypertonia in the chronic stroke survivors, particularly the effect on reflex and non-reflex component of spastic hypertonia. Also, the effect of WBV on peripheral blood perfusion was also checked. The WBV protocols used in Chapter 6 was based on the results of Chapter 4 and Chapter 5, and outcome measurement for the non-reflex component of spastic hypertonia was supersonic shear imaging which was investigated in the Chapter 3. The framework of the thesis was illustrated in Figure 1-3

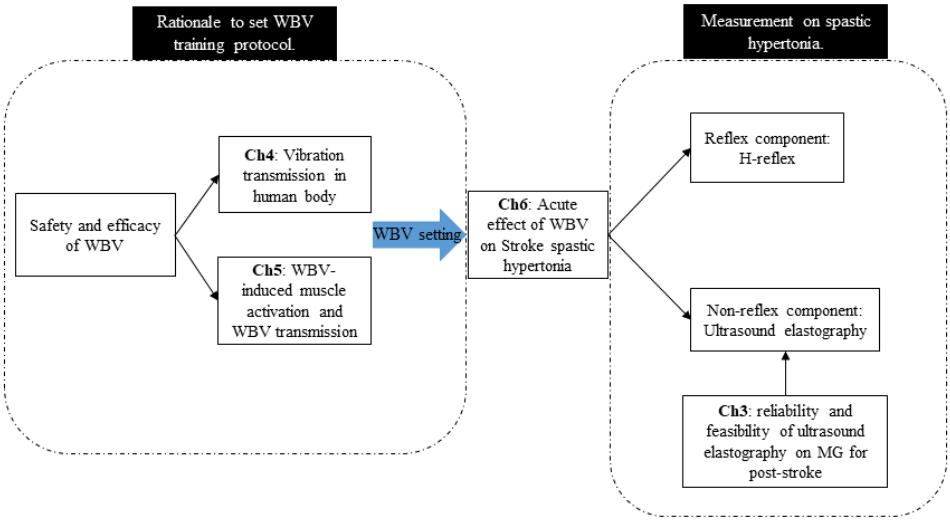

Figure 1-3 Framework of thesis.

1.5 Objectives and hypotheses

1.5.1 Overall objectives

The overall objective of this thesis was to examine the effects of WBV on spastic hypertonia in the individuals with chronic stroke.

1.5.2 Objectives and hypotheses for individual chapters of the thesis

1.5.2.1 Chapter 2: Effects of whole-body vibration on muscle spasticity for people with central nervous system disorders: a systematic review.

The primary objective of this systematic review was to examine the effects of WBV on spasticity in patients with central nervous system disorders. The secondary objective was to examine whether the WBV-induced improvement in muscle spasticity, if present, was associated with changes in functional performance. This study was published in a peer-reviewed journal (*Huang M, Liao LR, Pang MYC. Effects of whole body vibration on muscle spasticity for people with central nervous system disorders: a systematic review. Clin Rehabil. 2017;31:23-33*).

1.5.2.2 Chapter 3: Morphological and passive mechanical properties of the medial gastrocnemius muscle and their association with functional mobility in individuals with chronic stroke

The objectives of this study were to

(1) investigate the feasibility and reliability of Supersonic Shear Imaging measurement of the medial gastrocnemius muscle in chronic stroke survivors;
(2) compare the elasticity-angle curves of the medial gastrocnemius muscle between the paretic and nonparetic legs of chronic stroke survivors and the dominant leg of age-matched control subjects; and
(3) compare muscle architecture (e.g., muscle thickness, pennation angle of muscle fascicles, fascicle length) and echogenicity using B-mode ultrasound between the paretic and nonparetic legs of chronic stroke survivors and the dominant leg of age-matched control subjects.
(4) investigate the potential association between the functional mobility and both passive mechanical and architectural muscle properties.

The hypotheses of this study were

(1) supersonic shear imaging is a reliable tool for measurement of the medial gastrocnemius muscle's elasticity in long-term stroke survivors;
(2) no significant differences exist in passive muscle properties between the paretic and nonparetic sides among ambulatory long-term stroke survivors, and between the nonparetic leg of ambulational chronic stroke survivors and dominant leg of the age-matched control subjects;
(3) the muscle architecture differs significantly between the paretic and nonparetic sides in ambulatory long-term stroke survivors and between the nonparetic leg of stroke survivors and the dominant leg of age-matched control subjects; and
(4) a significant association between measures of functional mobility and both passive mechanical and architectural muscle properties.

1.5.2.3 Chapter 4: Use of whole-body vibration in individuals with chronic stroke: transmissibility and signal purity.

The objectives of this study were to

(1) investigate the influence of WBV frequency and amplitude and body posture on WBV transmissibility and signal purity; and
(2) examine the effects of stroke motor impairment and spasticity on WBV transmissibility.

The hypotheses of this study were

(1) WBV transmissibility and signal purity are influenced by vibration frequency and amplitude, body posture, and their interactions;

(2) WBV transmissibility and signal purity demonstrate a significant difference between the paretic and nonparetic sides; and

(3) WBV transmissibility is associated with the level of motor impairment or the muscle spasticity of the affected leg.

(The results of this study were published in a peer-reviewed journal (*Huang M, Tang CY, Pang MYC. Use of whole body vibration in individuals with chronic stroke: Transmissibility and signal purity. J Biomech. 2018;73:80-91*).

1.5.2.4 Chapter 5: Muscle activity and vibration transmissibility during whole-body vibration in chronic stroke

This study aimed

(1) to investigate the influence of WBV frequency and amplitude and body postures on leg muscle activation in the chronic stroke survivors

(2) to exam whether the EMG response to vibration stimulus differed between the paretic and nonparetic sides.

(3) to examine the relationship between muscle activation and WBV transmission.

We hypothesized that

(1) the addition of WBV would significantly increase muscle activation in all tested lower limb muscles compared with the no-WBV condition;

(2) for a given posture, muscle activation would increase as the vibration frequency or amplitude increased;

(3) for a given vibration frequency and amplitude, the increase in muscle activation depends on body posture;

(4) muscle activation would be greater on the paretic side than on the nonparetic side during WBV;

(5) higher WBV-induced muscle activation would be associated with lower WBV transmission in the more proximally located joints.

(The results of this study were published in a peer-reviewed journal *(Huang M, Pang MYC.: Muscle activity and vibration transmissibility during whole-body vibration in chronic stroke. Scand J Med Sci Sports. In press*).

1.5.2.5 Acute effect of the whole body on neuromuscular excitability, muscle blood volume and muscle stiffness: a randomized cross-over study

This study aimed to investigate the acute effects of WBV on the H-reflex, the muscle mechanical properties, and blood perfusion of the bilateral soleus muscles in the chronic stroke survivors.

We hypothesized that

(1) inhibition of the H-reflex and decreased elasticity and increased vascularity of the bilateral soleus muscle would be observed immediately after WBV

(2) the effect of WBV on aforementioned factors would be greater in the paretic side compared to the nonparetic side.

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2. Chapter 2: Effects of whole-body vibration on muscle spasticity for people with central nervous system disorders: a systematic review

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2.1 Abstract

Objectives: To examine the effects of whole-body vibration on spasticity among people with central nervous system disorders.

Methods: Electronic searches were conducted using CINAHL, Cochrane Library, MEDLINE, Physiotherapy Evidence Database, PubMed, PsycINFO, SPORTDiscus and Scopus to identify randomized controlled trials that investigated the effect of whole-body vibration on spasticity among people with central nervous system disorders (last search in August 2015). The methodological quality and level of evidence were rated using the PEDro scale and guidelines set by the Oxford Centre for Evidence-Based Medicine.

Results: Nine trials with totally 266 subjects (three in cerebral palsy, one in multiple sclerosis, one in spinocerebellar ataxia, and four in stroke) fulfilled all selection criteria. One study was level 1b (PEDro$\geqslant$6 and sample size>50) and eight were level 2b (PEDro<6 or sample size $\leqslant$50). All three cerebral palsy trials (level 2b) reported some beneficial effects of whole-body vibration on reducing

leg muscle spasticity. Otherwise, the results revealed no consistent benefits on spasticity in other neurological conditions studied. There is little evidence that change in spasticity was related to change in functional performance. The optimal protocol could not be identified. Many reviewed studies were limited by weak methodological and reporting quality. Adverse events were minor and rare.

Conclusion: Whole-body vibration may be useful in reducing leg muscle spasticity in cerebral palsy but this needs to be verified by future high quality trials. There is insufficient evidence to support or refute the notion that whole-body vibration can reduce spasticity in stroke, spinocerebellar ataxia or multiple sclerosis.

2.2 Introduction

Whole-body vibration has attracted much interest in rehabilitation in the past decade. In whole-body vibration treatment, vibration stimuli with combinations of different amplitudes and frequencies are delivered to the body from the feet which make contact with the vibration platform. Typically, static or/and dynamic exercises are performed while standing on the whole-body vibration platform (Rittweger, 2010).

Vibratory stimulus has been shown to modulate Ia afferent–motoneuron synaptic transmission by causing presynaptic inhibition (Nielsen*, et al.*, 1995). Recent studies have found that H-reflex was depressed during and after whole-body vibration in young healthy adult population (Ahmadi*, et al.*, 2015, Armstrong*, et al.*, 2008, Games and Sefton, 2013, Kipp*, et al.*, 2011). Measured by transcranial magnetic stimulation, whole-body vibration was shown to increase the excitability of the corticomotor pathway and intracortical inhibition while decreasing

intracortical facilitation (Mileva*, et al.*, 2009). In addition, there is some evidence that whole-body vibration could increase temperature and blood flow in both skin and lower limb muscles (Beijer*, et al.*, 2015, Cochrane*, et al.*, 2008, Coza*, et al.*, 2011, Gerodimos*, et al.*, 2010, Lythgo*, et al.*, 2009). These changes in thermoregulation and muscle perfusion may lead to alterations in viscoelastic properties of soft tissue (Beijer*, et al.*, 2015) and may partially explain the increase in flexibility of the lower extremities among athletes after whole-body vibration (Gerodimos*, et al.*, 2010, Jacobs and Burns, 2009).

The effects of whole-body vibration on reflex activity and mechanical properties of muscles may thus have therapeutic implications for people with central nervous system disorders, in which muscle spasticity is a common manifestation (Lance, 1981). The secondary problems stemming from muscle spasticity are diverse and may include reduced functional mobility and activity participation (Dietz and Sinkjaer, 2007, Lieber*, et al.*, 2004). Hence, much research effort has been directed to determine effective treatment strategies to tackle the issue of spasticity in central nervous system disorders.

The past decade saw considerable increase in research studies that investigated the influence of whole-body vibration on muscle spasticity in people with central nervous system disorders. It is thus timely to conduct a systematic review to examine the overall evidence, which can be used to guide clinical decision making. The primary objective of this systematic review was to examine the effects of whole-body vibration on spasticity in people with central nervous system disorders. The secondary objective was to examine whether the whole-

body vibration-induced improvement in muscle spasticity, if present, was associated with changes in functional performance.

2.3 Materials and methods

2.3.1 Research question

This systematic review aimed to answer the following two questions. First, does whole-body vibration therapy lead to better muscle spasticity outcomes compared with no vibration under the same exercise condition, or other forms of intervention among individuals with central nervous system disorders? Second, is there a relationship between change in muscle spasticity and improvement of functional level after whole-body vibration intervention? The PICO (P=Patients, I=Intervention, C=Comparison, O=Outcomes) method was used to define the four major components of the research question(Oxford, 2012): P=individuals with central nervous system disorders; I=whole-body vibration; C=(1) comparison with no whole-body vibration under the same exercise condition, and (2) comparison with other forms of physical activity/intervention; O=muscle spasticity (primary outcome), and all measures of functional performance (secondary outcomes).

2.3.2 Study selection

The inclusion criteria for article were (1) randomized controlled trials that investigated the effects of whole-body vibration in people whose primary diagnosis was a central nervous system disorder; (2) the study had included at least one measurement related to muscle spasticity and (3) published in English. Exclusion criteria were (1) studies that used focal vibration or physioacoustic

vibration as an intervention rather than whole-body vibration, or (2) animal studies, or (3) reported in books, conference proceedings, theses or dissertations.

2.3.3 Data sources and searches

An extensive literature search was done using the following electronic databases: MEDLINE (1950 to 21 August 2015), PubMED (until 24 August 2015), Cumulative Index to Nursing and Allied Health Literature (CINAHL)(1982 to 24 August 2015), SPORTDiscus (1830 to 24 August 2015), PsychoINFO (1806 to 24 August 2015), Cochrane Library (1898 to 24 August 2015) and Physiotherapy Evidence Database (PEDro) (until 24 August 2015). A combination of search terms pertaining to whole-body vibration therapy and central nervous system disorders (e.g., cerebrovascular disease, cerebral palsy, multiple sclerosis, spinal cord injury, etc) was generated to identify potential studies. The specific search strategy for MEDLINE database is described in the Appendix. A similar search strategy was used for other database, with the exception of PEDro in which the key word “vibration” was used in simple search. The search strategy and search terms used were validated by a librarian in biological sciences and confirmed with the principal investigator.

Two well-trained researchers conducted the article search and screening independently. Any disagreement was resolved by discussion with the principal investigator. Duplicate articles generated by the different databases were removed using an electronic reference management tool RefWorks (Bethesda, MD, USA). The titles and abstracts of the articles were first screened to eliminate the irrelevant studies. The full-text of the remaining articles was reviewed in detail to determine the eligible ones. The reference list of each selected article was extensively

checked to identify other potentially relevant studies. A forward search was conducted using Scopus on 30 August 2015 to identify all relevant articles that had referenced the selected articles.

2.3.4 Methodological quality assessment

The Physiotherapy Evidence Database (PEDro) scale was used to evaluate the scientific rigor of the selected clinical trials (9-10=excellent, 6-8=good, 4-5=fair, and ⩽4 =poor) (Physiotherapy). It was developed to assess both external validity (i.e. item 1 in PEDro scale, not considered in calculation of total score) and internal validity (i.e. item 2-11) (Table 1, supplementary material). The PEDro score of these studies could be obtained by searching PEDro database except Cheng et al (Cheng, *et al.*, 2015). Therefore, this article was rated independently by two researchers who were experienced with using the PEDro.

The Oxford Centre for Evidence-Based Medicine Levels of Evidence (2009) was used to determine the level of evidence for each reviewed articles based on the study design and methodological quality.(Oxford, 2012) For randomized controlled trials, level 1b indicated good-quality (PEDro score ⩾6 and sample. size >50), while the level 2b indicated poor quality (PEDro score <6 or sample size ⩽50) (Pang, *et al.*, 2013a). The evidence level of each study was determined independently by two researchers who were familiar with the Oxford Centre for Evidence-Based Medicine Levels of Evidence (2009), and any inconsistent results were resolved after discussion with the principal investigator.

Table 2-1 Rating of the methodological quality and level of evidence [a]

PEDro criterion	Study								
	Cerebral Palsy			Multiple Sclerosis	Spino-cerebellar ataxia	Stroke			
	Ahlborg et al., 2006 [1]	Ibrahim et al., 2014[18]	Cheng et al., 2015[8]	Schyns et al., 2009[35]	Kaut et al., 2014[20]	Brogårdh et al., 2012[6]	Chan et al., 2012[7]	Pang et al., 2013[30]	Tankisheva et al., 2014[36]
Eligibility Criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Random Allocation	1	1	1	1	0	1	1	1	1
Concealed Allocation	0	0	0	0	0	1	1	1	1
Baseline Comparability	1	1	0	0	1	0	1	1	1
Blind Subjects	0	0	0	0	1	1	1	0	0
Blind Therapists	0	0	0	0	0	1	0	0	0
Blind Assessors	0	0	0	1	1	1	1	1	1
Adequate follow-up	1	0	1	0	1	1	1	1	1
Intention-to-treat analysis	0	0	0	0	0	1	0	1	0
Between group comparisons	0	1	1	1	1	1	1	1	1
Point estimates and variability	1	1	1	1	1	1	1	1	1
TOTAL	**4**	**4**	**4**	**4**	**6**	**9**	**8**	**8**	**7**
Sample size ≥50	No	No	No	No	No	No	No	Yes	No
Level of Evidence	**2b**	**2b**	**2b**	**2b**	**2b**	**2b**	**2b**	**1b**	**2b**

[a] NA= Not applicable; RCT= Randomized Clinical Trial.

2.3.5 Quality of whole-body vibration reporting

It is important to clearly report the whole-body vibration protocol in order to facilitate clinical application of scientific findings. Thus, the quality of whole-body vibration reporting was assessed using the checklist adapted from the one endorsed by the International Society of Musculoskeletal and Neuronal Interactions (Rauch*, et al.*, 2010). There are 13 items in the original checklist related to various aspects of the whole-body vibration protocols. In addition, we also added an item related to the supervision received during the whole-body vibration exercise training, which may have important impact on treatment outcomes (Emerenziani*, et al.*, 2014). A score was given if the criterion described in a particular item was fulfilled. The maximum possible score was 14 (Table 2-2).

2.3.6 Data synthesis and analysis

Information about the key demographic characteristics of the participants, whole-body vibration intervention protocols, and outcomes of each study was extracted. After reviewing the results of the selected studies, it was decided that meta-analysis was not appropriate because only few studies (<5) used the same outcome measures, and the treatment protocols also varied substantially among the different studies. To estimate the size of the treatment effect for those outcomes that yielded

Table 2-2 Quality of WBV Reports [a,b]

Criterion[a]	Study								
	Cerebral Palsy			Multiple Sclerosis	Spino-cerebellar ataxia	Stroke			
	Ahlborg et al., 2006	Ibrahim et al., 2014	Cheng et al., 2015	Schyns et al., 2009	Kaut et al., 2014	Brogårdh et al., 2012	Chan et al., 2012	Pang et al., 2013	Tankisheva et al., 2014
Brand name and type	1[b]	1	1	1	1	1	1	1	1
Type of vibration	0	1	1	1	1	1	1	1	1
Frequency	1	1	1	1	1	1	1	1	1
Amplitude	0	1	1	1	1	1	1	1	1
Peak acceleration	0	0	0	0	0	0	0	1	0
Calibration	0	0	0	0	0	0	0	1	0
Skidding of feet	0	1	0	0	0	0	0	0	0
Progression	1	1	0	0	0	1	0	1	1
Rationale for protocol	1	1	0	1	1	1	1	1	1
Support device	1	1	1	0	0	1	1	0	1
Footwear	0	1	0	0	1	1	0	0	0
Body posture	1	1	1	0	1	1	1	1	1
Exercise	1	1	1	1	1	1	1	1	1
Supervision	0	1	1	0	0	1	1	1	1
Total	**7**	**12**	**8**	**6**	**8**	**11**	**9**	**11**	**10**

[a] Item 1-13 are in accordance with the descriptions in Rauch F, Sievanen H, Boonen S, et al. Reporting whole-body vibration intervention studies : Recommendations of the International Society of Musculoskeletal and Neuronal Interactions. 2010;10(3):193–198.

[b] 1:Yes;0:No, NA: not applicable

significant results, the standardized effect size (SES) with Hedges' correction was computed (small SES= 0.2, medium= 0.5, large=0.8) based on the data provided in the selected articles (Dunlap*, et al.*, 1996, Liao*, et al.*, 2014). Kappa statistic was used to assess the degree of agreement between the tworesearchers in selection and rating of the articles, using IBM SPSS software (version 20.0, IBM, Armonk, NY, USA).

2.4 Results

A total of 296 records were identified after duplicates were removed. Of these, nine articles met our selection criteria (Figure 2-1). Excellent inter-rater agreement for article selection was found at the stage of title and abstract screening (kappa=0.830, P<0.001), as well as full text screening (kappa=0.856, P<0.001).

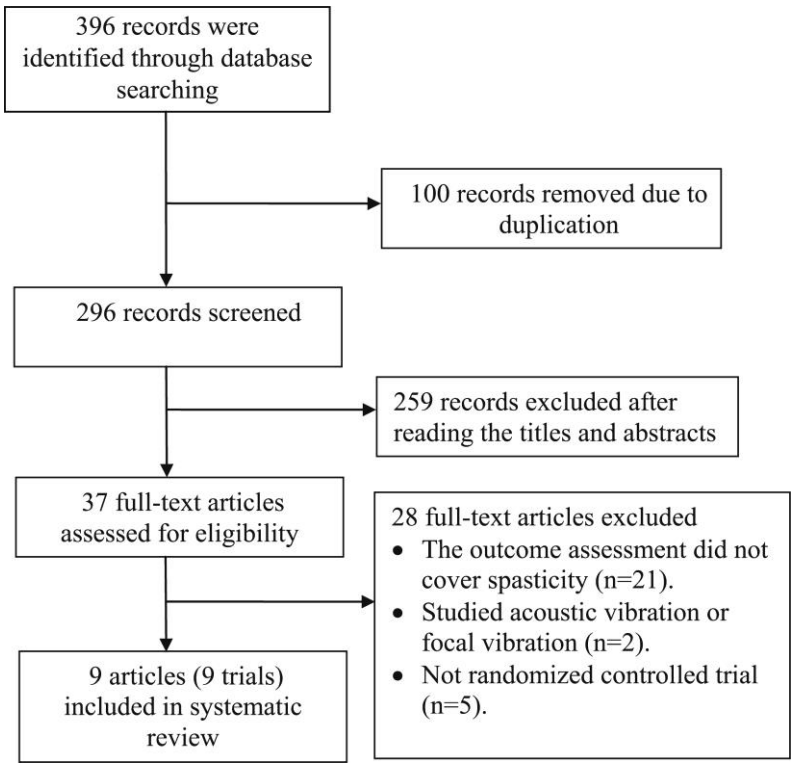

Figure 2-1 Study flowchart.

A total of 9 articles were included in this systematic review.

2.4.1 Study population

Three trials studied the effects of whole-body vibration on muscle tone in cerebral palsy (Ahlborg, *et al.*, 2006, Cheng, *et al.*, 2015, Ibrahim, *et al.*, 2014), one in multiple sclerosis (Schyns, *et al.*, 2009), one in spinocerebellar ataxia (Kaut, *et al.*, 2014), and four in stroke (Brogardh, *et al.*, 2012, Chan, *et al.*, 2012, Pang, *et al.*, 2013b, Tankisheva, *et al.*, 2014). A total of 266 subjects with central nervous system disorders were involved, with the mean age ranging from 9.8 to 69.7 years. The key characteristics of participants in each study are summarized in Table 2-3.

2.4.2 Whole-body vibration training protocol

The summary of whole-body vibration training protocols adopted in various studies is provided in Table 2-4. Six studies used synchronous (vertical) vibrations (Brogardh, *et al.*, 2012, Chan, *et al.*, 2012, Cheng, *et al.*, 2015, Pang, *et al.*, 2013b, Schyns, *et al.*, 2009, Tankisheva, *et al.*, 2014), one used side-alternating vibrations (Ibrahim, *et al.*, 2014), and one utilized stochastic vibrations (Kaut, *et al.*, 2014). One study did not report the type of vibration used (Ahlborg, *et al.*, 2006). The frequency and amplitude of vibrations varied from 6–50Hz and 0.44mm-6mm, respectively. The theoretical peak acceleration of the signals, calculated by [Amplitude × $(2\times\pi\times\text{frequency})^2$], ranged from 0.4g to 20.1*g*, where g denotes the unit of Earth's gravity (9.81m/s^2). One trials investigated the acute effect of whole-body vibration (Chan, *et al.*, 2012), while eight trials examined the effects of long-term whole-body vibration training (Ahlborg, *et al.*, 2006, Brogardh, *et al.*, 2012, Cheng, *et al.*, 2015, Ibrahim, *et al.*, 2014, Kaut, *et al.*, 2014, Pang, *et al.*, 2013b, Schyns, *et al.*, 2009, Tankisheva, *et al.*, 2014).

Table 2-3 Subject Characteristics in the reviewed studies.[a,b]

Study	PEDro Score / WBV reporting quality[c]	Disease	Sample size	Subject characteristics			Impairment level at baseline	
				Age (years)	Disease duration	Relevant medications	Measure	Value
Studies that the assessed acute effects of WBV on spasticity								
Chan et al., 2012[7] (comparision 1)	RCT-level 2b PEDro=8 Report Quality=9	Stroke	*n*=30 WBV, *n*=15 CON, *n*=15	55.5 (9.4)	34.7(32.6) mo	Antispastic drug WBV, *n*=7; CON, n= 6	MAS (0-5) VAS (0-10) Achilles tendon reflex (0-4)	2.4(0.5) 5.8 (1.8) 2.7(0.5)
Studies that assessed the effects of multiple sessions of WBV on spasticity								
Brogärdh et al., 2012[6] (comparision 1)	RCT-level 2b PEDro=9 Report Quality=11	Stroke	*n*=31 WBV, *n*=16 CON, *n*=15	62.6 (7.3)	35.3(30.6) mo	NR	FIM(18-126) MAS(sum, 0-35)	83.3(3.2) WBV1.5(0–7)[d] CON 1.0(0–9)[d]
Kaut et al., 2014[20] (comparision 1)	RCT-level 2b PEDro=6 Report Quality=8	SCA	*n*=32 WBV, *n*=17 CON, *n*=15	59.4 (12.5)	10.85(5.43)	NR	SARA sum(0-40)	12.89(6.03)
Pang et al., 2013[30] (comparision 1)	RCT-level 1b PEDro=8 Report Quality=11	Stroke	*n*=82, WBV, *n*=41 CON, *n*=41	57.4 (11.2)	5.0(3.9) y	NR	MAS(0-5)	Knee 0(0–1) [d] Ankle2(1–3) [d]
Schyns et al., 2009[35] (comparision 1)	RCT-level 2b PEDro=4 Report Quality=6	MS	*n*=16	47.7 (7.4)	WBV: 6.7y (range:10 mo - 23y) CON: 11.8y (range: 3.5 –18 y)	"Subjects were asked to stabilize their medications, especially antispasmodic drugs"	NR	NR
Cheng et al., 2015[8] (comparison 1)	RCT-level 2b PEDro=4 Report Quality=8	CP	*n*=16	9.2 (2.1)	NR	NR	MAS	4.61 (0.95)
Ahlborg et al., 2006[1] (comparision 2)	RCT-level 2b PEDro=4 Report Quality=7	CP	*n*=14 WBV, *n*=7 CON, *n*=7	31 (6.5)	NR	None	MAS(0-5)	3(2–3)[d]
Ibrahim et al., 2014[18] (comparision 2)	RCT-level 2b PEDro=4 Report Quality= 12	CP	*n*=30 WBV, *n*=15 CON, *n*=15	9.6 (1.4)	NR	None	MAS(0-4)	"range 1-2"
Tankisheva et al., 2014[36] (comparision 2)	RCT-level 2b PEDro=7 Report Quality= 10	Stroke	N=15 WBV, *n*=7 CON, *n*=8	61.6 (9.2)	6.4(6.4) y	NR	AS(sum score 0-24)[f] Fugl-Meyer test(0-44)	WBV: 4 (0–9)[d] CON: 5 (0–14)[d] 22.92(5.3)

[a]Comparison 1: compared with no WBV under the same exercise condition; Comparison 2: compared with other forms of physical activity/intervention.
[b]AS: Ashworth Scale; CON: Control group; CP: Cerebral palsy; F: Female; FIM: Functional Independent Measure; FSE: First swing ex; GMFM: Gross Motor Function Measurement; M: male; MAS: Modified Ashworth Scale; mo: month; MS: Multiple Sclerosis; NR: Not report; PROM: Passive Range of Motion; RCT: Randomized Control Trial; SARA: Scale for the Assessment and Rating of Ataxia; SCA: Spinocerebellar Ataxia; SCI: Spinal Cord Injury; UPDRS: Unified Parkinson Disease Rating Scale; VAS: Visual Analog Scale; WBV: Whole-body Vibration group; y: Year.
[c]PEDro score ranges from 0 to 10. Reporting quality score ranges from 0 to 14.
[d]Mean(SD) presented unless otherwise.
[e]Median (IQR).
[f]Sum score of gastrocnemius, soleus, quadriceps, hamstrings, adductors, and psoas muscles.

Table 2-4 Training Protocol of WBV group and Control group [a,b]

Study	Disorder	WBV Training group									Control group
		Protocol of WBV									
		Frequency of Sessions × Duration of Program	No. of Vibration Bouts × Duration per Bout	Rest Between Bouts	Frequency (Hz), Amplitude (mm), and Peak Acceleration (g) of vibration stimuli	Vibration type	Foot wear	Posture and exercise on WBV platform	Additional intervention	Supervision	Protocol
Studies that assessed the acute effects of WBV on spasticity											
Chan et al, 2012[8] (Comparison 1)	Stroke	Single session	2 bouts × 10 min	60s	12 Hz 4 mm (2.3 g)	Vertical	NR	Semi-squatting	None	Physician	Followed the same procedures, but the vibration machine was not turned on
Studies that assessed effects of multiple sessions of WBV on spasticity											
Brogardh et al.2012[6] (comparision1)	Stroke	2×/wk x 6 wk	4 bouts × 40s to 12 bouts × 60s	60s	25 Hz 3.75 mm (9.4 g)	Vertical	Barefoot	Static standing with flexed knees at 45°–60°	None	Physical therapist	Same exercises on a vibration platform with an amplitude of 0.20 mm and a frequency 1 Hz
Kaut et al., 2014[20] (comparision1)	SCA	4 different days within 8 days period	5 bouts × 60s	60s	6-6.5Hz 3mm, (0.4-0.5g)	Stoch-astic	With shoes	Semi-squat with knees slightly flexed	None	NR	Same treatment with 1 Hz, 3mm

Pang et al, 2013[30] (comparision1)	Stroke	3×/wk x 8 wk	6 bouts × 1.5 min to 6 bouts × 2.5 min	3–4.5 min	20–30 Hz 0.44–0.60mm 1.0–1.6 g	Vertical	NR	Side-to-side weight shift, semi-squat, forward and backward, weight shift, forward lunge, standing on one leg, deep squat	15 min of warm-up exercises (general mobilization and stretching) in a sitting position	Therapist	Same exercises on the same WBV platform as the WBV group but without vibration
Schyns et al., 2009[35] (comparision1)	MS	(WBV + exercise) 3x/wk × 4wk, wash period 2wk, exercise 3x/wk×4 wk	10 × 30s	NR	Amplitude 2mm Warm up/ cool down 50 Hz, (20.1g) Exercise 40 Hz, (12.9g)	Vertical	NR	NR	Stretch and strength exercise	NR	Same stretch and strength exercise without vibration
Cheng et al., 2015[8] (comparision1)	CP	3×/wk x 4 wk	10 min	0	20Hz, 2mm (3.2g)	Vertical	NR	Passive standing with knee flexed at 30°	None	Researcher	Followed the same procedures, but the vibration machine was off
Ahlborg et al.,2006[1] (comparision2)	CP	3x/wk × 8wk 6min/ session	8 bouts × 30s ~ 3 bouts ×110s	0~120s	25 Hz~40 Hz Amplitude NR, Peak Acceleration NR	NR	NR	Static standing with hips with flexed knees in 50°	5 min warm up and short program of muscle stretching.	NR	Resistance training (70% of 1 RM) in a leg press device for the same amount of time

Ibrahim, et al, 2013[18] (comparision2)	CP	3×/wk × 12wk	3 bouts × 3min	3min	12-18Hz, 4-6mm, (2.3-7.8g)	Side-alternating	Gym nastic shoes	Knees slightly bent	selected physical therapy: stretching, strengthening, postural control training	Researcher	Selected physical therapy: stretching, strength-ening, postural control training
Tankisheva et al,2014[36] (comparision2)	Stroke	3×/wk x 6 wk	1–12 sessions: 5 bouts × 30s 13–18 sessions: 17 bouts × 60s	NR	1–12 sessions: 35 Hz 1.7 mm (8.4 g) 13–18 sessions: 40 Hz 2.5 mm (16.1 g)	Vertical	NR	Standing on their toes, knee flexion of 50°–60° (high squat), Knee flexion of 90° (deep squat), wide-stance squat, and 1-legged squat	None	Trainer	Habitual activities

[a] Comparison 1: compared with no WBV under the same exercise condition; Comparison 2: compared with other forms of physical activity/intervention

[b] CP=Cerebral Palsy; MS= Multiple Sclerosis; NR=Not Report; SCA=Spinocerebellar Ataxia

2.4.1 Methodological quality

The PEDro score of selected studies could be obtained by searching PEDro database, which ranged from 4 to 9. Overall, only one trial in stroke was considered to have excellent methodological quality (PEDro score=9) (Pang*, et al.*, 2013b), and four studies (one in spinocerebellar ataxia (Kaut*, et al.*, 2014), and three in stroke (Brogardh*, et al.*, 2012, Chan*, et al.*, 2012, Tankisheva*, et al.*, 2014)) were regarded as having good methodological quality (PEDro score= 6–8), and four studies (three in cerebral palsy (Ahlborg*, et al.*, 2006, Cheng*, et al.*, 2015, Ibrahim*, et al.*, 2014), one in multiple sclerosis) (Kaut*, et al.*, 2014) were fair quality trials (PEDro score=4).

The level of evidence of each study was rated by two researchers and the agreement was excellent with kappa=0.886 (P<0.001).One stroke trial were level 1b (PEDro⩾6 and sample size>50) (Pang*, et al.*, 2013b), eight were level 2b (PEDro< 6 or sample size⩽50) (Ahlborg*, et al.*, 2006, Brogardh*, et al.*, 2012, Chan*, et al.*, 2012, Cheng*, et al.*, 2015, Ibrahim*, et al.*, 2014, Kaut*, et al.*, 2014, Schyns*, et al.*, 2009, Tankisheva*, et al.*, 2014).

2.4.2 Quality of whole-body vibration reporting

All the selected studies explicitly reported the specific vibration device and vibration frequency used. Vibration amplitude and vibration type (i.e. synchronous, side-alternating, stochastic) was unknown in one study (Ahlborg*, et al.*, 2006). Six studies clearly reported whether the patients were supervised during whole-body vibration invention (Brogardh*, et al.*, 2012, Chan*, et al.*, 2012, Ibrahim*, et al.*, 2014, Pang*, et al.*, 2013b, Tankisheva*, et al.*, 2014). However, only one study calibrated the

whole-body vibration device and reported the validated peak acceleration (Pang, *et al.*, 2013b).

2.4.3 Muscle spasticity measurement tools

Various measurement tools were used to assess muscle spasticity in different studies. The clinical measurement tools included Modified Ashworth Scale (Ahlborg, *et al.*, 2006, Brogardh, *et al.*, 2012, Chan, *et al.*, 2012, Cheng, *et al.*, 2015, Ibrahim, *et al.*, 2014, Pang, *et al.*, 2013b, Schyns, *et al.*, 2009, Tankisheva, *et al.*, 2014), Multiple Sclerosis Spasticity Scale-88 (Schyns, *et al.*, 2009), Inventory of Non-Ataxia Symptoms (Kaut, *et al.*, 2014), and Visual Analogue Scale for measuring self-perceived level of spasticity (Chan, *et al.*, 2012). Other assessment tools included H-reflex (Chan, *et al.*, 2012), tendon reflex testing (Chan, *et al.*, 2012) and Pendulum test (Cheng, *et al.*, 2015). Five of the studies used only one measurement tool to examine muscle spasticity (Ahlborg, *et al.*, 2006, Brogardh, *et al.*, 2012, Ibrahim, *et al.*, 2014, Pang, *et al.*, 2013b, Tankisheva, *et al.*, 2014), while four studies involved two or more measurement tools (Brogardh, *et al.*, 2012, Chan, *et al.*, 2012, Cheng, *et al.*, 2015, Schyns, *et al.*, 2009).

2.4.4 Comparison group

Six studies involved a comparison group that performed the same exercises as the whole-body vibration group but without the vibration stimuli (Chan, *et al.*, 2012, Cheng, *et al.*, 2015, Pang, *et al.*, 2013b, Schyns, *et al.*, 2009) or with sham vibrations (Brogardh, *et al.*, 2012, Kaut, *et al.*, 2014) (i.e., comparison 1 as defined in the Methods section) so that the effects of the whole-body vibration alone could be delineated. Three studies incorporated a control group that was involved in other

activities (e.g. routine treatment, strength training) (i.e., comparison 2) (Ahlborg*, et al.*, 2006, Ibrahim*, et al.*, 2014, Tankisheva*, et al.*, 2014). This comparison would determine whether the whole-body vibration training overall (whole-body vibration and exercise components) was better than other interventions.

2.4.5 Acute effect of whole-body vibration on muscle spasticity

The results of each study are presented in Table 2-5.

Comparison 1. Only one trial studied the acute effect of whole-body vibration on spasticity when compared with the same exercise training but without whole-body vibration (Chan*, et al.*, 2012). Chan et al. employed four measurement tools (i.e. Modified Acworth Scale, Visual Analogue Scale, H-reflex, Achilles tendon jerk) to measure the change of ankle spasticity in patients with chronic stroke after a single session and the results were inconsistent (Chan*, et al.*, 2012). The Modified Ashworth Scale and Visual Analogue Scale score were significantly more reduced in the whole-body vibration group compared to the control group after whole-body vibration, but not the H-reflex response (H-reflex, H_{max}/M_{max}) and Achilles tendon reflex on the affected side (Chan*, et al.*, 2012). Postural control and functional mobility were also improved significantly more in the whole-body vibration group (Chan*, et al.*, 2012).

Table 2-5 Summary of outcome in reviewed studies [a,b,c]

Study	Muscle tone measurement			Other outcome measurements	
		Results		Results	
	Measurement (body site / time point)	Between-group analysis	Within-group analysis	Between- group analysis	Within-group analysis
Studies that assessed the acute effects on spasticity					
Chan et al.,2012[30] (Stroke/comparision1)	Ankle Pretest Posttest	**↓MAS(SES=3.70)** [d] **↓VAS (SES=1.96)** **H_{max}/M_{max}** **↓Unaffected side (SES=0.87)** H-reflex Affected side (-) Unaffected side (-) Hmax/Mmax Affected side (-) Achilles tendon reflex (-)	**H_{max}/M_{max}** **Affected side** **↓WBV (SES=0.66)**[e] CON(-) **Un-affected side** **↓WBV (SES=0.54)** CON(-) MAS (-) VAS (-) H-reflex Affected side (-) Unaffected side (-) Achilles tendon reflex (-)	**↓TUG(time) (SES=1.80)**[d] **↓10MWT (time) (SES=0.79)** **↑weight bearing in affected side (SES=0.87)** **↓ weight bearing in unaffected side (SES=0.87)** Cadence(-)	TUG (-) 10MWT(-)

Studies that assessed the effects of multiple sessions of WBV on spasticity					
Brogårdh et al., 2012[29] (Stroke / comparison 1)	Affected side: Hip flexors Hip extensors Hip adductors Knee extensors Knee flexors Ankle PF Ankle DF Pretest Posttest (week 6)	MAS (-)	MAS (-)	BBS (-) TUG (-) 10MWT (-) 6MWT (-) SIS (-)	**BBS** **↑WBV(SES=0.73)[e]** CON(-) **TUG(time)** **↓WBV(SES=0.30)** **↓CON (SES=0.17)** **10MWT(comfort-able speed)** **↑WBV(SES=0.17)** CON (-) **6MWT(distance)** **↑WBV(SES=0.16)** **↑CON (SES=0.19)**
Pang et al., 2013[31] (Stroke/comparison 1)	Knee Ankle Pretest posttest 1 (week 8) posttest 2 (week 12)	None	**Posttest 1** Knee MAS (-) Ankle MAS (-) **Posttest 2** **Knee MAS** **↓WBV[f]** CON (-) Ankle MAS (-)	None	Posttest 1 & 2 CMSA (-)

Kaut et al., 2014[28] (SCA /comparison 1)	NA Pretest Posttest (end of week 1)	None	INAS Spasticity (-)	SARA ↓ **postural gait (SES=0.36)**[h]	INAS Sum (-) SARA Postural gait (-) Limb kinetics (-) Sum (-) SCAFI Total score(-) Time for 8-meter walking ↓ **WBV(SES=0.12)**[g] CON(-)
Tankisheva et al., 2014[32] (Stroke /comparison 1)	Gastroc-nemius Soleus Quad-riceps Ham-strings Add-uctors Psoas Pretest Posttest 1 (week 6) Posttest 2 (week 12)	MAS (-)	MAS (-)	None	None

Cheng et al., 2015[27] (CP /comparison 1)	Quadriceps Pretest Post-test 1 (Post-WBV day 1) Post-test 2 (Post-WBV day 2) Post-test 3 (Post-WBV day 3)	**↓MAS(SES=0.85-1.61)[i]** **↑ RI (SES=0.42-1.37)**	**↓MAS** **(SES=0.68-1.36)[j]** **↑RI** **(SES=1.50-2.17)[i]**	**↑AROM** **(SES=1.24-1.83)[i]** **↑6MWT(distance)** **(SES=0.41-1.34)** **↓TUG(time)** **(SES=1.33-1.43)** PROM(-)	**↑6MWT(distance)[j]** **SES=1.03-2.11)** TUG(time)(-) AROM(-) PROM(-)
Ahlborg et al.,2006[25] (CP/ comparison 2)	Hip flexors Hip adductors Knee extensors Knee flexors Ankle PF Pretest Posttest (week 8)	None	**MAS:** **knee extensors** **(stronger side)** **↓WBV[f]** CON (-) Hip flexors (-) Hip adductors (-) Knee flexors (-) Ankle PF (-)	None	**GMFM (D + E)** **↑WBV[g]** CON (-) 6MWT (-) TUG (-)
Ibrahim et al., 2014[26] (CP /comparison 2)	Hip adductors Knee extensors Ankle PF Pretest Posttest (week 12)	MAS Hip adductors (-) Knee extensors (-) Ankle PF (-)	**MAS:** **Knee extensor (weaker side)** **↓WBV** **(SES=2.53)[e]** CON (-) Hip adductors (-) ankle PF (-)	**↑6MWT (speed)[h]** **(SES=3.59)** **↑GMFM (E)** **(SES=4.77)** TUG(-) GMFM (D) (-)	**6MWT** **↑WBV (SES=3.11)[e]** CON(-) TUG(-) **GMFM (D)** **↑WBV (SES=1.95)** **↑CON (SES=0.98)** **GMFM(E)** **↑WBV (SES=11.02)** CON(-)

[a] 6MWT=Six-Minute Walk Test; 10MWT= Ten-Minute Walk Test; AROM=Active Range of Motion; BBS=Berg Balance Scale; CMSA= Chedoke-McMaster Stroke Assessment; CP=Cerebral Palsy; DF=dorsiflexors; FRT=Functional Reaching Test; FSE= First Swing Excursion for Pendulum test; GMFM= Gross Motor Function Measurement; INAS=Inventory of Non-Ataxia Symptoms; MAS= Modified Ashworth Scale; MSIS-29 = Multiple Sclerosis Impact Scale; MSSS-88= Multiple Sclerosis Spasticity Scale-88; OSC= Oscillation for Pendulum test; PF=plantarflexors; PROM=Passive Range of Motion; RI= Relaxation Index of Wartenburg Pendulum test; SARA= Scale for the Assessment and Rating of Ataxia; SCA= Spinocerebellar Ataxia; SCAFI=Spinocerebellar Ataxia Functional Index; SCI-Spinal Cord Injury; SES=Standard Effect Size; SIS= Stroke Impact Scale; SLR =Straight Leg Raising; SOT = Sensory Organization Test; TUG= Timed Up and Go test; VAS= Ankle Spasticity Visual Analogue Scale.

[b] Comparison 1: compared with no WBV under the same exercise condition; Comparison 2: compared with other forms of physical activity/intervention

[c]↑ =significant increase in the quantity;↓= significant decrease in the quantity; (-) = no significant change.

[d] The SES values of this study were calculated based on the mean and standard deviation of the change scores of WBV and control group.

[e] The SES values of this study were calculated based on the pretest and posttest mean scores and standard deviation of pretest score of WBV or control group.

[f] The SES was not reported because MAS is ordinal data.

[g]The standard effect size was not reported as the exact mean and standard deviation values were not presented.

[h] The SES values of this study were calculated based on the mean and standard deviation of the posttest scores of WBV and control group.

[i] The SES values shown here were derived from the between-group comparison of change scores (difference from baseline scores) for the following time points (post-test 1, post-test 2 and post-test 3).

[j]An significant overall time effect was reported. Separate analysis for each of the WBV and control groups was not done. The SES values shown here were derived from the data from the WBV group.

2.4.6 Effects of multiple sessions of whole-body vibration on spasticity

Comparison 1. Five studies (one multiple sclerosis trial (Schyns*, et al.*, 2009), one cerebral palsy trial (Cheng*, et al.*, 2015), two stroke trials (Brogardh*, et al.*, 2012, Pang*, et al.*, 2013b), one spinocerebellar ataxia trial) (Kaut*, et al.*, 2014) involved a control group in which the participants underwent the same exercise as whole-body vibration group but without vibration stimulus or sham vibration (Table 4, supplementary material). The results were mixed. In between-group analysis, Schyns et al. (multiple sclerosis trial) reported significantly more reduction of muscle spasm (muscle spasm item of Multiple Sclerosis Spasticity Scale-88) after 4 weeks of treatment, but no significant results on Modified Ashworth Scale score were found(Schyns*, et al.*, 2009). In patients with cerebral palsy, Cheng et al. found significantly more reduction of quadriceps spasticity in the whole-body vibration group than the control group (medium to large effect sizes) as measured by the Modified Ashworth Scale and Pendulum test after a 4-week intervention period, and the effects lasted up to 3 days after the termination of the intervention (Cheng*, et al.*, 2015). In the two stroke trials, only Pang et al. reported some favorable effects on spasticity (Pang*, et al.*, 2013b). The knee Modified Ashworth Scale score in the affected leg was significantly reduced in whole-body vibration group but not in the control group (Pang*, et al.*, 2013b). However, no between-group analysis was done (Pang*, et al.*, 2013b). Another stroke trial by Brogardh et al. reported no treatment effect of whole-body vibration on spasticity (Brogardh*, et al.*, 2012). Finally, no significant effect on spasticity

was detected after whole-body vibration in patients with spinocerebellar ataxia (Kaut*, et al.*, 2014).

Among those studies that reported favorable effects of whole-body vibration on reducing spasticity (Cheng*, et al.*, 2015, Pang*, et al.*, 2013b, Schyns*, et al.*, 2009), only Cheng et al. found the changes in six-minute-walk distance and timed up-and-go performance were significantly correlated with the improvement of the relax index derived from the Pendulum test (Cheng*, et al.*, 2015). Otherwise, no other study showed significant between-group differences in mobility functions after the treatment period (Pang*, et al.*, 2013b, Schyns*, et al.*, 2009). In contrast, Kaut et al., which produced negative results on muscle tone, reported significantly more improvement in postural and gait stability in the whole-body vibration group than controls (Kaut*, et al.*, 2014).

Comparison 2. Three studies (two cerebral palsy trials (Ahlborg*, et al.*, 2006, Ibrahim*, et al.*, 2014), one stroke trial(Tankisheva*, et al.*, 2014)) compared the effect of multiple sessions of whole-body vibration treatment with other treatment modalities. Ahlborg et al. found significant reduction in Modified Ashworth Scale score of knee extensors on the stronger side after whole-body vibration treatment among children with cerebral palsy, but comparison with the resistance training group was not performed (Ahlborg*, et al.*, 2006). In another cerebral palsy trial, Ibrahim et al. found a significant reduction of Modified Ashworth Scale score on the weaker side after whole-body vibration (Ibrahim*, et al.*, 2014). However, as revealed by between-group analysis, whole-body vibration did not lead to better outcomes in lower limb Modified Ashworth Scale scores than conventional physical therapy (Ibrahim*, et al.*, 2014). Improvement of Gross Motor Function

Measurement in domain D (standing) and E (walking, running, and jumping) was found in the whole-body vibration group but not the control group (Ahlborg*, et al.*, 2006, Ibrahim*, et al.*, 2014). However, no between-group analysis of these outcomes was presented. Finally, Tankisheva et al. did not find any improvement of Ashworth Scale score in both the whole-body vibration group and control group (habitual activity) after 6 weeks of whole-body vibration among people with stroke (Tankisheva*, et al.*, 2014).

2.4.7 Side effects

A total of 150 people with central nervous system disorders were exposed to whole-body vibration in the nine selected studies. Eight studies actually reported whether there were any adverse events or not (Ahlborg*, et al.*, 2006, Brogardh*, et al.*, 2012, Chan*, et al.*, 2012, Cheng*, et al.*, 2015, Ibrahim*, et al.*, 2014, Kaut*, et al.*, 2014, Pang*, et al.*, 2013b, Schyns*, et al.*, 2009, Tankisheva*, et al.*, 2014). Among these, three studies explicitly stated that no adverse events occurred (Ibrahim*, et al.*, 2014, Kaut*, et al.*, 2014, Schyns*, et al.*, 2009). Brogardh et al. reported that 15 out of 31 participants had transient mild muscle soreness or muscle fatigue, but did not specify the number of these cases in each of the whole-body vibration and sham treatment groups (Brogardh*, et al.*, 2012). Tankisheva et al. reported that "some of the participants described some itching in the legs after the first vibration sessions but this phenomenon resolved spontaneously" (Tankisheva*, et al.*, 2014). Isolated cases of dizziness (n=3) (Pang*, et al.*, 2013b), muscle stiffness (n=2) (Ahlborg*, et al.*, 2006, Cheng*, et al.*, 2015), back muscle soreness (n=1) (Cheng*, et al.*, 2015) and lower limb soreness (n=2) (Pang*, et al.*, 2013b) were also

reported in other studies. It is not clear whether any adverse effect occurred in Chan et al (Chan*, et al.*, 2012).

2.5 Discussion

This is the first systematic review to examine the effects of whole-body vibration on spasticity among people with central nervous system disorders. The results showed that whole-body vibration may be useful in reducing leg muscle spasticity in cerebral palsy, but the effect is uncertain in multiple sclerosis, stroke and spinocerebellar ataxia. No clear association was found between the reduction in muscle spasticity and changes in functional measures.

2.5.1 Effect of whole-body vibration on muscle spasticity

The evidence related to the acute effect on spasticity of people with chronic stroke was provided by one level 2b study only (Chan*, et al.*, 2012). Although favorable results were shown with Modified Ashworth Scale and Visual Analogue Scale, they were not accompanied by any significant between-group differences in results generated from neurological assessment (H-reflex and tendon reflex testing) (Chan*, et al.*, 2012). It should be noted that Visual Analogue Scale is a subjective measure of perceived level of spasticity. The change in Visual Analogue Scale may be explained by placebo effect of the whole-body vibration, as sham vibrations were not used (Liao*, et al.*, 2014). The Modified Ashworth Scale, on the other hand, is a single-item assessment tool that is ordinal in nature. However, parametric rather than non-parametric statistics were used by the authors to analyze the data, which leads to questions about the validity of the results (Chan*, et al.*, 2012). Therefore, no solid conclusion can be made on the acute effect of whole-body

vibration alone on spasticity in people with stroke. It was suggested in quasi-experimental studies that whole-body vibration would significantly inhibit H-reflex in healthy populations (Ahmadi, *et al.*, 2015, Armstrong, *et al.*, 2008, Games and Sefton, 2013, Kipp, *et al.*, 2011) and people with spinal cord injury (Sayenko, *et al.*, 2010). The vibration intensity used in the these studies was higher (frequency in 20~40 Hz and peak-to-peak amplitude 1~4mm) than that adopted in Chan et al (Chan, *et al.*, 2012). Therefore, apart from difference in subject characteristics, the difference in whole-body vibration intensity may also explain the discordance of the results related to the acute effect on H-reflex.

Is there any evidence that whole-body vibration can effectively reduce spasticity after training of longer durations (e.g., in the order of weeks)? All three cerebral palsy trials (Ahlborg, *et al.*, 2006, Cheng, *et al.*, 2015, Ibrahim, *et al.*, 2014) reported results in favor of whole-body vibration training but they provided level 2b evidence only. Cheng et al. demonstrated that adding whole-body vibration to exercise induced a significant treatment effect on reducing quadriceps spasticity than exercise alone without whole-body vibration (Cheng, *et al.*, 2015). The other two cerebral palsy trials also found significant reduction in quadriceps spasticity within the whole-body vibration group, but the comparison with the control group (resistance training, conventional physical therapy) was either not done or not statistically significant (Ahlborg, *et al.*, 2006, Ibrahim, *et al.*, 2014). Given the study design, it was impossible to delineate the effects of the vibratory stimuli alone in these two studies (Ahlborg, *et al.*, 2006, Ibrahim, *et al.*, 2014). In addition, even if the imposed vibrations, rather than the exercises done while receiving vibrations, are the main cause of the observed reduction in spasticity, the findings of these two studies provided no evidence that whole-body vibration

training is better than other treatments in reducing spasticity in individuals with cerebral palsy. Taken together, while all three cerebral palsy trials reported some positive effects on whole-body vibration training on reducing spasticity with medium to large effect sizes (Ahlborg, *et al.*, 2006, Cheng, *et al.*, 2015, Ibrahim, *et al.*, 2014), the overall evidence is not strong, considering the limitations of the study design of the latter two studies (Ahlborg, *et al.*, 2006, Ibrahim, *et al.*, 2014).

The evidence found in the stroke population is inconsistent. Of the three stroke trials, only Pang et al. (level 1b) found significant reduction in spasticity within the whole-body vibration group (Pang, *et al.*, 2013b). Upon examining the difference in subject characteristics and treatment protocols among these studies, no specific trends were identified that may explain the difference in results, except that the intervention period was longer in Pang et al. (Pang, *et al.*, 2013b) (8 weeks) than the other two studies (6 weeks).[29,32] Overall, there is no strong evidence that the added whole-body vibration can confer additional effects on reducing spasticity post-stroke.

Similar to stroke, there is not sufficient evidence to support or refute the use of whole-body vibration in reducing spasticity in individuals with multiple sclerosis (one level 2b study)(Schyns, *et al.*, 2009) and spinocerebellar ataxia (one level 2b study) (Kaut, *et al.*, 2014), due to the limited number of studies.

When considering the overall evidence related to the effects of whole-body vibration on muscle spasticity, only one cerebral palsy trial (Cheng, *et al.*, 2015), one stroke trial (Chan, *et al.*, 2012) and one multiple sclerosis trial (Schyns, *et al.*, 2009) reported some results that clearly point to beneficial effects of the imposed vibratory stimulation alone. The protocols used in these three studies were very

different (Chan*, et al.*, 2012, Cheng*, et al.*, 2015, Schyns*, et al.*, 2009). In the cerebral palsy (Cheng*, et al.*, 2015) and multiple sclerosis trials (Kaut*, et al.*, 2014), the vibration intensities used were greater (2.3g–20.1g Vs 1.6–2.3g), but the duration of the vibration exposure per session (3–10 minutes Vs 15 minutes) was shorter when compared with the stroke trial (Chan*, et al.*, 2012). Due to the small number of studies that reported significant results, and the vast differences in the intervention protocols, we could not determine the specific parameters that may account for the positive treatment outcomes.

2.5.2 Relationship to functional level

There is no consistent evidence to show that improvement in spasticity is correlated with improvement in functional ability of the study participants. In Chan et al. (stroke trial), although the improvement in spasticity was accompanied by improvement in balance and mobility function, it is difficult to determine whether it was related to modification of post-stroke spasticity after whole-body vibration, as correlation analysis was not performed (Chan*, et al.*, 2012). Only Cheng et al. specifically reported that the change in timed up-and-go score was significantly associated with the change in the relax index (Pendulum test) in children with cerebral palsy(Cheng*, et al.*, 2015). Overall, the evidence pertaining to the relationship between changes in muscle tone and those in functional ability after whole-body vibration treatment is weak.

2.5.3 Quality of reviewed articles

Only one of the nine reviewed studies provided level 1b evidence (Pang*, et al.*, 2013b). Four of nine studies had very small sample size (<20) (Ahlborg*, et al.*,

2006, Cheng, *et al.*, 2015, Schyns, *et al.*, 2009, Tankisheva, *et al.*, 2014), which lowered the statistical power and limited the generalizability of the results to the wider patient populations.

With few exceptions, the protocols of whole-body vibration were not described in adequate details, particularly the use of footwear and supportive device. Only one trial has calibrated and validated the whole-body vibration dosage delivered to the patients (i.e. amplitude and frequency) (Pang, *et al.*, 2013b). However, a recent study has shown that for most whole-body vibration platforms, the actual frequency and amplitude of vibrations delivered are different from the intended values (Alizadeh-Meghrazi, *et al.*, 2014). The body weight of subjects would often influence the vibration intensity generation (Alizadeh-Meghrazi, *et al.*, 2014). Future studies should thoroughly describe the protocols in detail in accordance with the guidelines set by the International Society of Musculoskeletal and Neuronal Interactions and validate the vibration signals of platform before conducting the study (Rauch, *et al.*, 2010).

Finally, the Modified Ashworth Scale was extensively used in the reviewed studies, despite its low reliability, validity, and responsiveness (Fleuren, *et al.*, 2010, Hobart, *et al.*, 2007). Future research should use measurement tools with good psychometric properties to examine the effects of whole-body vibration on muscle spasticity.

2.5.4 Limitations at the review level

Some potentially relevant studies may have been missed because reports not written in English were excluded. Those articles that did not use appropriate words in the titles or abstracts may also have been missed.

We used spasticity only as the outcome of interest. Other outcome measures were considered only if spasticity was measured in the same studies, so as to examine whether changes in spasticity were related to changes in functional performance. This review, therefore, was not designed to assess whether whole-body vibration has therapeutic value on improving outcomes other than spasticity (e.g., gait, balance, quality of life, etc.).

As the intervention protocols used differed on more than one whole-body vibration parameter (whole-body vibration type, frequency, amplitude, treatment duration and frequency), it is difficult to make meaningful comparisons across studies and delineate the independent effects of different whole-body vibration parameters. Meta-analysis was not possible due to the heterogeneity of the studies.

In conclusion, based on extensive review of the literature, there is some evidence that whole-body vibration may be useful in reducing leg muscle spasticity in patients with cerebral palsy but the evidence is of level 2b only. More high quality trials should be conducted to verify the results. There is insufficient evidence to support or refute the notion that whole-body vibration alone confers any significant effects on spasticity in stroke, multiple sclerosis and spinocerebellar ataxia or that whole-body vibration is better than other alternative physical therapy or exercise training in modifying spasticity in these patient populations. There is little evidence that whole-body vibration induced change in

spasticity is related to change in functional performance among people with central nervous system disorders.

2.6 Clinical messages

- Whole-body vibration may be useful in reducing leg muscle spasticity in cerebral palsy.
- The use of whole-body vibration on reducing muscle spasticity in multiple sclerosis was supported by one level 2b study only.
- There is insufficient evidence to support or refute the use of whole-body vibration on reducing muscle spasticity in stroke or spinocerebellar ataxia.

2.7 Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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3 Chapter 3: Morphological and passive mechanical properties of the medial gastrocnemius muscle and their associations with functional mobility in individuals with chronic stroke

3.1 Abstract

Background: The musculoskeletal system may undergo considerable structural changes post-stroke, which may affect functional performance.

Objectives: To investigate the morphological and passive mechanical properties of the medial gastrocnemius (MG) muscle among stroke survivors, and their association with functional mobility.

Methods: This was a cross-sectional study. Fifteen ambulatory chronic stroke survivors and fourteen age-matched healthy individuals participated in the study. Supersonic shearwave elastography was used to measure the shear modulus of the MG during continuous passive motion from ankle plantarflexion to dorsiflexion. Relationships between the shear modulus and joint angle were modeled. The elasticity-angle model outcomes included (1) slack angle: the joint angle beyond which the muscle begins to develop passive elastic force upon further stretch, (2) slack elasticity: the shear modulus value measured at the slack angle. Muscle architecture was also assessed using B-mode ultrasound. The association between the elasticity-angle model or muscle architecture parameters and performance of the timed up-to-go test (TUG) was examined.

Results: Paretic MG muscles had significantly lower degrees of pennation ($p=0.019$) and higher echogenicity ($p=0.003$) than non-paretic counterparts. A positive association was observed between the echogenicity of paretic MG muscles and TUG duration ($r=0.765$, $p<0.001$). No significant differences in slack angle (paretic: -16.2°±6.13°, non-paretic: -16.9°±6.8°), slack elasticity (paretic: 4.4 ±1.9 kPa, non-paretic: 4.5 ±1.2 kPa) and other architectural parameters were identified between the two sides.

Conclusion: Passive mechanical properties of the MG were similar between the two sides in individuals with chronic stroke. Altered morphological properties were identified in paretic MG muscles, which may contribute to poor functional mobility.

3.2 Background

Stroke is one of the leading causes of long-term disability in adults (Crichton*, et al.*, 2016). Possible sequela associated with upper motor neuron lesions following stroke include muscle weakness, fatigability and spasticity, all of which contribute to impaired motor function (Dietz and Sinkjaer, 2007, Katz and Rymer, 1989). Evidence suggests that both alterations in musculoskeletal structure and composition occur post-stroke (Hafer-Macko*, et al.*, 2008, Lieber*, et al.*, 2004). Muscle biopsies isolating single muscle cells obtained from patients with spasticity have shown decreased resting sarcomere length and increased stiffness compared with normal muscle cells (Friden and Lieber, 2003). Conversely, fiber bundles from spastic muscle were found to be less stiff than normal muscle (Lieber*, et al.*, 2003). While findings from biomechanical studies using dynamometer coupling with surface electromyography or B-mode

ultrasonography suggest that passive stiffness of plantarflexors' muscle fascicles is higher for the paretic side than the non-paretic side in stroke patients with spasticity (Gao, *et al.*, 2009, Gao, *et al.*, 2011, Sinkjaer and Magnussen, 1994). However, these results may be affected in large part by other joint structures such as capsules, ligaments and tendons (Gao, *et al.*, 2009). Additionally, in-vivo studies suggest passive muscle stiffness may also be influenced by the contractility of intramuscular connective tissue and the extracellular matrix (Gillies and Lieber, 2011, Schleip, *et al.*, 2006), while biopsy and kinetic studies provide little information in this regard (Schleip, *et al.*, 2006).

Shear wave elastography has been used to quantify muscle material properties in vivo (Brandenburg, *et al.*, 2014). Theoretically, the shear wave speed is related to the shear modulus, a measurement of stiffness. The higher the shear wave propagation speed, the more severe the stiffness (Brandenburg, *et al.*, 2014). The Supersonic Shear Imaging (SSI) technique employs a combination of acoustic radiation force, generated by an ultrasonic beam to introduce shear waves into soft tissues, with an ultrafast framerate imaging capability for capturing real-time propagation of shear waves within a region of interest (ROI) (Bercoff, *et al.*, 2004). The ROI may encompass both muscle fibers and intramuscular tissues (Gennisson, *et al.*, 2010).

Using the SSI technique, elasticity-angle curves can be developed to quantify the passive mechanical properties of skeletal muscle (Hirata, *et al.*, 2015, Hug, *et al.*, 2013b, Koo, *et al.*, 2014). Three meaningful physiological parameters are extracted from these curves: (1) slack angle, the joint angle beyond which the muscle begins to develop passive force; (2) slack elasticity, the muscle elasticity

measured when muscle is at its slack length; and (3) increasing (slope) rate, the rate of elastic build-up as muscle is being stretched(Koo, *et al.*, 2014). Feasibility of the elasticity-angle curve has been previously demonstrated among healthy young populations when investigating the medial gastrocnemius (MG) muscle (Hirata, *et al.*, 2015, Hug, *et al.*, 2013b, Maisetti, *et al.*, 2012). However, no quantitative elasticity-curve measures have been reported among stroke survivors.

The primary objective of this study was to investigate the elasticity-angle curves of the MG muscle by comparing these parameters between the paretic and non-paretic limbs of stroke survivors, and the dominant leg of age-matched control subjects. A secondary objective was to assess muscle architecture (e.g., muscle thickness, pennation angle of muscle fascicles, fascicle length) and echogenicity using B-mode ultrasound. Muscle architecture was hypothesized to be associated with strength and function (Gray, *et al.*, 2012, Lieber, 2002, Strasser, *et al.*, 2013), while echogenicity is demonstrative of tissue composition (Berenpas, *et al.*, 2017). A tertiary objective was to examine the association of functional mobility with biomechanical or architectural characteristics of the MG muscle. Thus, the present study attempts to present a comprehensive picture of morphological and passive mechanical characteristics of muscle post-stroke, and their association with functional mobility.

In considering the adaptation of the mechanical properties lower limb muscles would occur following stroke (Hoang, *et al.*, 2009, Jakubowski, *et al.*, 2017), we hypothesized that there would be no significant difference in passive elastic muscle properties between the paretic and non-paretic side among ambulatory chronic stroke survivors, even though the muscle architecture may

potentially differ between the two sides. We also hypothesized the likelihood of a significant association between measures of functional mobility and both passive mechanical and architectural muscle properties.

3.3 Methods

3.3.1 Participants

Convenience sampling was used to recruit individuals with chronic stroke and healthy age-matched controls from the local community. The inclusion criteria for the control group were: age ≥55; medically stable; passive ankle range of motion >15°; ability to walk independently for at least 1 minute; community-dwelling. Exclusion criteria were: neurological conditions; ankle pathology; recent surgery or metal implants in the lower extremities and lumbar spine. In addition to the criteria described above, stroke group participants also met the following inclusion criteria: a diagnosis of hemiparetic stroke > 6 months; and exclusion criteria: brainstem or cerebellar stroke; botulinum toxin therapy within the previous 6 months. The study was approved by the Human Subjects Ethics Sub-committee of the University (Application Number: HSEARS20150411001). All procedures have been performed in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from participants before data collection.

3.3.2 Experimental setup

This was a cross-sectional study with repeated measures. The MG of each participant was measured using ultrasound elastography conducted by the same examiner and all procedures completed at the university rehabilitation laboratory

with the same environmental setting (e.g., temperate 25°C). Surface electromyography (EMG) was used to monitor muscle activation and ensure relaxation of the MG during elastography recording trials. The EMG electrode (Biometrics SX230, Gwent, UK) was placed over the muscle belly near the ultrasound transducer. Signals were pre-amplified at 1000 with a band-pass filter of 20-460Hz at the source. MG ultrasound measures were taken during isokinetic dynamometer-assisted passive ankle joint movement. For individuals with stroke, the paretic and non-paretic sides were measured in randomized order. For the control group, only the dominant side was measured. Leg dominance was determined by a ball kicking task (Hoffman*, et al.*, 1998). Demographic information was obtained via interviews, and clinical measures of lower limb spasticity and function were conducted by a physical therapist after the ultrasound measurement.

3.3.3 Measurements of the ankle joint angle

Neutral ankle joint position was defined using a MyoMotion 3D motion analysis system (MyoMotion system, Noraxon Inc., Arizona, USA). MyoMotion inertial sensors were placed on the upper foot and mid-shank of the tibia. Participants were seated in a chair with the soles of their feet contacting the ground and toes pointing forward. The ankle joint was carefully adjusted to neutral position and confirmed with a goniometer (i.e., talocrural joint and subtalar joint angle degree was 0°, respectively). Once the neutral ankle position was set, MyoMotion system was calibrated accordingly. Participants were then asked to assume a prone lying position on the plinth of the Cybex isokinetic dynamometer system (Lumex Inc., New York, USA). The foot was secured to the footplate, and

the ankle joint was maintained in alignment with the dynamometer axis of dorsi/plantarflexion. The knee joint was fully extended (i.e., 180°) and firmly strapped to the plinth to avoid rotational movement. Once the participant was properly positioned, the ankle joint reading of the dynamometer was set to zero when the joint reached a neutral position as defined by the Myomotion system (Koo, *et al.*, 2014). All following joint angle readings were based upon readings from the dynamometer (Koo, *et al.*, 2014).

3.3.4 Measurement of ultrasound shear wave elastography

An Aixplorer ultrasound scanner (Supersonic Imagine, Aix en Provence, France) coupled with a linear transducer array (4-15MHz, SuperLinear 15-4, Vermon, Tours, France) was set to a musculoskeletal preset for measuring the shear modulus of the MG. The transducer was positioned perpendicularly along the longitudinal axis of the proximal one-third of the leg (Lacourpaille, *et al.*, 2012) and held by an artificial arm with a gap between the probe interface and the skin filled with adequate gel (Appendix 1) (Koo, *et al.*, 2014). Three elastography images were captured with the ankle in neutral or 10° of dorsiflexion. The MG was then recorded using elastography during continuous passive motion (CMP) from plantarflexion to dorsiflexion at a rate of 1°/s (Hirata, *et al.*, 2015, Hug, *et al.*, 2013b). The CPM movement range was set between 45° of plantarflexion and 80% of individual maximal dorsiflexion (mean=11.6°) (Hug, *et al.*, 2013b). During passive stretching, participants were asked to relax and avoid resisting the footplate movement. EMG signals were monitored for muscle activation during elastography recordings (Lee, *et al.*, 2015). Images were discarded and recaptured in the event of muscular activation (Hug, *et al.*, 2013b). Participants became

familiarized with the experimental procedures within the first 2 CPM cycles. Three elastography videos (ROI: 12mm*12mm) were recorded during three cycles (i.e., from the 3rd cycle) (Hirata, *et al.*, 2015). A synchronizer with tailor-made circuits was used to synchronize elastography recordings with the commencement of dorsiflexion.

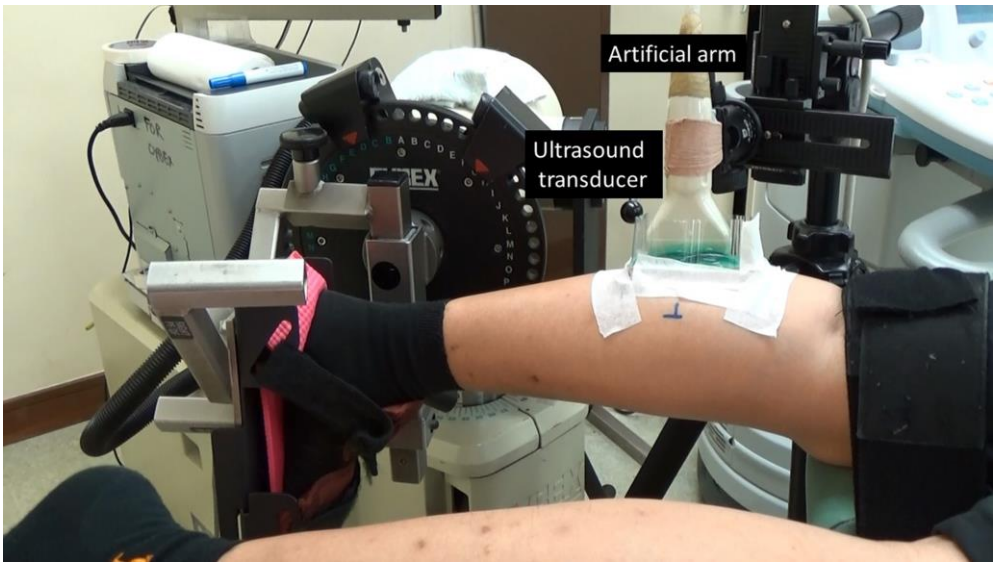

Figure 3-1 Position of the ultrasound transducer.
The ultrasound transducer was positioned perpendicularly along the longitudinal axis of proximal one-third of the leg. The transducer was steadily held by an artificial arm with a small gap between the skin and transducer filled with adequate gel. Our subject wore thin socks during assessment to (1) keep warm and (2) prevent any uncomfortable pressure to secure relax condition. When securing the foot to the footplate, we exposed the ankle join line of the subject to make sure the proper position of the ankle.

3.3.5 Data processing

All data processing was performed using a custom-written MATLAB program (2016a, MathWorks, MA, USA). Elastography videos were exported in "mp4" format from the ultrasound system (Hug, *et al.*, 2013b), and each video was sequenced (1 second per frame) in "png" image format (Hug, *et al.*, 2013b). Due to the difference in muscle size between stroke subjects, color maps were cropped to cover the maximum area within the ROI. Color maps were then converted to shear modulus values (Hug, *et al.*, 2013b). Elasticity-angle data were fitted with a

piecewise exponential model derived from the passive muscle length-tension relationship. The following elasticity-angle model has been validated by Koo et al. (Koo*, et al.*, 2014).

$$G(\theta) = G_0 \qquad \text{if } \theta < \theta_0$$

$$G(\theta) = G_0\,(e^{\alpha(\theta-\theta_0)}) \qquad \text{if } \theta > \theta_0$$

In the above equations, $G(\theta)$, slack elasticity, is the elasticity of the MG at joint angle θ. θ_0, slack angle, is defined as the angle below which the MG becomes slack. G_0 represents the slack elasticity, the elasticity of the MG when it becomes slack; and α is the rate of elasticity build-up during stretch (Koo*, et al.*, 2014). The Levenberg-Marquardt algorithm was used to optimize these three parameters (i.e., θ_0, G_0 and α) by minimizing the difference between the measured and modeled values (Figure.1) (Koo*, et al.*, 2014). The coefficient of determination (R^2) of each fit was then calculated. For each measurement session, the median values of all three parameters were used for statistical analysis.

Using B-Mode ultrasound, muscle thickness, fascicle length, pennation angle, subcutaneous fat thickness and echogenicity were measured with the ankle in neutral position (Figure 2). In quantifying echogenicity, gain and focal zone were kept the same during image acquisition (Berenpas*, et al.*, 2017, Lee*, et al.*, 2015). Images were processed off-line using the customized program in MATLAB. Pixels within the ROI were measured according to a greyscale of 256 degrees, from 0 (i.e., black) to 255 (i.e., white), with brighter pixels corresponding to higher

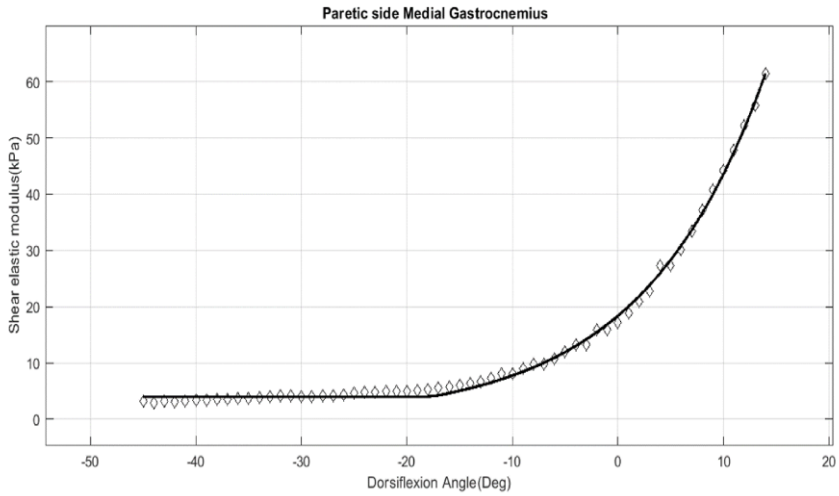

Figure 3-2 Passive elasticity-angle curve
Illustration of the passive elasticity-angle curve of the paretic MG from one participant. The dot is plotted based according to the measured data, and the line is the fitted curve from the piecewise exponential model. Slack angle (θ_0), is defined as the angle below which the MG becomes slack; slack elasticity (G_0), is the elasticity of the MG when it becomes slack; and α is related to the rate of elasticity build-up as the MG is being stretched. For this participant, $\theta_0 = -17.7°, G_0 = 2.7kPa, \alpha = 0.088$.

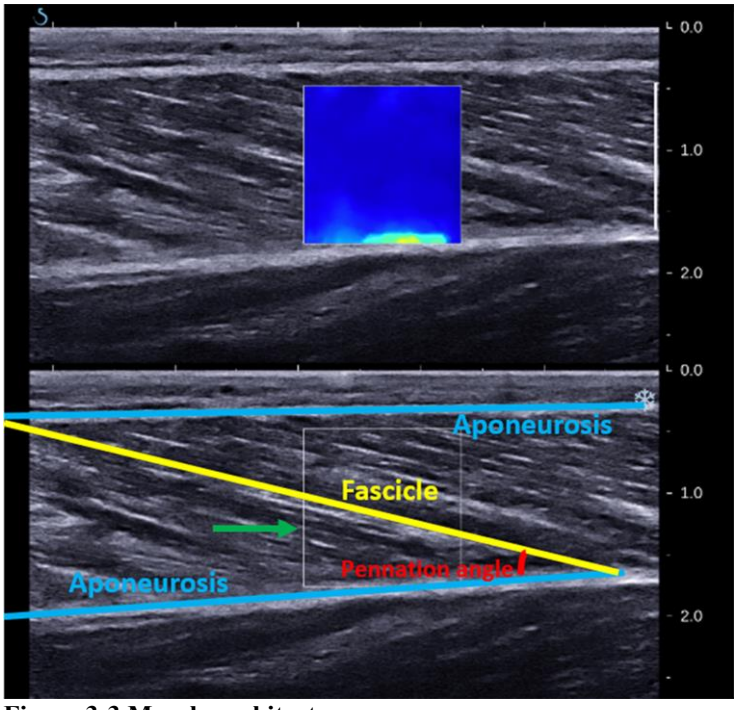

Figure 3-3 Muscle architecture measures.
Longitudinal image of the medial gastrocnemius muscle when ankle angle was in neutral while knee was fully extended. The upper image with color box is the shear wave elastography and the lower one is the B-model images. The skin is on the top of the image. The subcutaneous adipose tissue, muscle thickness, muscle fascicle length and pennation angle were measured in the B-model image. The echogenicity was measured within the box label in green arrow.

echogenicity (Lee*, et al.*, 2015). Subcutaneous thickness was measured from the skin to the lower boundary of the fat tissue. Muscle thickness was determined as the distance between the superficial and deep aponeurosis of the MG muscle (Jakubowski*, et al.*, 2017). Fascicle length was calculated by extrapolating the intersection with both aponeuroses and calculating the distance between their respective intersection points (Jakubowski*, et al.*, 2017). The pennation angle was defined as the angle between the fascicle and the deep aponeurosis (Gao*, et al.*, 2009). Fascicle length and pennation angle were measured for three fibers and the average was used for analysis (Strasser*, et al.*, 2013).

3.3.6 Clinical assessment

Lower limb motor recovery was assessed using the Fugl-Meyer Assessment (FMA). Higher scores denote less impaired motor function (Sullivan*, et al.*, 2011). Mobility was assessed using the timed up-and-go test (TUG) (Hiengkaew*, et al.*, 2012). Spasticity of ankle plantar flexors, knee flexors, and extensors were rated using the Modified Ashworth (MAS) (Bohannon and Smith, 1987) and Modified Tardieu Scales (MTS) (Singh*, et al.*, 2011), with higher scores indicating more severe spasticity (Bohannon and Smith, 1987, Singh*, et al.*, 2011).

3.3.7 Statistical methods

All statistical analyses were conducted using SPSS 20.0 (IBM Corp, New York, USA) at an α level of 0.05. Test-rest reliability was calculated using the intraclass correlation coefficient ($ICC_{3,1}$) (Koo*, et al.*, 2014). For stroke subjects, paired t-tests were used to compare the parameters of the elasticity-angle model (i.e., slack elasticity, slack angle, slope rate) and muscle architecture (i.e., muscle

fascicle length, pennation angle, muscle thickness, echogenicity) between paretic and non-paretic sides. Independent t-tests were used to compare the parameters of the elasticity-angle model and muscle architecture between the non-paretic sides (stroke group) and the dominant sides of controls. To verify the elasticity model, the estimated elasticity values for 0° and 10° were compared with recorded elasticity parameters captured when the ankle joint was fixed at 0° and 10 using paired t-tests. Spearman's rho was used to examine the relationship between spasticity (i.e., MAS score or MTS score) and elasticity-angle model parameters for the paretic MG. Pearson's correlation was used to evaluate the association between the parameters of elasticity-angle model / muscle architecture and functional mobility (TUG).

3.4 Results

Fourteen individuals with chronic stroke and fifteen healthy older adults (controls) participated in the study. There was no significant difference in age ($p=0.096$), women: men ratio ($p=0.272$) or body mass index ($p=0.102$) between the two groups. Demographic results are summarized in Table 4-1. For stroke subjects, the interquartile range of the Fugl-Meyer scale and Modified Ashworth scale was 22-28 and 1-2. Stroke subjects had significantly longer TUG time compared to controls ($p<0.05$).

The elasticity-angle relationship fitted the piecewise exponential model well. The coefficient of determination ranged from 0.912-0.998. Test-retest reliability for all parameters of the elasticity-angle model was moderate (Table 3-2). No significant difference was found between the measured and computed MG elasticity at 0° and 10° dorsiflexion (Table 3-3). There was no significant

difference in slack angle, slack elasticity, and slope rate between the paretic side and non-paretic side in the stroke group ($p>0.05$). There was also no significant difference between the non-paretic side of the stroke group and the dominant side of the controls ($p>0.05$) (Table 3-4). No significant correlations were found between parameters of elasticity-angle model and TUG.

Table 3-1 Demographic data of participants*

Variable[a]	Stroke (n=14)	Control (n=15)	p
Age, year	63.4±6.0	59.6±8.4	0.096
Sex, men/women, n	8/6	8/5	0.272
Body height, cm	163.9±9.2	160.0±9.5	0.563
Body mass index, kg/m^2	24.0±2.1	22.1±2.5	0.102
Total number of commodities, n†	1.5 (0-2.5)	0 (0-0)	0.100
Total number of medications, n†	2.5 (1-4)	0 (0-1)	0.001‡
Lower Extremity Functional Scale (full score: 80)†	60 (55-63)	80 (75-80)	<0.001‡
Using walking aid outdoor, n	7	0	
Time-up-and-go test, second	25.6 ±9.5	12.9±2.5	<0.001‡
Post-stroke duration, year	6.6±4.4	--	
Type of stroke, hemorrhagic/ischemic, n	2/12	--	
Side of paresis, left/right, n	7/7	--	
Passive range of paretic ankle dorsiflexion	11.9 (8.8)		
Fugl-Meyer Lower limb motor score (full score: 34) †	25 (22-28)	--	
Planterflexor Modified Ashworth Scale scores (range:0-4) †	1.5 (1-2)		
Planterflexor Modified Tardieu Scale scores (range:0-4)†	2. 5(1.75-3)		

* Mean±SD indicated unless specified otherwise.

Paretic MG demonstrated significantly smaller pennation angles ($p=0.019$) and higher echogenicities ($p=0.003$) compared to non-paretic sides, while no significant difference was observed in these same parameters between non-paretic sides and the dominant legs of the controls (Table 3-5). People with stroke had

Table 3-2 Test-retest reliability coefficients*

	Controls	Stroke	
		Paretic side	Non-paretic side
Slack elasticity	0.984 (0.961-0.994)	0.993 (0.983-0.998)	0.985 (0.959-0.995)
Slack angle	0.875 (0.704-0.955)	0.949 (0.876-0.982)	0.963 (0.901-0.988)
Slope rate	0.936 (0.848-0.977)	0.983 (0.959-0.994)	0.941 (0.843-0.981)

*Intraclass Correlation Coefficients$_{(3,1)}$(95% Confidence Interval)

Table 3-3 Measured and estimated elasticity-angle curve parameters *, †, ‡

	Controls			Stroke					
				paretic side			non-paretic side		
	Measured	Estimated	p	Measured	Estimated	p	Measured	Estimated	p
G_0	14.7±4.6	13.6±5.2	0.056	15.2±7.0	15.8±7.0	0.723	13.9±8.5	14.6±9.0	0.348
G_{10}	30.4±14.7	27.0±15.8	0.072	32.0±15.7	32.1±15.6	0.690	31.8±17.7	31.8±18.3	0.390

*Mean ± Standard deviation
†Paired-t sample test was conducted to compare the measured values with the estimated values.
‡G_0=ankle was in neural position; G_{10} =ankle was in dorsiflexion 10°.

Table 3-4 Elasticity-curve parameters*

	Controls	Stroke		p	
		paretic side	non-paretic side	paretic vs. non-paretic	paretic vs. control
Slack elasticity(kPa)	4.2±1.4	4.4±1.9	4.5±1.2	0.385	0.103
Slack angle (°)	-17.0±5.0	-16.2±6.1	-16.9±6.8	0.367	0.801
Slope rate	0.07±0.02	0.07±0.02	0.07±0.01	0.212	0.117

*Mean ± Standard deviation

Table 3-5 Muscle Architecture and subcutaneous fat thickness of medial gastrocnemius*

	Controls	Stroke: paretic side	Stroke: non-paretic side	P-values (Comparison between controls and non-paretic side)†	P-values (Comparison between paretic and non-paretic side)‡
Subcutaneous fat thickness (cm)	0.4±0.2	0.6±0.2	0.6±0.2	0.031§	0.999
Muscle thickness (cm)	1.6±0.3	1.5±0.3	1.6±0.2	0.568	0.255
Pennation angle (°)	14.9±2.5	13.6±2.9	15.9±2.0	0.209	0.019§
Muscle fascicle length (cm)	6.2±0.8	6.6±1.9	7.1±2.2	NA‖	0.216
Echogenicity	67.2±11.9	80.5±13.6	63.4±17.1	0.510	0.003§

* Mean ± Standard deviation
†Independent t-test was conducted to compare between controls and non-paretic side (stroke group).
‡ Paired-t sample test was conducted to compare between the paretic and non-paretic side within the stroke group.
§ Statistically significant difference. $P<0.05$.
‖Inter-personal comparison was not conducted as the muscle fascicle length was not normalized with the length of the leg

significant thicker subcutaneous fat (p=0.031), while no significant difference was found between the paretic and non-paretic side. The echogenicity of paretic MG was significantly associated with the duration of TUG only (r=0.765, p<0.001). No significant association was observed between plantarflexor MAS or MTS scores and parameters of the elasticity-angle model in the paretic MG.

3.5 Discussion

To our knowledge, this is the first study using shear-wave elastography to investigate the elasticity-angle curve for slack angle and slack elasticity of MG among stroke survivors. Both the passive mechanical and morphological properties of the muscle were studied. Their association with functional mobility were also examined.

Our study showed that shear wave elastography is reliable in evaluating passive muscle stiffness post-stroke. Moreover, the elasticity-angle curve model modified by Koo et al.(Koo*, et al.*, 2014) is feasibly assessed among stroke survivors, which is further supported by (1) the goodness of fit ranging from 0.916 to 0.967 for all measures; and (2) the similarity between estimated values and shear modulus values of the MG measured at 0° and 10° dorsiflexion. The computational methods employed in this study potentially offer greater measurement consistency compared to visual determination alone (Hirata*, et al.*, 2015, Hug*, et al.*, 2013a, Maisetti*, et al.*, 2012). The calibration and joint angle control procedures and the use of a transducer stabilization arm may have also contributed to the high reliability achieved in this study (Koo*, et al.*, 2014).

Our findings demonstrated no significant difference in the passive mechanical muscle properties between the paretic and non-paretic sides, nor any

significant difference between the stroke subjects and healthy controls. In particular, the slack angle of the MG was similar among both legs for stroke subjects [mean(SD): -18.2° (3.2°)] and controls [mean(SD): -18.2° (5.2°)] (Table 3). These results were comparable to studies using similar methods to detect MG slack angles in the general population, which were estimated at 20° of plantarflexion (Hirata, *et al.*, 2015, Hug, *et al.*, 2013a, Maisetti, *et al.*, 2012).

Previous studies show that adaptation of passive mechanical properties may occur in lower limb muscles of ambulatory individuals with chronic stroke (Freire, *et al.*, 2017, Galiana, *et al.*, 2005, Jakubowski, *et al.*, 2017, Kwah, *et al.*, 2012). Hoang et al. also reported that there was no significant difference in the mean slack length and mean maximal strains of muscle fascicles, tendons or muscle-tendon units between subjects with multiple sclerosis and healthy controls (Hoang, *et al.*, 2009). Biopsy studies have shown that although spastic muscle cells are stiffer than normal cells among people with cerebral palsy, spastic muscle bundles are less stiff than normal bundles and spastic cells occupied a significantly smaller fraction of the total muscle specimen area (Lieber, *et al.*, 2003). This suggests that the property of stiffness is perhaps non-uniform along the structural continuum of muscle. As stated by Röhrle et al., muscle fibers are coupled mechanically but are cellularly independent in terms their electro-physiological excitation properties (Röhrle, *et al.*, 2012). This may also be true of stiffness. Moreover, it was suggested that with low contractile tension, the length of the muscle-tendon unit and fascicle of the MG muscle are not significantly different between ambulatory stroke survivors without contractures and control subjects (Kwah, *et al.*, 2012). Thus, the aforementioned explanation

may support the similar passive material properties of the MG observed on the paretic and non-paretic-side.

The paretic MG muscles had significantly higher echogenicity and smaller pennation angles compared with non-paretic and control MG muscles. This is perhaps indicative of muscle architecture alterations post-stroke. In addition, longer TUG duration, indicating reduced functional mobility, was associated with higher echogenicity of the paretic MG among stroke group subjects. Higher echogenicity may be suggestive of altered extracellular matrix of muscle, for example increased intramuscular fat, connective or contractile tissues (Gillies and Lieber, 2011, Reimers*, et al.*, 1993) as confirmed by previous studies using dual-energy X-ray absorptiometry and tissue biopsies (Ryan*, et al.*, 2011a, Ryan*, et al.*, 2002, Ryan*, et al.*, 2011b). Furthermore, the subcutaneous fat thickness was found larger among stroke group subjects than the controls. Increased intramuscular fat infiltration may have deleterious effects on glucose metabolism (Ryan*, et al.*, 2011a). Muscle fascicle orientation may also be affected by fat infiltration (Hafer-Macko*, et al.*, 2008, Ivey*, et al.*, 2010, Ryan*, et al.*, 2011a, Ryan*, et al.*, 2017) as was apparent by the difference in pennation angles observed in this study and others (Gao*, et al.*, 2009). Therefore, active muscle force development may be affected by the alteration of muscle architecture and extracellular matrix, leading to decreased force production capacity and diminished functional mobility (Holt*, et al.*, 2016, Lieber, 2002).

The authors acknowledge several limitations of the current study. Due to the ultrasound transducer fixation method employed, it was not possible to trace the same region of the muscle all of the time. However, as muscle tissues have

structural continuity, the tension measured at one point may be consistent along the same muscle (Koo*, et al.*, 2014). Also, the angle between the muscle fiber and the transducer plane changed. Although the probe angle has a significant effect on the shear modulus relative to the fascicle, these differences were considered negligible (Miyamoto*, et al.*, 2015). Additionally, the chronic stroke subjects recruited for this study exhibited only mild to moderate spasticity. Future investigations should involve a larger sample size consisting of subjects with a broader range of spasticity. Finally, only the relationship between passive stiffness and muscle architecture of the MG was reported. During states of high active muscle tension, stroke subjects had shorter muscle-tendon units and fascicles compared to healthy controls (Kwah*, et al.*, 2012). Therefore, the relationship between muscle stiffness and active motor control among people with chronic stroke warrants further investigation.

3.6 Declarations

3.6.1 Ethics approval and consent to participate

This study was approved by the Human Subjects Ethics Sub-committee of The Hong Kong Polytechnic University (Application Number: HSEARS20150411001). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

3.6.2 Competing interests

The authors declare that they have no competing interests.

3.6.3 Funding

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4 Chapter 4: Use of Whole Body Vibration in Individuals with Chronic Stroke: Transmissibility and Signal Purity.

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4.1 Abstract

This study examined (1) the influence of whole body vibration (WBV) frequency (20 Hz, 30 Hz, 40 Hz), amplitude (low: 0.8 mm and high: 1.5 mm) and body postures (high-squat, deep-squat, tip-toe standing) on WBV transmissibility and signal purity, and (2) the relationship between stroke motor impairment and WBV transmissibility/signal purity. Thirty-four participants with chronic stroke were tested under 18 different conditions with unique combinations of WBV frequency, amplitude, and body posture. Lower limb motor function and muscle spasticity were assessed using the Fugl-Meyer Assessment and Modified Ashworth Scale respectively. Nine tri-axial accelerometers were used to measure acceleration at the WBV platform, and the head, third lumbar vertebra, and bilateral hips, knees, and ankles. The results indicated that WBV amplitude, frequency, body postures and their interactions significantly influenced the vibration transmissibility and signal purity among people with chronic stroke. In all anatomical landmarks except the ankle, the transmissibility decreased with increased frequency, increased amplitude or increased knee flexion angle. The transmissibility was similar between the paretic and nonparetic side, except at the ankle during tip-toe standing. Less severe lower limb motor impairment was

associated with greater transmissibility at the paretic ankle, knee and hip in certain WBV conditions. Leg muscle spasticity was not significantly related to WBV transmissibility. In clinical practice, WBV amplitude, frequency, body postures need to be considered regarding the therapeutic purpose. Good contact between the feet and vibration platform and symmetrical body-weight distribution pattern should be ensured.

4.2 Introduction

Whole-body vibration training (WBV) has become increasingly popular as an exercise modality (Rittweger, 2010). It is believed that vibration stimulus can activate muscle spindles causing alpha-motoneurons excitation, thus augmenting muscle contraction (Luo*, et al.*, 2005, Ribot-Ciscar*, et al.*, 1998) and motor unit synchronization (Jackson and Turner, 2003). As bone tissue is very sensitive to mechanical loading, the dynamic mechanical loading involved in WBV training would also enhance bone anabolic response (Torcasio*, et al.*, 2008). However, significant reduction of touch-pressure sensation on the sole of the foot and balance ability was found immediately after exposure to vibration (Sonza*, et al.*, 2015). Long-term occupational exposure to high-magnitude vibrations may lead to deleterious effect in the spinal and reproductive systems (Bovenzi, 2006). Excessive transmission of vibration to the head could also cause damage to the retina (Ishitake*, et al.*, 1998) and inner ear(Bochnia*, et al.*, 2005).

During WBV treatment, the vibration is transmitted from the vibration source (e.g., vibration platform) to the target body part(s) (Luo*, et al.*, 2005). However, the biodynamic responses to vibration depend on many factors, including the vibration amplitude and frequency of platform (Matsumoto and Griffin, 1998),

body posture (Lafortune, *et al.*, 1996), muscular activation (Tarabini, *et al.*, 2014) and musculoskeletal compliance (Wakeling, *et al.*, 2002). Thus, the vibration characteristics (e.g., magnitude) would vary in different body parts (Matsumoto and Griffin, 1998) and the response of the human body to the platform vibration is non-linear (Lafortune, *et al.*, 1996, Matsumoto and Griffin, 1998). In addition, there may be a distortion of sinusoidal waveforms as the signals are transmitted upward. The degree of signal attenuation (i.e., transmissibility) and how well the original signal waveforms are retained during transmission (i.e., signal purity) may have major impact on therapeutic efficacy (Kiiski, *et al.*, 2008). Moreover, transmissibility to the head and resonance effect should be minimized for safety concerns (Caryn, *et al.*, 2014, Kiiski, *et al.*, 2008). To this end, the ratio of acceleration measured at the level of the vibration platform and that at the target body part has been used as a measure of transmissibility (Kiiski, *et al.*, 2008). The site-specific vibration frequency profile (i.e., signal purity) can be evaluated using vibration spectral analysis (Griffin, 1996, Kiiski, *et al.*, 2008).

Previous research on vibration transmissibility was only conducted in healthy young adults (Abercromby, *et al.*, 2007, Avelar, *et al.*, 2013, Caryn, *et al.*, 2014, Cook, *et al.*, 2011, Crewther, *et al.*, 2004, Kiiski, *et al.*, 2008, Lafortune, *et al.*, 1996, Matsumoto and Griffin, 1998, Rubin, *et al.*, 2003, Tankisheva, *et al.*, 2013). Generally, the signals are attenuated as they are transmitted from the feet upward to other body sites (Cook, *et al.*, 2011, Harazin and Grzesik, 1998, Tankisheva, *et al.*, 2013). Increased frequency was found to be associated with lower vibration transmissibility (Caryn, *et al.*, 2014, Cook, *et al.*, 2011, Kiiski, *et al.*, 2008). However, amplification of signals can be found in certain anatomical landmarks (Kiiski, *et al.*, 2008, Matsumoto and Griffin, 1998), particularly when the

frequency was lower than 20 Hz (Crewther*, et al.*, 2004, Kiiski*, et al.*, 2008, Matsumoto and Griffin, 1998, Tankisheva*, et al.*, 2013). Changes in posture could also modify the vibration transmission. However, only the effect of knee flexion angle was studied in previous research (Abercromby*, et al.*, 2007, Avelar*, et al.*, 2013, Cook*, et al.*, 2011, Rubin*, et al.*, 2003, Tankisheva*, et al.*, 2013). The interaction effects of vibration frequency, amplitude, and postures on transmissibility were reported in one study, but transmissibility was measured at the head only (Caryn*, et al.*, 2014). Moreover, WBV signal distortion during transmission is very understudied. Only Kiiski et al. have examined WBV signal purity during erect standing in healthy young adults. Signal purity in other postures that are often used in WBV exercise training has not been studied (Kiiski*, et al.*, 2008).

Although WBV has been widely used and examined among people with stroke (Brogardh*, et al.*, 2012, Chan*, et al.*, 2012, Liao*, et al.*, 2016, Marin*, et al.*, 2013, Miyara*, et al.*, 2014, Pang*, et al.*, 2013, Tankisheva*, et al.*, 2014, Tihanyi*, et al.*, 2007, van Nes*, et al.*, 2006), mixed results on various clinical outcomes are found. The discrepancies in results may be due to the difference in WBV protocols used. Thus, it is important to conduct more fundamental research on transmissibility and signal purity in the stroke population. The information gained would inform the design of WBV protocols, which can be formally tested in efficacy studies. Stroke survivors may have altered musculoskeletal characteristics (Cruz*, et al.*, 2009). Moreover, the muscle activation patterns with WBV stimulation among individuals with stroke were also different from healthy young adults (Liao*, et al.*, 2014). Because the musculoskeletal system is a major pathway through which the WBV is transmitted, it is highly likely that WBV

transmissibility in stroke patients could be very different from that in able-bodied individuals. However, to date, the research on vibration transmission and signal purity for the stroke population is lacking.

The objectives of this study were (1) to investigate the influence of WBV frequency, amplitude, and body posture on WBV transmissibility and signal purity; and (2) to examine the impact of stroke motor impairment and spasticity on WBV transmissibility. It was hypothesized that (1) WBV transmissibility and signal purity would be influenced by vibration frequency, amplitude, body postures, and their interactions; (2) WBV transmissibility and signal purity would demonstrate a significant difference between the paretic and non-paretic side; and (3) WBV transmissibility would be associated with the motor impairment level or muscle spasticity of the affected lower extremity.

4.3 Method

4.3.1 Subjects

Individuals with chronic stroke were recruited from the local community using convenience sampling. The inclusion and exclusion criteria are shown in Table 4-1. The study was approved by the Human Subjects Ethics Sub-committee of the University and conducted according to the Declaration of Helsinki. Written informed consent was obtained from each participant before data collection.

4.3.2 Experimental setting

This was an experimental study with repeated measures. A WBV device (Fitvibe Excel, GymnaUniphy, Belgium) generating sinusoidal vertical vibrations

Table 4-1 Subject inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥18 • Diagnosis of a hemispheric stroke > 6 months • Medically stable • Able to stand independently for at least 1 minute	• Brainstem or cerebellar stroke • Other neurological conditions • Serious musculoskeletal or cardiovascular diseases • Metal implants or recent fractures in the lower extremities or spine • Pregnancy or in menstruation period.

was used. Eighteen WBV conditions generated by different combinations of two vibration amplitudes (low: 0.8 mm; high: 1.5 mm), three vibration frequencies (20 Hz, 30 Hz, 40 Hz), and three postures (deep-squat with knee flexion at 60°, high-squat with knee flexion at 30°, tip-toe standing) were tested. The specific requirements for each posture are described in Figure 4-1. The rationale of the above protocols is explained in Table 4-2. Due to safety, all participants were asked to hold the handrail lightly for balance only. Each trial was about 20 s. The 18 trials were conducted in randomized order with a 1-min rest period between each trial. Two researchers provided standby supervision to ensure safety and correct postures (e.g., correct knee angle and no trunk/head movement). The trial would be terminated immediately if any adverse symptoms (e.g., fatigue, dizziness) were reported. All the experimental procedures were completed in the same laboratory of the university. The session was about 1.5 h, including the set-up time and rest periods.

4.3.3 Measurements

The demographic information was obtained first by interviewing the participants. Motor function of the paretic leg was assessed by a physiotherapist using Fugl-Meyer Assessment (FMA). Higher scores denoted less

Figure 4-1 Body postures used in testing.
(a) Deep-squat position: standing with feet placed apart at shoulder width and knees flexed at 60°; (b) high-squat position: standing with feet placed apart at shoulder width and knees flexed at 30°; (c) tip-toe standing: standing with both ankles plantarflexed as much as able. During testing, participants were required to stand on the vibration platform barefoot, and place the two feet in parallel with a shoulder-width distance in between and put equal body weight on each foot as much as possible. Two goniometers were attached in the lateral aspect of each knee to ensure that the desired amount of knee flexion was reached.

impaired motor function (Sullivan*, et al.*, 2011). The spasticity of ankle plantar flexors, knee flexors, and extensors was also rated using the Modified Ashworth Scale (MAS), and a higher score indicated more severe spasticity (Bohannon and Smith, 1987).

Seven tri-axial accelerometers (Dytran Model 7523A5, Chatsworth, Canada) were mounted on tailor-made polyester board (weight 10 g; Otto Bock, Duderstadt, Germany) using screws, which were attached to the skin overlying the specific body sites using tapes (Omnifix® elastic, Hartmann-Conco, Heideman, Germany) and self-adherent wraps (Coban®, 3 M, Saint Paul, US): bilateral medial malleolus (ankle), bilateral medial condyle of the femur (knee), bilateral greater trochanter (hip), and third lumbar vertebra (L3) (Matsumoto and Griffin, 1998). To measure the acceleration at the head, one tri-axial accelerometer was fixed on the disposable dental impression that was held firmly between the upper

and lower teeth (Harazin and Grzesik, 1998). Another tri-axial accelerometer was attached to the center of WBV platform to measure platform acceleration. Before data collection, the orientation of accelerometers was calibrated and checked to secure proper alignment of axis coordinates.

4.3.4 Data processing

Acceleration signals were recorded and digitized via a 32-channel analog-to-digital converter (Model DT9844, Data Translation, Norton, US) using a custom program written in LabView (version 8.6, National Instruments, Austin, US) with a resolution of 20-bit and sampling frequency of 1000 Hz.

Table 4-2 Choice of vibration settings and postures with rationale

Protocol	Rationale
Vibration frequency (20, 30 & 40Hz)	• These frequencies were commonly used in previous WBV studies in stroke [7, 23, 30, 38, 41,43]. • Frequencies below 20Hz were not used due to potential resonance effect, causing damage to internal organs [16, 19]. • Frequencies above 40Hz were not used because the accelerations generated would be very high. Discomfort was reported by some subjects in our pilot testing when 40Hz was used. • Testing more frequencies would prolong the experimental session and may cause fatigue. • As the goal was to compare the effect of various vibration frequencies on transmissibility, it was important that the frequencies used were substantially different from one another.
Vibration amplitude (0.8 & 1.5mm)	• These amplitudes were within the range of amplitude values commonly used in previous WBV studies in stroke [7, 23, 30, 38, 41,43]. • Higher amplitudes (e.g., >2mm), when combined with the higher frequencies used here (e.g., 30 and 40Hz) would result in very high accelerations. • Testing more amplitudes would prolong the experimental session and may cause fatigue. • As the goal was to assess the effect of vibration amplitude on transmissibility, it was important that the amplitudes used were substantially different from one another while considering the other limitations stated above.
Postures (high squat, low squat, tip-toe standing)	• Major leg muscle groups were activated by these postures [21, 22]. • These same postures were also adopted in many previous stroke WBV trials [7, , 23, 30, 38, 41,43].

Offline data analysis was performed using a custom-written script in MATLAB (version R2014b, MathWorks, Natick, US). For each 20-s trial, the data from one 3-s period in the middle section were selected for analysis (Kiiski*, et al.*, 2008). This single 3-s period should contain 40–120 vibration cycles, depending on the vibration frequency. The DC offset induced by the gravitational acceleration was removed. In the time domain, resultant accelerations were calculated from the vector sum of x, y, z-axis, which represented the absolute acceleration of each vibration trial. The root-mean-square (RMS) value of the resultant acceleration was calculated in a 3-s window for each vibration trial (Caryn*, et al.*, 2014). The transmissibility of vibration to each body site was calculated as the ratio of the acceleration RMS of the site-specific signal to the acceleration RMS of the WBV platform (Kiiski*, et al.*, 2008). A transmissibility ratio larger than 1.0 indicated amplification of vibration signals transmitted from the platform to the measured body site, while the ratio less than 1.0 indicated dampening of signals during its transmission.

For each trial, the frequency domain of the acceleration signals at the platform, and each body site was also analyzed by performing fast Fourier transform. The proportion of signal power with ±1 Hz of the vibration frequency at the level of the platform (i.e., nominal frequency) was computed to assess the signal purity of the sinusoidal waveform using the following formula (Kiiski*, et al.*, 2008):

$$\text{Signal Purity} = \frac{Px(nominal\ frequency \pm 1) + Py(nominal\ frequency \pm 1) + Pz(nominal\ frequency \pm 1)}{Px + Py + Pz} \times 100\%$$

in which the Px (nominal frequency ±1 Hz), Py (nominal frequency ±1 Hz), Pz (nominal frequency ±1 Hz) indicated the power of nominal frequency ±1 Hz in x,

y, and z-axis respectively; and Px, Py, and Pz indicated signal power at the level of the platform in x, y, and z-axis respectively Figure 4-2. The greater the signal purity value, the better the sinusoidal waveforms were maintained. A value of greater than 80% was considered to be adequate (Kiiski*, et al.*, 2008).

4.3.5 Statistical analysis

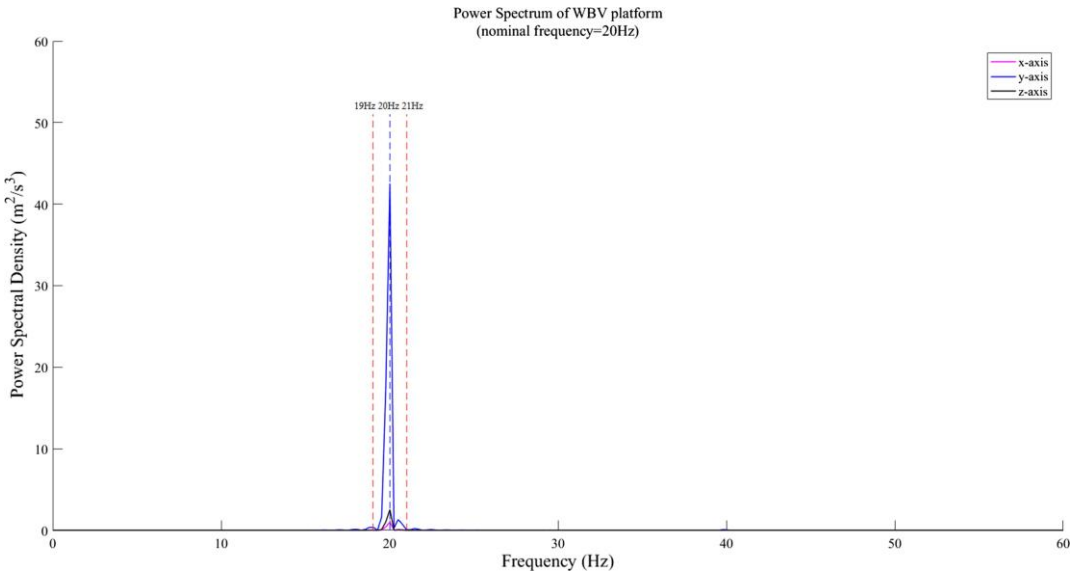

Figure 4-2 Power spectrum of the vibration signals generated by the WBV platform. This figure illustrates the power spectrum of the signals generated by the vibration platform when the nominal frequency was 20 Hz. Three axes (i.e., x, y, z-axis) of the accelerometer were represented in magenta, blue and black respectively. The vertical blue line represents the nominal frequency whereas the two vertical red lines denoted 19 Hz and 21 Hz. Only a very small proportion of data fell outside the range between 19 Hz and 21 Hz (20 ± 1 Hz), resulting in a high signal purity value of 96.2%.

Statistical analysis was conducted using SPSS (version 22, IBM, Armonk, NY). The significant level was set at $p < 0.05$. Normality was checked by Shapiro-Wilk test. Two separate three-way repeated-measures ANOVA (within-subject factors: three frequencies, two amplitudes, three postures) was performed to investigate the effect of vibration frequency, amplitude and body postures and their interactions on signal transmissibility and purity, respectively. The Greenhouse-Geisser epsilon adjustment was used when sphericity assumption was violated.

Post-hoc analysis using paired-t Bonferroni adjustment was performed if any overall significant results were identified. The effect size was expressed as partial eta squared (η_p^2)(Fritz, *et al.*, 2012). Next, paired t-tests with Bonferroni adjustment were used to compare the difference in vibration transmissibility and signal purity between the paretic and non-paretic side for each WBV condition. Spearman's rho was used to examine the relationship between (a) FMA score, (b) ankle plantarflexors MAS score, (c) knee flexor MAS score, (d) knee extensor MAS score and transmissibility on the paretic side.

4.4 Results

Thirty-four participants with chronic stroke [12 women, 22 men; mean age (SD): 62.3 (2.7) years] completed all testing. No adverse effect (e.g., dizziness, nausea) was reported during our study. The demographics are summarized in Table 4-3. The acceleration-RMS generated by the platform ranged from 0.79 g to 4.94 g ($1g \approx 9.81\ m/s^2$). The signal purity measured at the level of the platform ranged from 93.6% to 96.8%, indicating that the WBV platform was adequate in generating the intended sinusoidal signals as the signal purity value was greater than 80% (Kiiski, *et al.*, 2008).

Table 4-3 Demographics of study participants (n=32)[a]

Variable	Value
Age, year	62.1±6.8
Sex, men/women, n	20/12
Body mass index, kg/m^2	23.5±2.8
Poststroke duration, year	8.6±4.0
Type of stroke, hemorrhagic/ischemic, n	9/25
Side of paresis, left/right, n	13/19
Fugl-Meyer Lower limb motor score	20.4±3.9
Paretic plantarflexors MAS score, Median (IQR)	2 (1-3)

[a] MAS: modified Ashworth Scale; IQR: Interquartile range.

4.4.1 Transmissibility

The transmissibility in each measured body site under various vibration settings is illustrated in Table 4-4. Amplification of vibrations was observed at the ankle on both sides (transmissibility: 1.05–1.98).

The transmissibility decreased with increasing frequency in all sites except the ankles ($p < 0.001$) (Figure 4-3). The significant frequency × posture interaction effect was found in all measured body sites ($F = 4.01–56.54$, $p \leq 0.009$, $\eta_p^2 = 0.11–0.63$). The frequency × posture interaction effect was more prominent with high-amplitude WBV ($\eta_p^2 = 0.744$) comparing to the low-amplitude WBV ($\eta_p^2 = 0.538$) at the knee bilaterally, thus accounting for the significant frequency × posture × amplitude interaction effects at these two sites ($F = 3.35-3.97$, $p = 0.012–0.031$, $\eta_p^2 = 0.09–0.11$). The transmissibility decreased with increasing amplitude in all sites except the ankles ($p \leq 0.02$) (Figure 4-4).

4.4.2 Signal purity

The mean signal purity values are shown in Table 4-5. In general, the signal purity was satisfactory (≥80%), with a few exceptions. Frequency spectrum analysis revealed high-frequency components at the ankles when 20 Hz and high amplitude was used (Figure 4-5), which accounted for a relatively low signal purity value (73%).Signal purity was well below 80% at the paretic hip when 40Hz was used during high squat and tip-toe standing, and at the head during high-squat. WBV signal purity showed no significant frequency × posture × amplitude interaction effects in all measured sites. Frequency × posture interactions were significant at bilateral ankles, knees and hips ($F = 2.84–4.00$, $p \leq 0.011$, $\eta_p^2 = 0.12–$

0.18) (Figure4-6). Amplitude × posture interactions were significant in all measured sites ($F = 9.40–40.00$, $p \leq 0.001$, $\eta_p^2 = 0.22–0.55$) (Figure4-7).

4.4.3 Comparison between the paretic and non-paretic side

On the non-paretic side, there was significantly greater transmissibility in the ankle during most tip-toe standing conditions when compared with the corresponding values on the paretic side. There was no significant difference between the paretic side and non-paretic in signal purity, regardless of the WBV conditions.

4.4.4 Relationship to motor impairment and spasticity

There was no significant association of the MAS score of the knee flexors/extensors and ankle plantarflexors with transmissibility. The FMA score was positively associated with transmissibility values measured at the paretic ankle during most tip-toe standing conditions ($rho = 0.36–0.60$, $p \leq 0.039$). The FMA score was also positively associated with the transmissibility ($rho = 0.34–0.38$, $p \leq 0.028$) and signal purity ($rho = 0.38–0.47$, $p \leq 0.010$) at the paretic knee and hip when performing a deep squat and tip-toe standing (40 Hz/high amplitude).

Table 4-4 WBV transmissibility at different body sites[a]

Posture	Frequency	Amplitude	Paretic Ankle	Non-paretic Ankle	Paretic Knee	Non-paretic Knee	Paretic Hip	Non-paretic hip	Lumbar	Head
Low squat	20Hz	Low	1.25 (0.31)	1.40 (0.35)	1.15 (0.50)	1.21 (0.63)	0.43 (0.21)	0.36 (0.17)	0.45 (0.16)	0.29 (0.12)
		High	1.33 (0.39)	1.47 (0.42)	0.97 (0.50)	1.02 (0.61)	0.38 (0.24)	0.30 (0.20)	0.40 (0.18)	0.24 (0.13)
	30Hz	Low	1.40 (0.40)	1.57 (0.41)	0.66 (0.26)	0.68 (0.34)	0.23 (0.14)	0.18 (0.11)	0.32 (0.15)	0.22 (0.11)
		High	1.36 (0.42)	1.69 (0.47)	0.52 (0.28)	0.61 (0.35)	0.18 (0.14)	0.14 (0.11)	0.24 (0.14)	0.16 (0.10)
	40Hz	Low	1.44 (0.33)	1.63 (0.55)	0.44 (0.19)	0.48 (0.29)	0.12 (0.08)	0.10 (0.08)	0.21 (0.16)	0.14 (0.09)
		High	1.27 (0.43)	1.6 (0.63)	0.35 (0.14)	0.43 (0.27)	0.09 (0.09)	0.07 (0.06)	0.19 (0.12)	0.12 (0.08)
High squat	20Hz	Low	1.32 (0.31)	1.51 (0.26)	1.11 (0.41)	1.23 (0.42)	0.28 (0.16)	0.29 (0.16)	0.30 (0.09)	0.14 (0.05)
		High	1.23 (0.44)	1.58 (0.36)	0.87 (0.45)	0.99 (0.42)	0.20 (0.10)	0.24 (0.20)	0.27 (0.14)	0.13 (0.12)
	30Hz	Low	1.45 (0.43)	1.98 (0.42)	0.37 (0.18)	0.47 (0.21)	0.07 (0.08)	0.08 (0.05)	0.12 (0.06)	0.05 (0.02)
		High	1.43 (0.44)	1.81 (0.33)	0.50 (0.28)	0.55 (0.24)	0.10 (0.08)	0.10 (0.10)	0.15 (0.06)	0.06 (0.03)
	40Hz	Low	1.45 (0.43)	1.98 (0.42)	0.37 (0.18)	0.47 (0.21)	0.07 (0.08)	0.08 (0.05)	0.12 (0.06)	0.05 (0.02)
		High	1.52 (0.55)	1.93 (0.70)	0.35 (0.21)	0.41 (0.24)	0.06 (0.06)	0.06 (0.08)	0.10 (0.06)	0.04 (0.03)
Tip-toe standing	20Hz	Low	0.84 (0.19)	0.94 (0.21)	0.30 (0.12)	0.30 (0.01)	0.20 (0.07)	0.21 (0.07)	0.17 (0.04)	0.17 (0.05)
		High	0.94 (0.24)	1.06 (0.23)	0.29 (0.11)	0.27 (0.07)	0.17 (0.07)	0.19 (0.06)	0.16 (0.05)	0.15 (0.04)
	30Hz	Low	1.06 (0.32)	1.17 (0.36)	0.24 (0.12)	0.24 (0.11)	0.10 (0.06)	0.09 (0.03)	0.09 (0.02)	0.10 (0.02)
		High	1.17 (0.37)	1.38 (0.41)	0.24 (0.10)	0.25 (0.12)	0.08 (0.06)	0.07 (0.03)	0.08 (0.03)	0.08 (0.03)
	40Hz	Low	1.08 (0.30)	1.33 (0.40)	0.18 (0.11)	0.21 (0.10)	0.05 (0.02)	0.09 (0.25)	0.06 (0.03)	0.06 (0.03)
		High	0.91 (0.28)	1.24 (0.45)	0.14 (0.07)	0.18 (0.07)	0.03 (0.02)	0.03 (0.01)	0.05 (0.03)	0.04 (0.02)

[a] Mean and SD values are presented.

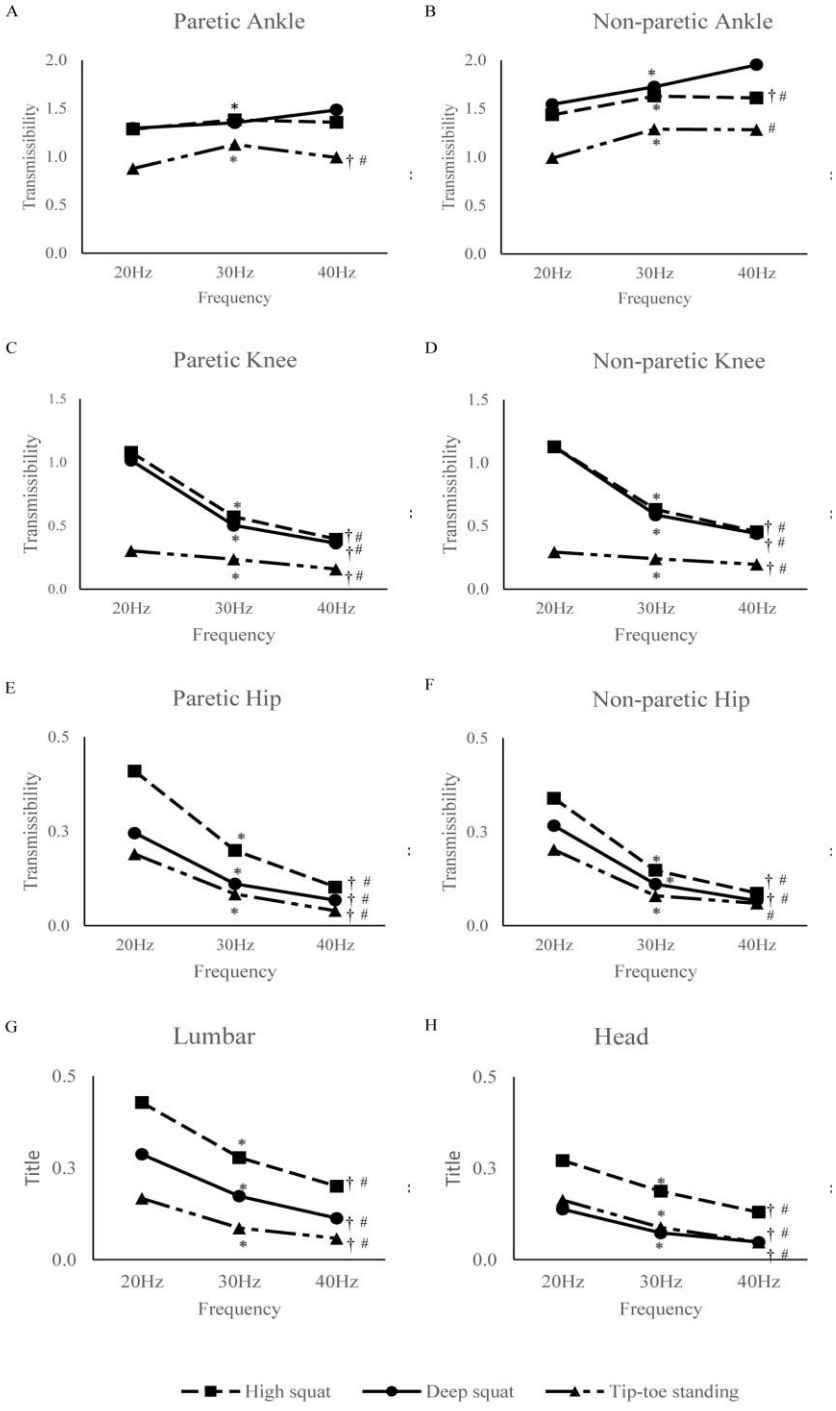

Figure 4-3 The interaction effect between WBV frequency and body postures on transmissibility. Site-specific WBV transmissibility under three different body postures (i.e., high squat, deep squat and tip-toe standing) and three different frequencies (i.e., 20 Hz, 30 Hz and 40 Hz) is illustrated. The difference in transmissibility across postures decreased with increasing frequency at all sites except the ankles, where the greatest difference in transmissibility across postures was observed at 30 Hz. * denotes significant difference between 20 Hz and 30 Hz; † indicates a significant difference between 30 Hz and 40 Hz; # denotes significant difference between 20 Hz and 40 Hz.

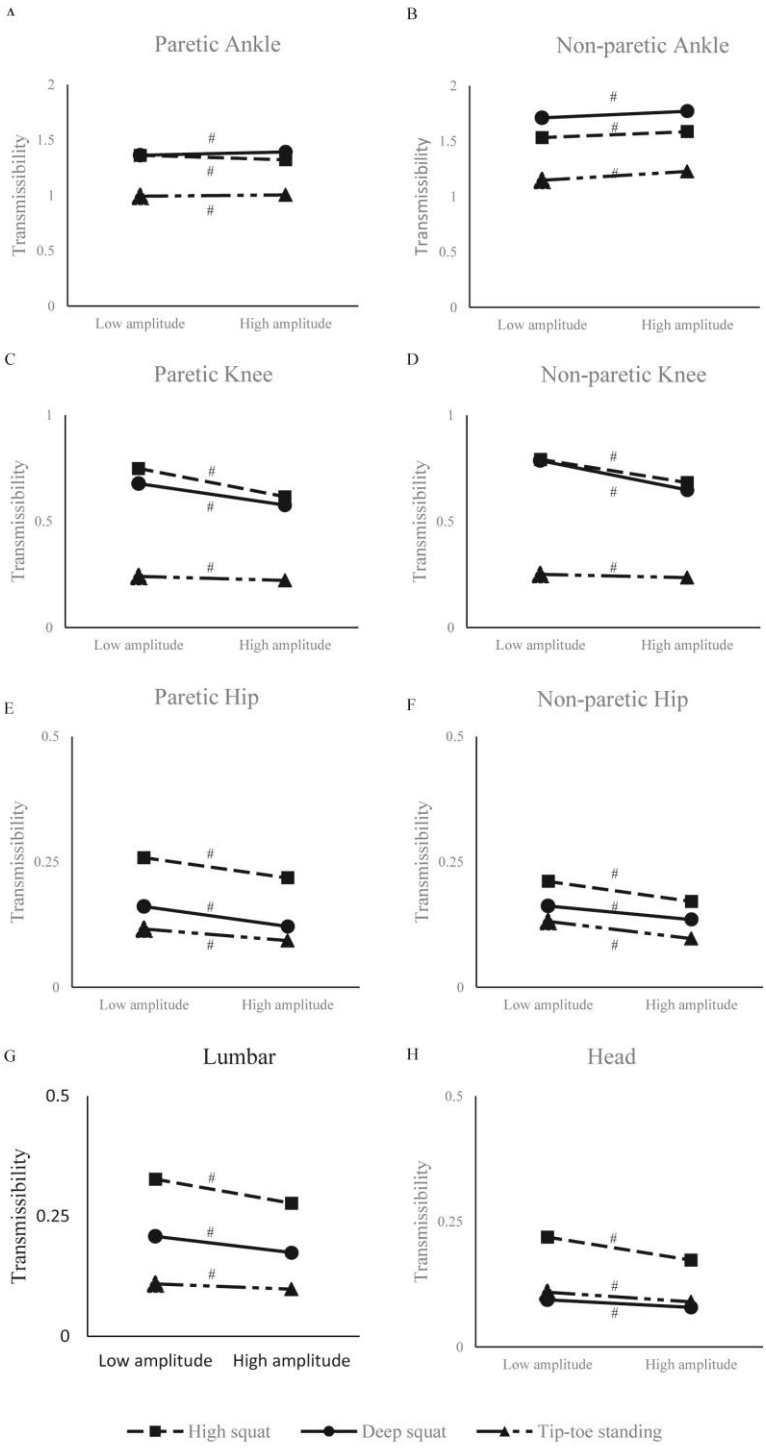

Figure 4-4 The interaction effect between WBV amplitude and posture on transmissibility.
Site-specific WBV transmissibility under three different body postures (i.e., high squat, deep squat and tip-toe standing) and two different amplitudes (low amplitude and high amplitude) is shown. There was only significant interaction effect in bilateral knees. The transmissibility difference between low amplitude and high amplitude was smaller when taking tip-toe standing compared to both squatting postures. # denotes a significant difference in transmissibility between low amplitude and high amplitude.

Table 4-5 Signal purity at different body sites[a]

Posture	Frequency	Amplitude	Paretic Ankle	Non-paretic Ankle	Paretic Knee	Non-paretic Knee	Paretic Hip	Non-paretic hip	Lumbar	Head
Low squat	20Hz	Low	86.0 (7.3)	84.3 (6.5)	91.8 (3.7)	91.3 (3.6)	86.8(5.5)	85.8 (7.0)	89.4 (3.1)	82.8 (8.2)
		High	73.0 (15.9)	73.5 (15.2)	85.0 (9.3)	83.9 (8.5)	83.4(7.9)	83.3 (9.7)	85.9 (9.8)	86.9 (4.8)
	30Hz	Low	92.5 (3.8)	93.0 (3.2)	93.0 (2.2)	93.3 (2.0)	84.5(11.3)	82.3 (11.6)	92.2 (2.7)	87.3 (10.0)
		High	87.3 (8.9)	88.0 (10.4)	86.4 (7.0)	87.6 (4.5)	84.4(7.0)	82.0 (7.9)	89.2 (7.6)	85.6 (11.3)
	40Hz	Low	94.8 (1.7)	94.5 (1.9)	93.4 (2.3)	93.7 (1.8)	80.7(13.8)	79.6 (11.8)	91.1 (4.8)	84.4 (10.9)
		High	86.1 (15.1)	84.6 (15.2)	86.1 (13.0)	85.8 (14.9)	80.3(15.7)	79.0 (15.3)	86.4 (15.6)	80.0 (18.5)
High squat	20Hz	Low	89.2 (4.9)	89.7 (4.4)	92.5 (3.6)	93.3 (1.8)	78.8(13.8)	80.3 (12.6)	85.9 (5.4)	52.6 (21.5)
		High	77.0 (17.3)	76.9 (13.7)	87.5 (6.7)	86.9 (5.3)	82.4(11.6)	83.9 (7.7)	89.4 (5.1)	75.6 (14.7)
	30Hz	Low	92.5 (8.5)	92.8 (5.8)	93.4 (1.9)	93.3 (2.3)	72.1(16.2)	72.2 (16.8)	89.8 (3.3)	59.2 (21.8)
		High	88.6 (7.0)	90.6 (3.6)	87.9 (4.2)	87.7 (5.4)	82.2(10)	82.6 (10.2)	90.7 (4.5)	71.7 (18.4)
	40Hz	Low	94.7 (2.3)	94.3 (1.8)	92.6 (2.8)	93.7 (1.5)	65.0 (16.2)	72.0 (17.5)	88.2 (10.6)	54.4 (22.9)
		High	80.4 (24.9)	78.7 (23.9)	79.1 (24.0)	80.3 (23.8)	70.4(24.7)	74.3 (22.7)	81.3 (24.2)	64.2 (25.2)
Tip-toe standing	20Hz	Low	95.7 (0.4)	95.9 (0.3)	88.0 (5.9)	89.6 (3.2)	77.2(13.1)	81.5 (7.4)	75.9 (8.6)	73.1 (10.4)
		High	93.1 (16.5)	93.1 (16.5)	90.1 (16.2)	90.0 (16.0)	85.2(15.9)	87.0 (15.7)	86.8 (15.6)	85.4 (15.8)
	30Hz	Low	96.3 (0.4)	96.5 (0.2)	89.8 (5.8)	90.2 (5.4)	60.5(21)	68.2 (14.9)	72.9 (9.5)	72.7 (12.7)
		High	94.2 (2.5)	95.0 (1.4)	92.7 (3.0)	92.7 (4.1)	76.2(16.6)	81.8 (10.8)	87.5 (6.8)	86.5 (9.5)
	40Hz	Low	95.5 (1.4)	95.9 (0.6)	91.7 (4.0)	93.9 (2.1)	56.3(16)	56.7 (17.5)	72.6 (15.2)	65.3 (17.5)
		High	92.0 (3.7)	93.1 (2.5)	93.3 (2.1)	94.4 (1.5)	69.2(17)	72.5 (18.1)	84.9 (11.1)	78.9 (15.8)

[a]Signal purity is expressed as mean percentage (SD) values

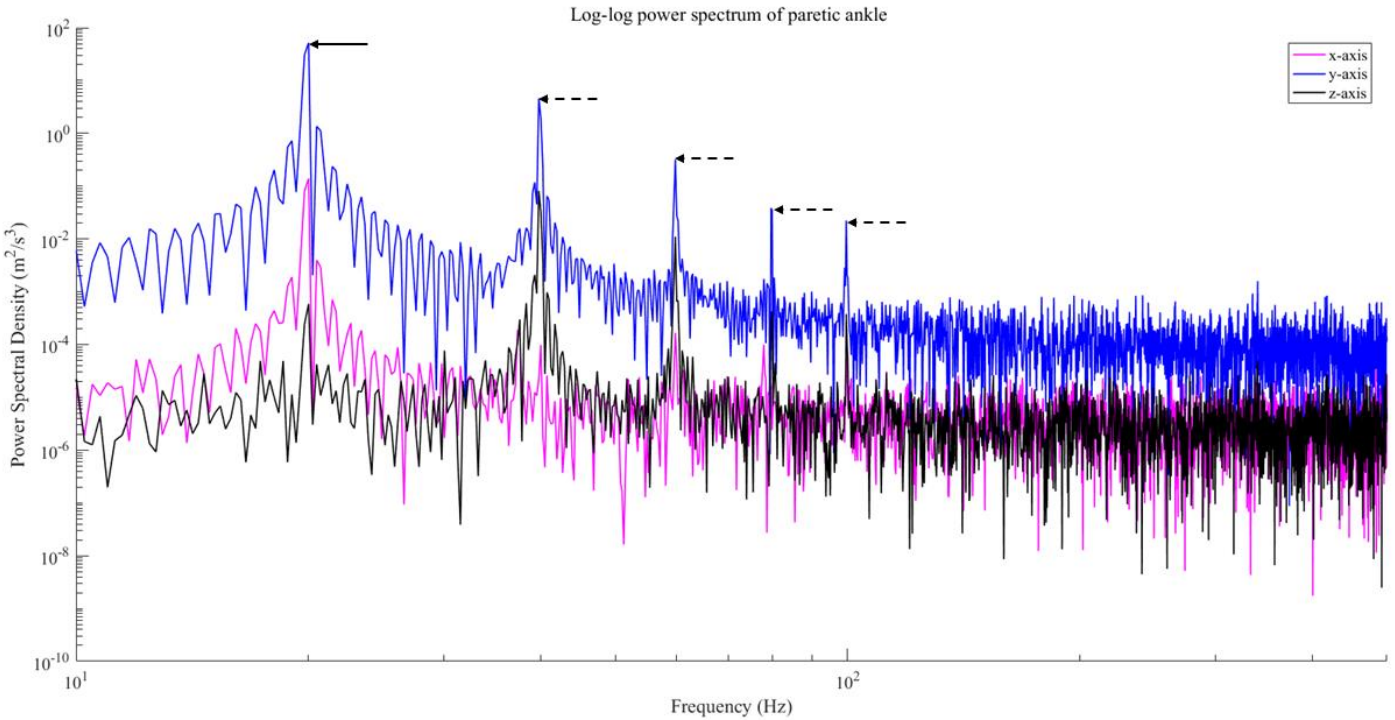

Figure 4-5 Log-log power spectrum analysis: paretic ankle.
The log-log power spectrum analysis of the vibration signals measured at the ankle of a representative subject is shown. Three axes (i.e., x, y, z-axis) of the accelerometer were represented in magenta, blue and black respectively. The vibration setting shown in this example was 20 Hz with high amplitude, and the subject was in a high squat position. The solid arrow indicates the nominal frequency (i.e., 20 Hz). The dashed arrows indicate the five higher frequencies that were generated. These higher frequency components would reduce the overall signal purity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

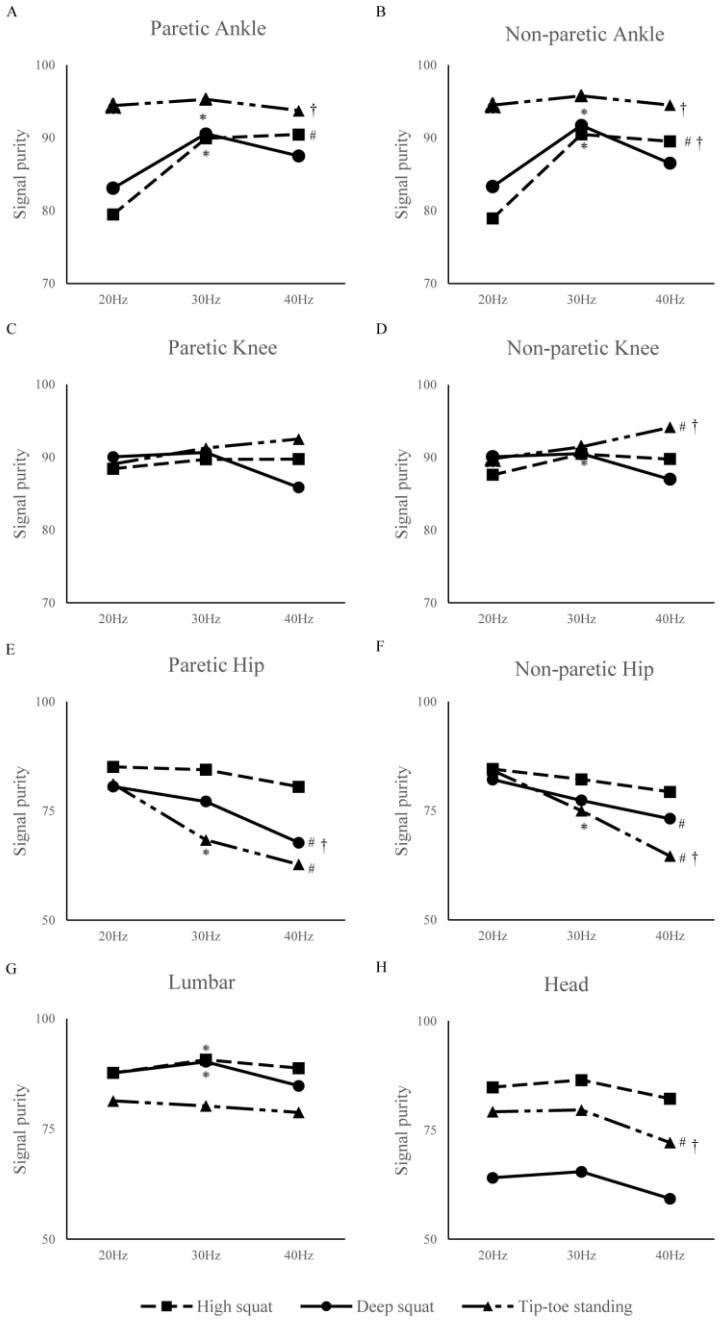

Figure4-6 The interaction effect between WBV frequency and body posture on signal purity. Site-specific WBV signal purity under three different body postures (i.e., high squat, deep squat and tip-toe standing) and three different frequencies (i.e., 20 Hz, 30 Hz and 40 Hz) is shown. In the ankles, the difference in signal purity across postures was the greatest with the lower frequency (20 Hz), whereas, in the hips and knees, the greatest difference was found when 40 Hz was used. * denotes significant difference between 20 Hz and 30 Hz; † indicates a significant difference between 30 Hz and 40 Hz; # denotes significant difference between 20 Hz and 40 Hz.

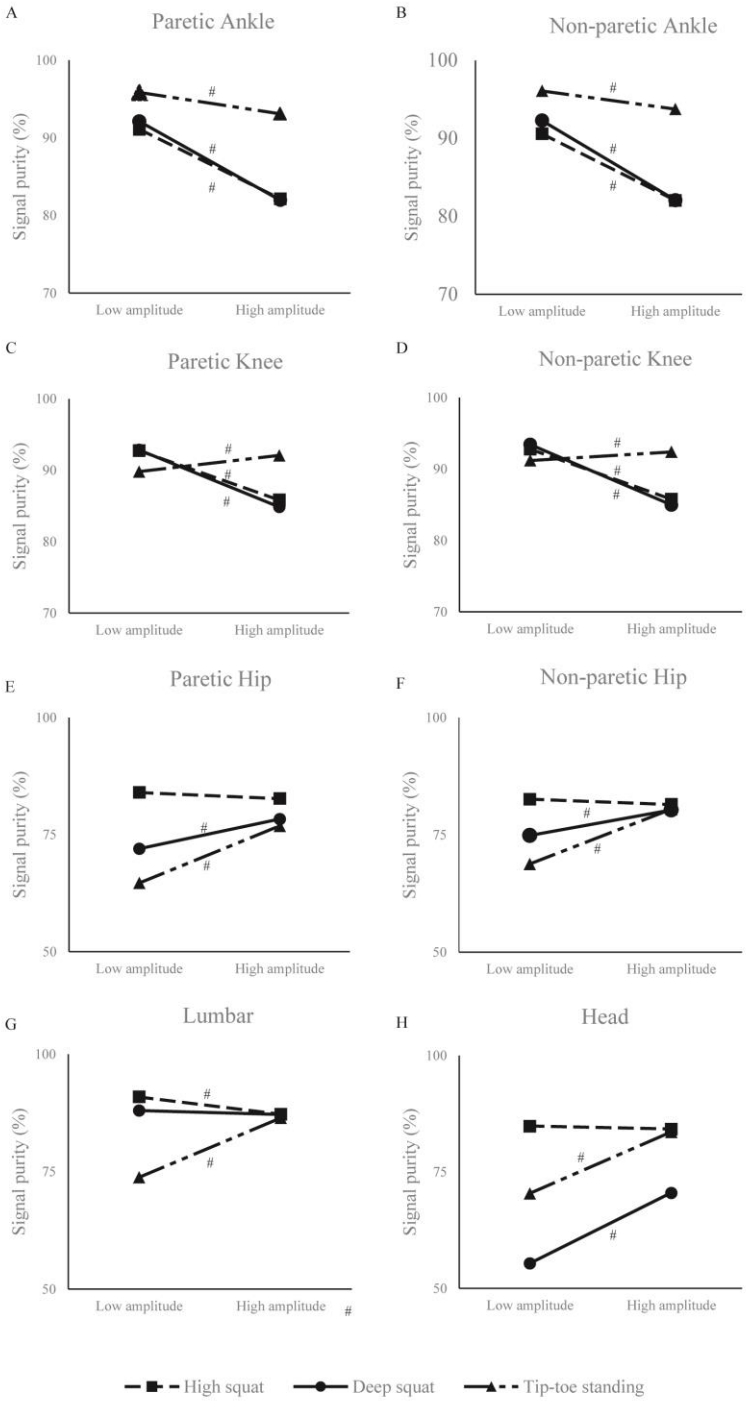

Figure4-7 The interaction effect between WBV amplitude and body posture on signal purity.
Site-specific WBV signal purity under three different body postures (i.e., high squat, deep squat and tip-toe standing) and two different amplitudes (low amplitude and high amplitude) is shown. In the ankles and knees, the difference in signal purity across postures increased with increasing amplitude, whereas in the hip, L3, and head, the opposite trend was demonstrated, with the greatest difference in signal purity across postures found when the low-amplitude protocol was used. # denotes a significant difference in signal purity between low amplitude and high amplitude.

4.5 Discussion

Our hypothesis was confirmed that WBV transmissibility and signal purity were influenced by vibration frequency, amplitude, body postures and their interactions. Generally, above the ankle, increased vibration frequency or amplitude led to deceased WBV transmissibility, although the magnitude of the trend was influenced by body posture. Postures and body segments were the main factor that influenced vibration transmissibility (Harazin and Grzesik, 1998). Bending motion of the knees with the rotational motion of the pelvis could contribute the attenuation of vibration in the upper body (Matsumoto and Griffin, 1998). Therefore, lower transmissibility above the knee joint was observed in the deep squat posture compared to the high-squat posture. This finding is largely in line with previous literature on healthy adults (Abercromby*, et al.*, 2007, Avelar*, et al.*, 2013, Rubin*, et al.*, 2003, Tankisheva*, et al.*, 2013).

In tip-toe standing, the relationship between vibration transmissibility and frequency showed a distinct pattern. Except at the head, the vibration transmissibility was significantly lower when assuming tip-toe standing compared with the two squat positions, which confirmed the speculation that more weight bearing on the forefoot when standing could lead to lower transmissibility (Rittweger, 2010, Tankisheva*, et al.*, 2013). Muscle activation induced by the vibration could attenuate the vibration energy (Tankisheva*, et al.*, 2013, Wakeling*, et al.*, 2002) and may alter the vibration transmissibility in body parts above the muscles activated. During tip-toe standing, the base of support was relatively small, which challenged postural stability. Muscle activity of the lower limbs may be increased to maintain the posture (Branthwaite*, et al.*, 2012), which in turn led to more substantial attenuation of the vibration energy (Branthwaite*, et al.*, 2012,

Liao*, et al.*, 2014). In addition, the foot arch created during tip-toe standing could further absorb the signals(Simkin*, et al.*, 1989). However, the transmissibility to the head was greater during tip-toe standing compared with deep squat, probably because the increased trunk rigidity related to augmented activation of trunk muscles (Branthwaite*, et al.*, 2012) and pressure to torso joints during tip-toe standing (Marouane*, et al.*, 2015).

Vibration amplification (i.e., transmissibility > 1.0) was observed at the ankles. The power spectrum analysis also showed that higher frequency components were generated (Figure 4-5). A similar phenomenon was previously found in healthy young adults (Harazin and Grzesik, 1998). It was believed that during vibration cycles, the feet might lose contact with vibration platform that led to an air-borne phase for the feet (Rittweger, 2010). As a result, the collision occurred between platform and feet, which may generate impact forces (Rittweger, 2010) and thus led to excessive loading in the ankle (Kiiski*, et al.*, 2008).

In contrast to our hypothesis, the non-paretic side showed greater transmissibility than the paretic side only at the ankle during tip-toe standing. Tip-toe standing, with a narrow base of support, was quite challenging for stroke patients. The participants may put more weight on the non-paretic side to improve stability, which resulted in lower transmissibility on the paretic side. This may also partly explain why better motor recovery of the paretic leg (i.e., higher FMA score) was correlated with greater transmissibility on the same side, as those with better motor recovery may have better ability to weight bear on the paretic side. Spasticity, on the other hand, was measured while the participants were in a resting state, and thus may not have a noticeable influence on the transmissibility of vibrations.

When setting WBV training protocol, safety should be the key consideration. Excessive vibration loading to the head should be avoided (Caryn*, et al.*, 2014) especially for people with stroke. In our study, although the average vibration intensity measured at the platform was up to 4.94 g, the vibration signals were substantially attenuated at the level of the head (transmissibility ratio: 0.04–0.30; vibration intensity: 0.11–0.60 g).

To achieve the desired therapeutic effect on bone and muscle, adequate vibration transmissibility and signal purity at the target treatment site is necessary (Pang*, et al.*, 2013). On the other hand, low vibration transmission to the head is important to ensure safety. Based on our study findings (Table 4-4 & Table 4-5), a combination of WBV frequency at 20 Hz, low amplitude and deep squatting position may be a better choice if the treatment goal was to enhance/maintain bone mass in the hip and lumbar spine. This concurred with the finding of a meta-analysis which showed low-frequency (20 Hz) and high-magnitude (>1g) vibrations could lead to significant increase of hip and lumbar bone density in healthy older adults(Oliveira*, et al.*, 2016). As our accelerometers were put in bony body areas rather than the muscles, vibration loading in muscle could not be directly detected. However, as muscle activation would have a major damping effect on vibration signals (Wakeling*, et al.*, 2002), lower transmissibility may indicate more muscle activation below the measured bony sites. Thus, to activate leg muscles, deep squatting with WBV at 30–40 Hz would be more appropriate. However, the above hypotheses will need to be tested in future research, with measurement of muscle activity/strength and bone quality.

As the aim was to examine the transmissibility and signal purity, the duration of exposure to WBV per testing condition was very brief (20 s). The period should

generate an adequate number of vibration cycles for our data analysis. To study the therapeutic or harmful effect of such exposure, probably a longer period of exposure is required and will need further investigation. Although some of the testing conditions involved high-intensity WBV and hence may induce a high level of muscle work, there should not be major concerns with muscle fatigue or damage. First, we did monitor closely the patients' condition throughout the experiment. No limb numbness, discomfort or muscle fatigue was reported by our subjects. Second, the actual level of muscle activation may not be very high. Previous studies examining the effect of WBV on muscle activation in stroke patients (Liao*, et al.*, 2014, Liao*, et al.*, 2015) showed that addition of vibration (20–30 Hz, 0.44–0.60 mm, 0.96–1.61 g) led to an increase in muscle activity by 10–25% of the maximal voluntary contraction. The levels of muscle activation attained did not exceed 40% maximal voluntary contraction while assuming various postures that were similar to those used in our study, even with their high-intensity protocol (1.61 g) (Liao*, et al.*, 2014, Liao*, et al.*, 2015). There was no further increase in muscle activation levels for the majority of muscle groups as the intensity was changed from 0.96 g to 1.61 g, indicating a possible saturation in muscle response (Liao*, et al.*, 2014, Liao*, et al.*, 2015). There was also no significant difference in WBV-induced EMG response between the affected and unaffected side (Liao*, et al.*, 2014, Liao*, et al.*, 2015). Moreover, we found that more severe motor deficit was associated with lower transmissibility. Taken together, it is unlikely that the protocol used here would induce a very high level of muscle activation and cause muscle damage. In fact, resistance training in stroke patients often involves a high level of muscle work (60–80% of 1 repetition maximum) in order to induce strength training effect (Patten*, et al.*,

2004). Tankisheva et al. also found that high-intensity vibrations (frequency: 35–40 Hz, amplitude: 1.7–2.5 mm, intensity: up to 16.1 g) could significantly increase knee extensor strength after 6 weeks of training without causing any fatigue or pain (Tankisheva, *et al.*, 2013).

Vibration amplification was found in the ankle joint at 20–40 Hz and knee joint at 20 Hz. Therefore, caution should be exercised when applying WBV to stroke patients who also have ankle or/and knee pathology, especially when the above frequencies are used. For people with severe stroke motor impairments, uneven weight bearing would occur during WBV. Hence, good contact between the feet and vibration platform and more symmetrical body-weight distribution pattern should be ensured (Emerenziani, *et al.*, 2014), thus to reduce the air-borne effect at the ankles and promote better vibration transmission to the paretic side (Rittweger, 2010).

Several limitations of our study should be considered. First, skin-mounted and bite-bar accelerometers were used. Although it may not be as accurate as the bone-mounted method, the non-invasive skin-mounted or bite-bar accelerometers provide a much safer and feasible option, and have been used in previous studies (Abercromby, *et al.*, 2007, Avelar, *et al.*, 2013, Caryn, *et al.*, 2014, Cook, *et al.*, 2011, Crewther, *et al.*, 2004, Harazin and Grzesik, 1998, Kiiski, *et al.*, 2008, Matsumoto and Griffin, 1998, Tankisheva, *et al.*, 2013). We also put light-weight plastic between the skin and accelerometer to minimize the influence of skin stretch, uneven bony surface, temperature and humidity (Matsumoto and Griffin, 1998). Our power spectrum analysis also showed that the signal purity could reach 96.5%, 94.4%, 87.0%, 92.2% and 87.3% in ankles, knees, hips, lumbar and head, respectively, which suggested that our accelerometers were well mounted. Second,

we did not report how muscle activation varied with the different WBV parameters tested in the current study. Future studies may explore the muscle activation and its relationship with the WBV transmission. We also did not assess the beneficial or harmful effects of long-term exposure of WBV. This issue awaits further research.

In summary, WBV amplitude, frequency, body postures and their interaction could significantly influence the vibration transmissibility and signal purity among people with chronic stroke. Leg muscle spasticity was not significantly related to WBV transmissibility. Less severe lower limb motor impairment was associated with greater transmissibility at the paretic ankle, knee, and hip in certain WBV conditions. In clinical practice, WBV amplitude, frequency, body postures need to be considered regarding the therapeutic purpose. Good contact between the feet and vibration platform and symmetrical body-weight distribution pattern should be ensured.

4.6 Complete with interest

The authors declare that they have no conflict of interest.

4.7 Acknowledgements

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5 Chapter 5: Muscle activity and vibration transmissibility during whole-body vibration in chronic stroke

(The results of this study were published in a peer-reviewed journal *(Huang M, Pang MYC.: Muscle activity and vibration transmissibility during whole-body vibration in chronic stroke. Scand J Med Sci Sports. In press*).

5.1 Abstract

Purpose: This study aimed to investigate the influence of whole-body vibration (WBV) frequency, amplitude and body posture on lower limb muscle activation among people with chronic stroke, and whether the EMG response to vibration stimulus differed between paretic and non-paretic side. The relationship between muscle activation and WBV transmission was examined.

Method: Thirty-two participants with chronic stroke performed three different exercises on the WBV platform with different vibration conditions (frequency: 20 Hz, 30 Hz, 40 Hz; amplitude:0.8 mm, 1.5 mm), or without vibration. Muscle activity in bilateral vastus medialis (VM), medial hamstrings (MH), tibialis anterior (TA), and medial gastrocnemius (MG) was measured by surface electromyography. Acceleration at the platform and bilateral hips and knees was measured by the tri-axial accelerometers.

Results: Significantly greater muscle activity was observed in the bilateral MG ($p<0.001$), TA ($p<0.001$), and MH ($p<0.001$), but not VM, compared with the same exercises without WBV. WBV with higher amplitude or higher frequency

led to greater augmentation of muscle activation ($p<0.05$). Body posture significantly affected leg muscle activation ($p<0.001$). WBV-induced muscle activation was largely similar between paretic and non-paretic sides, except the TA. Greater WBV-induced leg muscle activation was associated with lower WBV transmissibility measured at the more proximal joints ($p<0.05$).

Conclusion: Adding WBV to exercise significantly increased muscle activation in the MG, TA, and MH on both the paretic and non-paretic sides of chronic stroke survivors, and the increase was dependent on the WBV amplitude, frequency, and body posture.

5.2 Introduction

It is estimated that approximately 17 million people have a first-ever stroke annually worldwide (Crichton*, et al.*, 2016). More than half of stroke survivors have chronic hemiparesis along with muscle weakness and functional disability (Benjamin*, et al.*, 2018). Much effort has been devoted to identifying effective interventions to tackle this problem among stroke survivors.

Whole-body vibration (WBV) has gained popularity in sports training and rehabilitation for its potential effect on increasing muscle strength (Osawa*, et al.*, 2013). Individuals perform static or dynamic exercise on the WBV platform while mechanical stimuli are transmitted upward to the body via the feet (Rittweger, 2010). It is suggested that the vibration activates muscle spindles and causes α-motor neuron excitation, thus enhancing muscle activation (Rittweger*, et al.*, 2010). The sinusoidal vibration stimulation also exerts additional load on the neuromuscular system during WBV training, which is similar to that observed in

resistance training (Rittweger*, et al.*, 2010). In addition, the augmented muscle activation during WBV training may contribute to vibration damping and minimize the potential damage to soft tissues (i.e., muscle tuning) (Wakeling and Nigg, 2001, Wakeling*, et al.*, 2002). However, no study has simultaneously measured the transmission of the vibration signals and muscle response during WBV. Thus, the muscle-tuning response has not yet been shown.

Several studies have reported an increase in lower limb muscle activity during exposure to WBV in healthy young adults (**Abercromby***, et al.*, 2007, Avelar*, et al.*, 2013, Borges*, et al.*, 2017, Cardinale and Lim, 2003, Cochrane*, et al.*, 2009, Di Giminiani*, et al.*, 2015, Hazell*, et al.*, 2007, Krol*, et al.*, 2011, Lienhard*, et al.*, 2014, Lienhard*, et al.*, 2015b, Lienhard*, et al.*, 2015c, Marin*, et al.*, 2009, Perchthaler*, et al.*, 2013, Pollock*, et al.*, 2010, Ritzmann*, et al.*, 2013a, Roelants*, et al.*, 2006), older adults (Lam*, et al.*, 2016, Lienhard*, et al.*, 2017, Marin*, et al.*, 2012), and stroke survivors (Liao*, et al.*, 2014, Liao*, et al.*, 2015), as measured by surface electromyography (EMG). However, randomized controlled trials on the effect of WBV treatment on leg muscle strength have yielded mixed results (Brogardh*, et al.*, 2012, Lau*, et al.*, 2012, Liao*, et al.*, 2016, Marin*, et al.*, 2013, Pang*, et al.*, 2013). The inconsistency in results may be due to the use of different WBV settings. Indeed, previous studies on healthy young adults indicated that muscle activation induced by WBV was highly dependent on the WBV frequency (Cardinale and Lim, 2003, Hazell*, et al.*, 2007, Krol*, et al.*, 2011, Lienhard*, et al.*, 2014, Perchthaler*, et al.*, 2013, Pollock*, et al.*, 2010), WBV amplitude (Lienhard*, et al.*, 2014, Marin*, et al.*, 2012, Perchthaler*, et al.*, 2013, Pollock*, et al.*, 2010), additional load (Di Giminiani*, et al.*, 2015), posture

(Lienhard, *et al.*, 2015b, Perchthaler, *et al.*, 2013, Ritzmann, *et al.*, 2013a, Roelants, *et al.*, 2006), and a combination of these factors (Ritzmann, *et al.*, 2013b).

Stroke survivors may have increased fast-twitch (ie, Type II muscle) muscle fibers and decreased slow-twitch I muscle fibers (Severinsen, *et al.*, 2016). It is known that fast-twitch fibers are more sensitive to vibration.35 Therefore, the muscle response to WBV in poststroke patients may differ from that in their able-bodied counterparts. Despite the increasing popularity of applying WBV in stroke rehabilitation, only a few studies have investigated the EMG response during WBV in individuals with stroke, and the frequency and amplitude of the vibration signals were not varied independently in their testing protocols (Liao, *et al.*, 2014, Liao, *et al.*, 2015).

To address the knowledge gap in this field, this study aimed to investigate the effect of WBV amplitude, frequency, and body posture on lower limb muscle activation in people with chronic stroke, and to examine whether the EMG response to vibration differed between the paretic and nonparetic side. We also examined the relationship between muscle activation and WBV transmission. We hypothesized that (a) the addition of WBV would significantly increase muscle activation in all tested lower limb muscles compared with the no-WBV condition; (b) for a given posture, muscle activation would increase as the vibration frequency or amplitude increased; (c) for a given vibration frequency and amplitude, the increase in muscle activation would be affected by body posture; (d) WBV-induced muscle activation would be greater on the paretic than the non-paretic side; and (e) higher WBV-induced muscle activation would be associated with lower WBV transmission in the more proximally located joints.

5.3 Materials and methods

5.3.1 Study design

This was an experimental study with repeated measures. The EMG signals of the bilateral lower limb muscles and the acceleration in the bilateral knees and hips were recorded in different WBV conditions in random orders. All of the measurements were completed in the university rehabilitation laboratory in a single visit lasting about 3 hours.

5.3.2 Participants

People with chronic stroke were recruited from the local community using convenience sampling. The inclusion criteria were (a) adults with a diagnosis of a hemispheric stroke >6 months; (b) medically stable; and (c) able to stand independently for at least 1 minute. The exclusion criteria were (a) brainstem or cerebellar stroke; (b) other neurological conditions; (c) serious musculoskeletal or cardiovascular diseases; (d) metal implants or recent fractures in the lower extremities or spine; and (e) pregnancy or menstruation. The study was approved by the Human Subjects Ethics Sub-committee of the University. All participants gave written informed consent before data collection.

The demographic information was collected by interviewing the participants. Fugl-Meyer motor assessment scale lower extremity (FMA-LE) was used to assess the motor function of the paretic leg by a physiotherapist (Sullivan*, et al.*, 2011). Higher scores of FMA-LE indicated less impaired motor function (Sullivan*, et al.*, 2011). Modified Ashworth Scale (MAS) was used to assess the spasticity of the

ankle plantarflexors (Bohannon and Smith, 1987). Higher scores of MAS denoted more severe spasticity (Bohannon and Smith, 1987).

5.3.3 Surface electromyography

The surface EMG activities of the bilateral medial gastrocnemius (MG), tibial anterior (TA), vastus medialis (VM), and medial hamstring (MH) muscles were recorded using Ag/AgCl bipolar electrodes (Biometrics SX230, Gwent, UK). The reference electrode was placed on the right fibular head. After careful skin preparation, electrodes were attached to the skin and fixed with elastic tapes (Omnifix®; Hartmann-Conco, Heideman, Germany) according to the guidelinesof the Surface EMG for a Non-invasive Assessment of Muscles project (Hermens*, et al.*, 1999). The voltage signals were pre-amplified (gain = 1000) and filtered (bandwidth = 20-460 Hz) at the source. In addition, all electrodes and cables were secured with an elastic bandage to reduce motion artifacts.

5.3.4 Assessment of maximum voluntary contraction

The maximum voluntary contractions (MVC) during bilateral ankle plantarflexion/dorsiflexion and knee extension/flexion were assessed after a 5-minute warm-up period consisting of leg stretching and slow-paced walking exercises. The participants were seated on a chair with a backrest placed against a wall, thighs strapped by a belt and feet placed on a stool with the knees flexed at 60°. Participants were told to hold onto the edge of the chair on each side for further stabilization. To measure the MVC during knee extension (i.e., VM muscle) and flexion (i.e., MH muscle), the tested lower leg was strapped using a non-elastic belt that was attached to a fixed structure. Participants were asked to perform an

isometric knee extension or flexion by pushing/pulling against the belt for 5 seconds, with maximal effort. To test the MVC during ankle plantarflexion (i.e., MG muscle) and dorsiflexion (i.e., TA muscle), the knee was placed in a fully extended position with support and the foot was placed in a neutral dorsiflexion/plantar-flexion position (Burden, 2010). To measure the MVC during ankle plantarflexion, the participants were asked to isometrically push the ankle against the wedge with maximal effort for 5 seconds. To test ankle dorsiflexion, the participants performed a maximal isometric ankle dorsiflexion by pushing against the assessor's hands for 5 seconds (Burden, 2010). The assessor placed the hands on the dorsum of the tested foot while leaning backward during testing. In this way, the resistance provided by the assessor was mainly from his/her body weight, rather than the hands only. This would ensure accurate testing of the MVC on the non-paretic side, which is typically stronger than the paretic side. Verbal encouragement was given during the contractions. Three trials were performed for each muscle, with a 2-minute rest interval between trials (Burden, 2010).

5.3.5 Vibration acceleration recoding

Each of the four tri-axial accelerometers (Dytran Model 7523A5; Chatsworth, Canada) was fixed on a custommade polyester board (weight 10 g; Otto Bock, Duderstadt, Germany) using screws (Huang*, et al.*, 2018). Using elastic tapes and self-adherent wraps (Coban®, 3M, Saint Paul, USA), the boards were then fixed to the skin overlying the medial condyle of the femur (knee) and greater trochanter (hip) bilaterally (Huang*, et al.*, 2018). An additional tri-axial accelerometer was mounted on the center of the WBV platform to assess acceleration at the platform level (Huang*, et al.*, 2018). To ensure proper alignment

of the axis coordinates, the accelerometers were calibrated and their spatial orientation was carefully checked prior to data collection (Huang*, et al.*, 2018).

5.3.6 WBV exercise protocols

A WBV device (Fitvibe Excel; Gymna Uniphy, Belgium) was used to generate sinusoidal vertical vibrations. The WBV intensity (i.e., peak acceleration) was determined by the vibration frequency and amplitude, using the formula $a_{peak} = (2\pi f)^2 A$, where f and A denote frequency and baseline-to-peak amplitude, respectively.4 Our WBV protocols involved two vibration amplitudes (low: 0.8 mm; high: 1.5 mm) and three vibration frequencies (20 Hz, 30 Hz, 40 Hz), thus generating six WBV conditions (Table 1). A control condition without WBV (frequency = 0 Hz, amplitude = 0 mm) was also accessed. In all seven testing conditions (six WBV conditions and one no-WBV condition), each participant assumed three different static body postures (Table 2). Therefore, there were 21 testing conditions, each involving a specific combination of WBV amplitude, frequency, and body posture. These vibration parameters were chosen because they have been used in previous WBV studies of people with stroke and were proven to be safe (Huang*, et al.*, 2018).

The 21 conditions were tested in random order, and two trials were performed for each condition. Each trial lasted 15 seconds with at least a 1-minute rest period between trials. During testing, the participants were instructed to stand barefoot while placing equal body weight on each foot, and to put two feet in parallel at shoulder-width distance on the vibration platform. For preventing falls, all participants were required to slightly hold the handrail. The bilateral knee flexion angle was monitored by two goniometers (BaselineÒ HiResi plastic

360ISOM Goniometer; Fabrication Enterprises, White Plains, NY) attached to the lateral aspect of each knee. Practice trials were conducted before the actual data collection. Two researchers stood close to each participant to ensure safety and appropriate posture. Once any discomfort was reported, the trial would be stopped instantly.

5.3.7 Data processing

The acceleration and EMG signals were synchronously recorded and digitized using LabVIEW™ (version 8.6; National Instruments, Austin, USA) connected to a USB multiplexer card (NI USB-6218; National Instruments, Newbury, UK) with a 20-bit resolution and 1000 Hz sampling frequency.

The acceleration data were analyzed using a custom written script in MATLAB (version R2014b; MathWorks, Natick, USA). For each 15-second trial, the data from the 5th to the 10th second were selected for analysis. After removing the DC offset due to the gravitational acceleration, the root-mean-square (RMS) value of the absolute acceleration was calculated for each vibration trial, which was the resultant acceleration derived from the vector sum of the *x*, *y*, *z*-axis (Huang*, et al.*, 2018). The transmissibility of vibration to specific body site is a ratio which was computed as (acceleration RMS of the specific

body site)/(acceleration RMS of the WBV platform) (Huang*, et al.*, 2018). The acceleration signals at the platform were also analyzed in the frequency domain by applying a fast Fourier transform to identify the platform's nominal frequency (i.e., the dominant frequency of the platform) (Huang*, et al.*, 2018).

The EMG data were processed using a customized program in LabVIEW. The frequency domain of the collected raw EMG data was checked. Motion

artifacts indicated by prominent peaks were noted at the nominal frequency and its integral multiples (Abercromby, *et al.*, 2007, Lienhard, *et al.*, 2015a). Thus, all EMG data were filtered using a second-order Butterworth band-pass filter with a cutoff of 20-300 Hz and 4th-order Butterworth band-stop filter with cutoff frequencies of 20, 30, 40, and 50 Hz (i.e., local alternating current frequency) and their harmonics. The data were then rectified, and the RMS (EMG_{rms}) was calculated in 100 ms windows around every data point (Abercromby, *et al.*, 2007). The EMG_{rms} values of the two test trials were averaged to obtain the mean value for each testing condition. For each muscle, the highest EMG_{rms} portion of 100 ms duration from three MVC trails for each muscle was extracted and averaged (Burden, 2010), which was then used for normalization of the EMG_{rms} value in each WBV condition (Liao, *et al.*, 2014). Thus, the EMG activation of each muscle measured in each WBV condition was expressed as a percentage of the EMG_{rms} obtained during the MVC (i.e., $EMG_{mvc\%}$) (Liao, *et al.*, 2014). The following formula was used to quantify the augmented muscle activation during WBV (EMG ratio) (Abercromby, *et al.*, 2007, Ritzmann, *et al.*, 2013a).

$$\text{EMG ratio} = \frac{\text{EMGmvc\% of each WBV trial}}{\text{EMGmvc\% of the same body posture without vibration}}$$

A value greater than 100% indicates augmented neuromuscular activation with added WBV.

5.3.8 Statistical analysis

Statistical analyses were performed using SPSS (version 22, IBM, Armonk, NY, USA). A value of $P < 0.05$ was considered to be statistically significant. In all ANOVA models, the dependent variable (EMGmvc% or EMG ratio) was positively skewed, as determined by the Shapiro-Wilk test and probability-

probability plot. Thus, the Box-Cox transformation was applied to the data to obtain normally distributed responses (**Abercromby***, et al.*, 2007, Peltier*, et al.*, 1998).

To determine the effects of WBV on EMG (i.e., hypothesis 1), two-way repeated measures ANOVA [vibration intensity (7 levels). posture (3 levels)] was used to compare the $EMG_{mvc\%}$ values for the MG, TA, VM, and MH on each side. If the analysis showed that adding WBV significantly increased the muscle activation, four-way repeated measures ANOVA (i.e., body sides [2 sides] × WBV frequency [3 levels] × WBV amplitude [2 levels] × body posture [3 levels]) would be used to test the main effect of WBV frequency, amplitude, and body posture on EMG ratio (hypotheses 2-3) and check whether the increased muscle activation differed between the two sides (hypothesis 4). Partial eta squared (η_p) values of 0.14, 0.06, and 0.01 represent large, medium, and small effect sizes, respectively (Levine and Hullett, 2002). A post-hoc analysis using a paired *t* test with Bonferroni adjustment was performed if a significant main effect was found in the ANOVA models.

Finally, the relationship between the WBV-induced muscle activation (EMG ratio) and WBV transmissibility in the knee or hip of each leg was evaluated using Pearson's correlations. Specifically, we examined the correlation (a) between the EMG ratio of the MG or TA and the transmissibility in the knee of each leg, and (b) between the EMG ratio of the MG, TA, MH, or VM and the transmissibility in the hip of each leg.

5.4 Results

Thirty-two participants with chronic stroke (women/men ratio: 0.6; mean age ± SD: 62.1 ± 6.8 years) completed all of the tests. During the study, no adverse effects (e.g., dizziness, fatigue) were reported. The demographic results are presented in Table 3. The actual vibration frequencies delivered by the WBV device were 20, 30, and 38 Hz, as verified by the accelerometer. The average peak acceleration of the WBV platform at each nominal setting ranged from 1.11 to 7.00g (Table 4-1).

Table 5-1 Demographics of study participants (n=32)[a,b]

Variable	Value
Age, year	62.1±6.8
Sex, men/women, n	20/12
Body mass index, kg/m^2	23.5±2.8
Post-stroke duration, year	8.6±4.0
Type of stroke, hemorrhagic/ischemic, n	9/23
Side of paresis, left/right, n	13/19
Fugl-Meyer Lower limb motor score	20.4±3.9
Paretic plantarflexors MAS score, Median (IQR)	2 (1-3)

[a] Mean±SD presented unless indicated otherwise
[b] MAS: modified Ashworth Scale; IQR: Interquartile range.

Table 5-2 Measured peak accelerations of the vibration platform under nominal setting[a]

	Frequency	Peak accelerations (intensity)	Intensity ranking (low to high)
Low amplitude	20Hz	1.11±0.10g	1
	30Hz	2.05±0.01g	2
	40Hz	3.21±0.11g	4
High amplitude	20Hz	2.43±0.22g	3
	30Hz	3.81±0.21g	5
	40Hz	7.00±0.44g	6

[a] 1g=9.81m/s^2

5.4.1 Effect of adding WBV on muscle activation

There were significant main effects of vibration intensity on the bilateral MG ($P < 0.001$, $\eta_p^2 = 0.749$-0.780), MH ($P < 0.001$, $\eta_p^2 = 0.489$-0.545), TA ($P < 0.001$, $\eta_p^2 = 0.507$-0.520), and VM ($P < 0.001$, $\eta_p^2 = 0.287$-0.564). However, post-hoc analysis showed that adding WBV significantly increased EMG signals in the bilateral MG, MH, and TA, but not the VM (Figure 5-1). Overall, the highest level

of muscle activation ($EMG_{mvc\%}$) was found in forefoot standing for the bilateral MG and MH, and in deep squat for the bilateral VM (Figure 5-2).

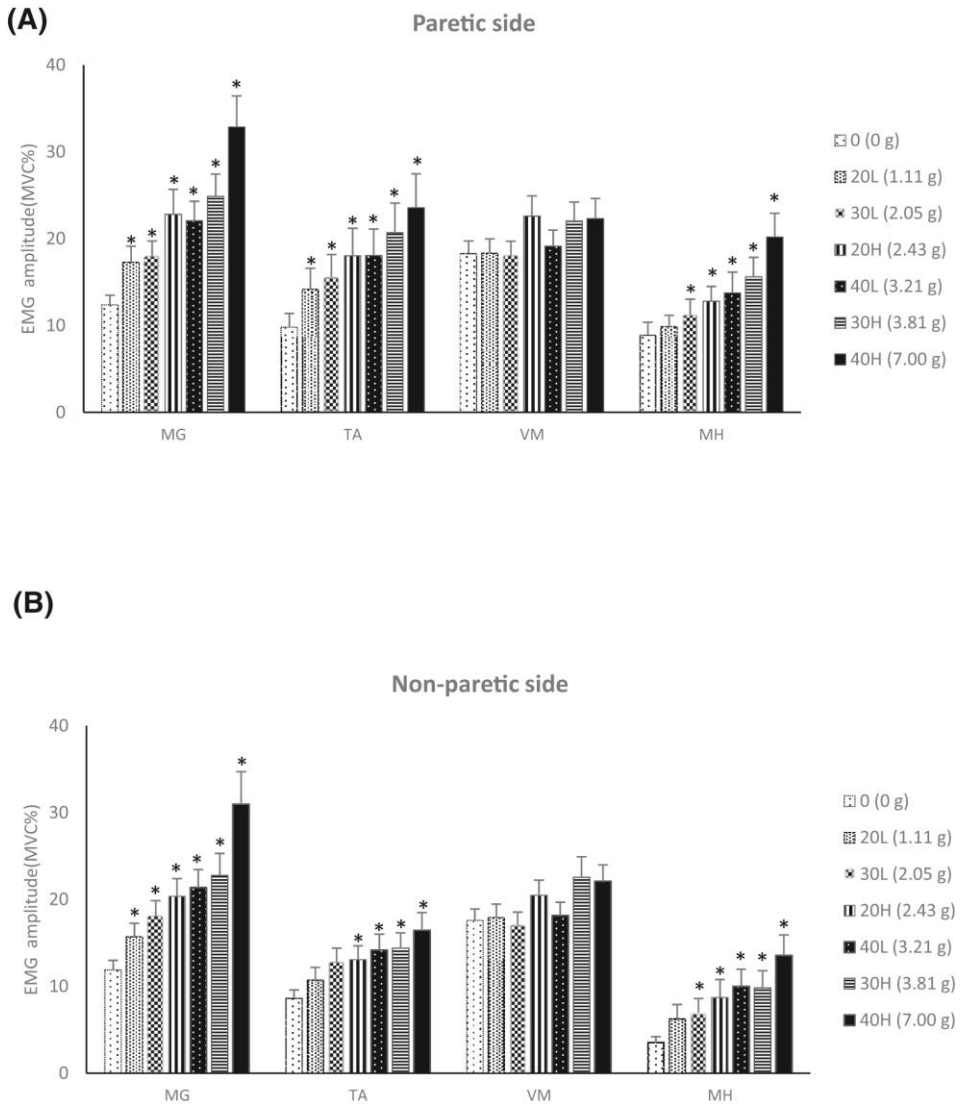

Figure 5-1 Untransformed muscle activity ($EMG_{mvc\%}$) of tested muscles with 7 different WBV magnitudes.

EMG amplitude (EMGmvc%) of tested muscles during exposure to WBV of seven different magnitudes. This figure illustrates the EMG data (expressed in %MVC) in the paretic (A) and non-paretic (B) sides under seven different WBV intensities ranging from 0 to 7.00 g. For each WBV intensity, the data for the three different postures were pooled; g denotes the gravitational force, which was 9.81 m/s2. The error bars represent one standardized error of the mean. *Significantly greater muscle activation relative to the control condition without WBV (ie, 0) (post-hoc analysis using paired t test with Bonferroni adjustment, $P < 0.05$). DS, deep squat; FF, forefoot standing; H, high amplitude; HS, high squat; L, low amplitude; MG, medial gastrocnemius; MH, medial hamstrings; TA, tibialis anterior; VM, vastus medialis

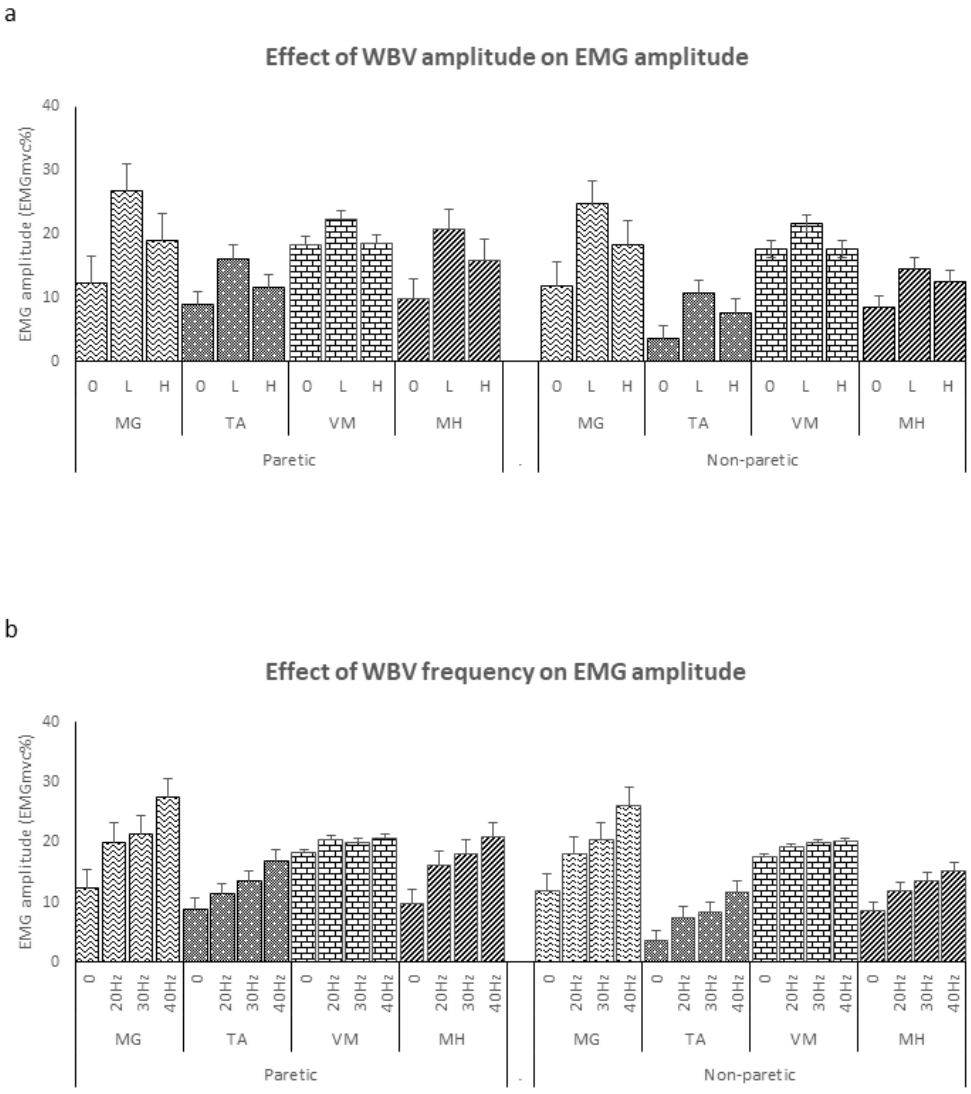

Figure 5-2 The effect of vibration frequency and amplitude on EMG amplitude
The EMG amplitudes (expressed in EMGmvc%) of the tested muscles are shown. The main effect of (a) amplitude and (b) frequency is illustrated. For a particular vibration amplitude or frequency, the data for the different postures were pooled for analysis to show the main effect of amplitude and freuqency.
MG: medial gastrocnemius; MH: medial hamstrings; TA: tibialis anterior; VM: vastus medialis; L: low amplitude; H: high amplitude; HS: high-squat; DS: deep-squat; FF: forefoot standing. The error bars represent one standardized error of the mean.

5.4.2 Effect of WBV frequency, amplitude and posture on WBV-induced muscle activation

As the above analyses showed that adding WBV increased the muscle activity in MG, MH, and TA, further analyses using 4-way ANOVA with repeated measures were done to examine the independent effect of WBV amplitude, frequency, and posture on activation of these three muscle groups. A significant main effect of WBV amplitude was found in all tested muscles, with higher amplitudes leading to significantly greater increases in EMG (i.e., EMG ratio >100%) ($P < 0.05$, $\eta_p = 0.212\text{-}0.597$, Figure 5-3A and Figure 5-2a). A significant main effect of frequency on EMG ratio was found in the bilateral MG ($P < 0.001$, $\eta_p = 0.290\text{-}0.465$), bilateral MH ($P < 0.001$, $\eta_p = 0.377\text{-}0.448$), and bilateral TA ($P < 0.05$, $\eta_p = 0.109\text{-}0.190$) (Figure 5-3B and Figure 5-2b). Post-hoc analysis showed that the highest EMG ratio occurred at 40 Hz (Figure 5-3). A significant main effect of body posture was found in the bilateral MG ($P < 0.001$, $\eta_p = 0.295\text{-}0.411$) and bilateral TA ($P < 0.05$, $\eta_p = 0.171\text{-}0.196$; Figure 5-3C and Figure 5-2). The highest EMG ratio was found in the high squat position for the bilateral MG and TA (Figure 5-3).

5.4.3 Difference in WBV-induced muscle activation between the paretic and non-paretic side

There was no significant difference in WBV-induced muscle activation between the two sides, with the exception of the TA, where the EMG% was higher on the non-paretic than the paretic side (P=0.047).

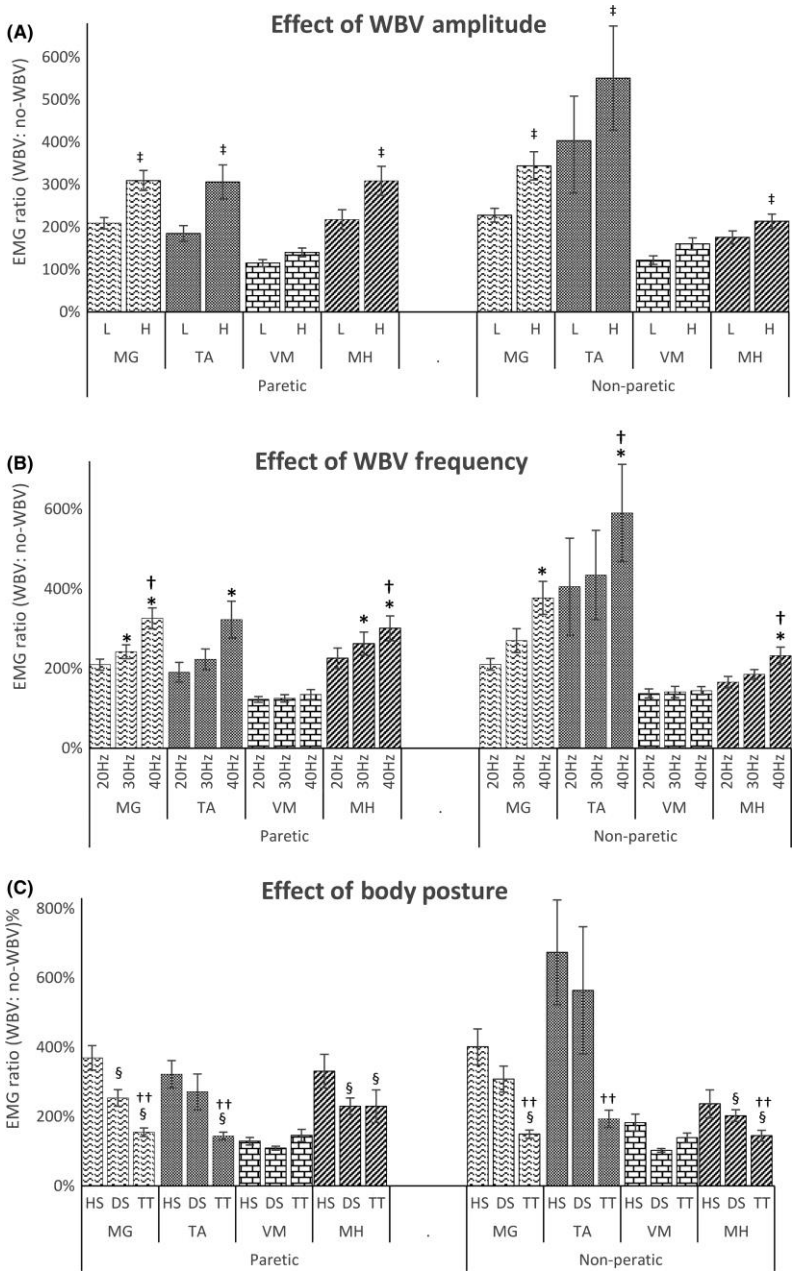

Figure 5-3 Untransformed WBV-induced muscle activity (EMG%) of tested muscles.
Effect of vibration frequency, amplitude, and body posture on WBV-induced muscle activition. This figure illustrates the effect of WBV frequency (A), amplitude (B), and body posture (C) on muscle activity. The data were expressed as a ratio of the EMGmvc% during the WBV condition to that during the no-WBV condition (%). A value of 100% indicates the EMG amplitude between the WBV and no-WBV conditions is the same, whereas a value greater than 100% indicates the EMG amplitude is increased by WBV. In A and B, the EMG data were pooled from the various postures to illustrate the main effect of frequency and amplitude, respectively. In C, the data were pooled from different vibration frequencies and amplitudes to show the main effect of posture. The error bars represent one standardized error of the mean. DS, deep squat; FF, forefoot standing; H, high amplitude; HS, high squat; L, low amplitude; MG, medial gastrocnemius; MH, medial hamstrings; TA, tibialis anterior; VM, vastus medialis. (A) * denotes a significant difference from 20 Hz; † indicates a significant difference from 30 Hz; (B) ‡ denotes a significant difference in EMG ratio between low and high amplitude; (C) § denotes a significant difference from high squatting; †† denotes a significant difference from deep squatting (post-hoc analysis using paired t test with Bonferroni adjustment, $P < 0.05$)

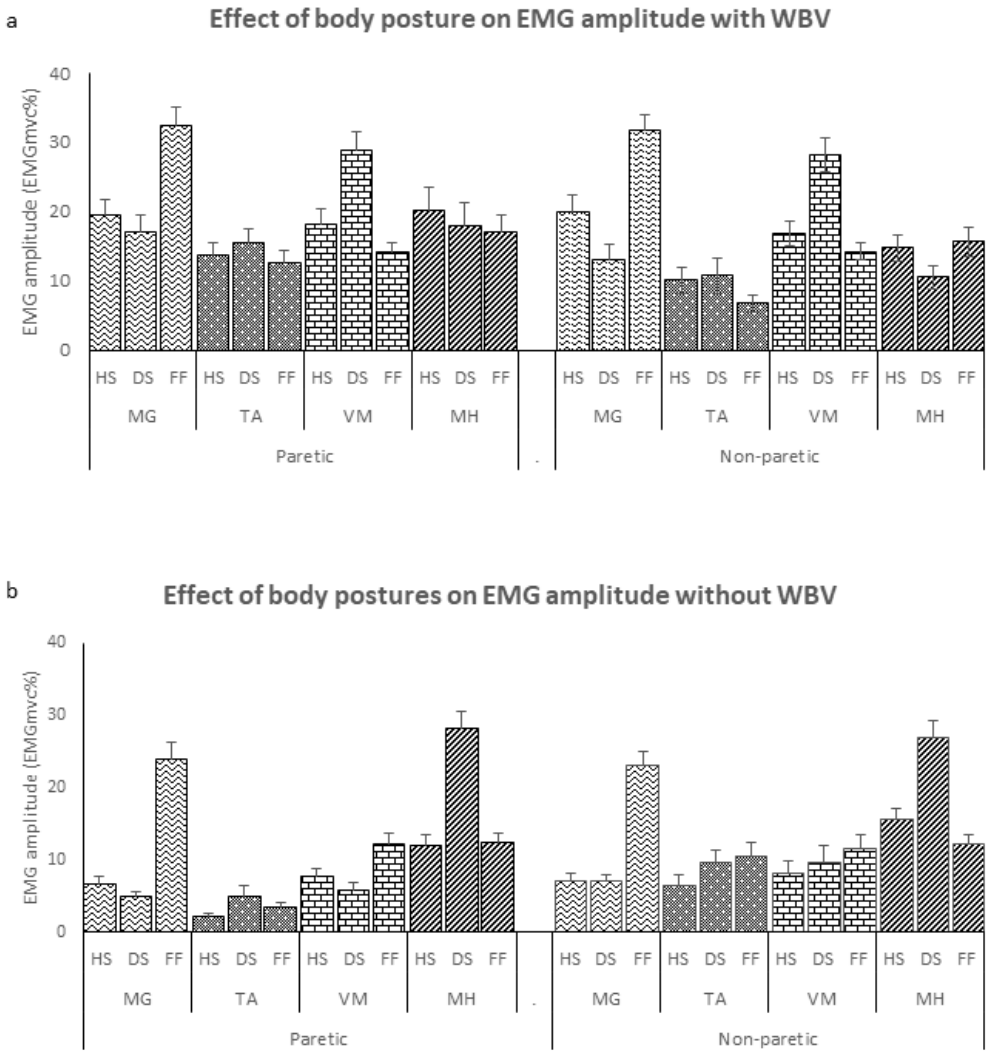

Figure 5-4 The effect of body posture on EMG amplitude
The EMG amplitudes (expressed in EMGmvc%) of the tested muscles are shown. The main effect of body posture during the (a) WBV and (b) no-WBV conditions is illustrated. The error bars represent one standardized error of the mean.
HS: high-squat; DS: deep-squat; FF: forefoot standing.

5.4.4 Relationship between WBV-induced muscle activation and WBV transmissibility

Significant negative associations were found between the transmissibility in the paretic knee and the EMG ratio of the paretic MG ($P < 0.001$) and TA ($P < 0.001$; Table 4). Transmissibility measured at the paretic hip was significantly negatively associated with the EMG ratio of the paretic MG ($P < 0.001$), TA ($P < 0.001$), and MH ($P < 0.001$). On the non-paretic side, the transmissibility in the knee was significantly negatively associated with the EMG ratio of the non-paretic TA ($P = 0.008$), and the transmissibility in the hip was negatively correlated with the EMG ratio of the MH ($P < 0.001$) and VM ($P < 0.001$).

Table 5-3 Correlation between vibration transmissibility and WBV-induced muscle activation

	Transmissibility	
	Knee (paretic)	**Hip (paretic)**
EMG ratio of paretic MG	-0.204 (p<0.001) †	-0.278 (p<0.001) †
EMG ratio of paretic TA	-0.170 (p<0.001) †	-0.199 (p<0.001) †
EMG% of paretic MH	--	-0.268 (p<0.001) †
EMG% of paretic VM	--	0.033 (P=0.429)
	Knee (non-paretic)	**Hip (non-paretic)**
EMG ratio of non-paretic MG	-0.110 (p=0.008) †	0.071 (p=0.090)
EMG ratio of non-paretic TA	-0.012 (p=0.776)	0.045 (p=0.285)
EMG ratio of non-paretic MH	--	-0.163 (p<0.001) †
EMG ratio of non-paretic VM	--	-0.404 (P<0.001) †

*MG: medial gastrocnemius; MH: medial hamstrings; TA: tibialis anterior; VM: vastus medialis.
†Statistical significance, p<0.05

5.5 Discussion

The key findings of the study were as follows: (a) adding WBV significantly increased muscle activation in the bilateral MG, TA, and MH, but not the VM; (b)

increasing the amplitude or frequency of the WBV led to greater augmentation of muscle activation; (c) the WBV-induced muscle activation was affected by body posture; (d) the bilateral WBV-induced muscle activation was largely similar; and (e) greater WBV-induced leg muscle activation was associated with lower WBV transmissibility measured at the more proximal joints. The first and second hypotheses were partially supported by the finding that activation of the bilateral MG, TA, and MH was enhanced by the addition of WBV. Moreover, higher WBV intensities (1.11-7.00 g) led to higher levels of muscle activation in bilateral MG (paretic: +54.8%-269.3%; non-paretic: +49.3%-301.0%), TA (paretic: +43.7%-221.9%; non-paretic: +93.4%-573.4%), and MH (paretic: +129.7%-230.4%; non-paretic: +44.6%-136.5%). These values are generally in line with those reported in previous studies in young healthy adults (Abercromby*, et al.*, 2007, Lienhard*, et al.*, 2014, Lienhard*, et al.*, 2015b, Lienhard*, et al.*, 2015c, Pollock*, et al.*, 2010, Tankisheva*, et al.*, 2013), older adults (Lam*, et al.*, 2016, Lienhard*, et al.*, 2017, Marin*, et al.*, 2012), and stroke patients (Liao*, et al.*, 2014, Liao*, et al.*, 2015) when using a similar EMG processing method. The degree of muscle activation induced by WBV was higher than that in the young healthy population. For instance, the healthy young subjects in the study by Abercromby et al assumed a similar squatting position while being exposed to a vibration intensity up to 7.24 g (Abercromby*, et al.*, 2007). The reported increases in EMG were 132%, 223%, and 9% in the MG, TA, and MH, respectively, which were lower than the values reported here (Abercromby*, et al.*, 2007). The higher degree of muscle activation among the stroke survivors may be due to the muscle fiber properties. Compared with healthy young adults, people with chronic stroke have a higher proportion of fast-twitch fibers (Severinsen*, et al.*, 2016), which are more sensitive to vibration

stimuli (Wakeling and Liphardt, 2006). This may partially explain why the WBV-induced increase in leg muscle activity was more substantial among chronic stroke survivors (Lienhard*, et al.*, 2017).

Contrary to our hypothesis, the results demonstrated that the EMG of the bilateral VM was not enhanced by additional WBV. Indeed, previous studies on the effects of WBV on knee extensor activation have reported inconsistent results, with some finding positive effects (Abercromby*, et al.*, 2007, Lienhard*, et al.*, 2014, Marin*, et al.*, 2009, Tankisheva*, et al.*, 2013) and others negative effects (Avelar*, et al.*, 2013, Lam*, et al.*, 2016, Lienhard*, et al.*, 2015c). In the no-WBV condition, the activation level of the VM was highest among the tested muscles (Figure 1). Additional WBV may thus be less effective in further augmenting the EMG activity. This may also explain why long term WBV treatment failed to increase knee extensor strength among people with chronic stroke in previous trials (Brogardh*, et al.*, 2012, Lau*, et al.*, 2012, Liao*, et al.*, 2016, Marin*, et al.*, 2013).

Our third hypothesis that WBV-evoked muscle activity would increase with increasing vibration frequency/amplitude was partly supported by our findings. Generally, the WBV-induced EMG was more affected by the WBV amplitude than the WBV frequency. First, the effect of amplitude was significant in all measured lower limb muscles, whereas the effect of frequency was significant in only a few WBV conditions for the bilateral MG, TA, and MH. Second, the effect size for the amplitude effect was generally greater than that for the frequency effect. This observation is largely in line with regression models for predicting muscle activation by WBV in young healthy adults (Perchthaler*, et al.*, 2013, Pollock*, et*

al., 2010, Ritzmann*, et al.*, 2013a). In their models, the amplitude rather than the frequency of vibration was able to significantly predict muscle activation during WBV (Lienhard*, et al.*, 2014).

Body posture was found to influence the WBV-induced muscle activation on the bilateral MG, TA, and MH, thus supporting our third hypothesis. The highest increase in EMG with WBV was observed in the high squat position, which is in concordance with previous studies in healthy young adults (Abercromby*, et al.*, 2007, Perchthaler*, et al.*, 2013). Muscle activation was lower at baseline in the high squat than the deep squat position, thus the increase in EMG by WBV was more apparent.

The difference between the paretic and non-paretic side was only observed in the TA muscle (i.e., hypothesis 4), as the WBV-induced muscle activation was greater on the nonparetic side. Weakness in the paretic TA muscle is common among chronic stroke survivors (Kimberley*, et al.*, 2004). Therefore, the motor excitation induced by WBV may be small due to impaired motor recruitment on the paretic side (Landau and Sahrmann, 2002).

The muscle-tuning hypothesis (i.e., hypothesis 5) was supported as the decreased WBV transmissibility measured at a given joint was associated with increased activation of the leg muscles located more caudal to the joint. According to the muscle-tuning hypothesis, there would be an increase of muscle activity when the input vibration frequency is close to the natural frequency of the muscle (Wakeling and Nigg, 2001). It is also known that muscle and bony structures vibrate at the same frequency as the platform (Friesenbichler*, et al.*, 2014, Huang*, et al.*, 2018, Pel*, et al.*, 2009).Transmissibility of vibration to the muscles, however, was dependent on the vibration frequency, amplitude, body posture, and the

individual muscle of interest (Friesenbichler, *et al.*, 2014, Huang, *et al.*, 2018, Pel, *et al.*, 2009). For example, Friesenbichler et al showed that the transmissibility measured at triceps surae and quadriceps soft tissue compartments was higher at 10 Hz than that at 28 Hz. At the same frequency of 28 Hz, the transmissibility was much higher for the triceps surae than the quadriceps (Friesenbichler, *et al.*, 2014). The muscle-tuning theory may explain why the same vibration protocol may lead to varying degrees of muscle activity augmentation in different muscles. The increased muscle activity may in turn damp the vibration and reduce the impact forces, thereby minimizing the potential risk of damage to other body structures (Abercromby, *et al.*, 2007, Di Giminiani, *et al.*, 2015, Lienhard, *et al.*, 2015b, Pollock, *et al.*, 2010, Wakeling, *et al.*, 2002).

A few limitations of the study should be acknowledged. First, the band-stop filter was applied to minimize the motion artifacts, which might underestimate muscle activation. However, the conservative approach confirmed that the increase in EMG reflected a true increase in neuromuscular activation (Abercromby, *et al.*, 2007). Second, we assessed the impact of stroke on WBV-induced EMG activity by comparing the paretic with the non-paretic side. While such within-subject comparisons would eliminate the influence of some confounding variables such as genetic or environmental factors, the non-paretic side may not respond to WBV in the same fashion as a healthy control participant. Third, only people with chronic stroke with mild to moderate motor impairment were included in this study. Stroke survivors with other levels of motor impairment should be included in future studies.

In summary, adding WBV to exercise significantly increased muscle activation in the MG, TA, and MH on both the paretic and non-paretic sides of

chronic stroke survivors, and the increase was dependent on the WBV amplitude, frequency, and body posture. With the exception of the TA, the effect of WBV was similar between the two sides. A greater level of EMG activity was associated with greater attenuation of the signals at more proximal anatomical sites, thus supporting the muscle-tuning mechanism of WBV exercise.

5.6 Perspective

Our study has important clinical implications. First, WBV can effectively increase muscle activation in the MG, TA, and MH even when assuming a static squatting posture. This is an important factor for people who may have impaired mobility functions after a disabling stroke and thus have difficulty with performing other forms of exercise. Second, higher WBV frequency or amplitude induces substantially higher levels of leg muscle activation, which in turn leads to lower transmissibility to the upper body (Huang*, et al.*, 2018). Considering these factors, a squatting position with WBV at 30-40 Hz with a high amplitude (e.g., 1.5 mm) is an appropriate choice if the treatment goal is to enhance leg muscle activation.

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6 Whole-body vibration modulates H-reflex and muscle blood perfusion in chronic stroke

6.1 Abstract

Background: This study aimed to investigate the acute effect of whole-body vibration (WBV) on leg soleus H-reflex, medial gastrocnemius muscle (MG) stiffness and blood perfusion of the among individuals with chronic stroke.

Methods: This is a single-blinded randomized cross-over trial. Thirty-six people with chronic stroke (mean±SD age: 61.4±6.9 years) participated in this study. Each participant was measured for the soleus H-reflex, muscle stiffness and blood perfusion of the MG muscle using ultrasound on both legs after a 5-min WBV intervention (30Hz, 1.5mm) or no-WBV, in randomized order. The measurements were performed at baseline and every 1-minute post-intervention up to 5 minutes. The outcomes, including the H/M ratio, muscle shear modulus and vascular index (VI), were used to quantify the reflex excitability, muscle stiffness, and intramuscular blood perfusion respectively.

Results: Significant inhibition of the soleus H-reflex (by 14-17%) was observed bilaterally after WBV ($p<0.001$), but not after the control conditions. The inhibition was sustained up to 4 min and 3min on the paretic and non-paretic side, respectively. The VI of the MG muscle was significantly increased on both sides by two-fold after WBV ($p<0.01$), which lasted up to 3 minutes and 5 minutes in the paretic side and non-paretic side, respectively. No significant change of the shear modulus in the MG was observed ($p>0.05$).

Conclusions: WBV had a short-term effect on inhibiting the soleus H-reflex and increasing the intramuscular blood perfusion of MG in people with chronic stroke.

ClinicalTrials.gov Registration: NCT03015545 (ClinicalTrials.gov)

6.2 Introduction

Spasticity, a consequence of upper motor neuron lesions, is commonly experienced after stroke (Zorowitz*, et al.*, 2013). Studies have shown that between 17% and 42.6% of stroke survivors suffer post-stroke spasticity 3 months after onset (Wissel*, et al.*, 2013). Although the primary origin of spasticity is impaired reflex function, changes in muscles' mechanical properties, such as stiffness and fibrosis, also occur (Dietz and Sinkjaer, 2007). A growing body of experimental evidence suggests that spastic hypertonia could be the result of changes to both neural pathways and intrinsic muscle properties (Katz and Rymer, 1989). Spastic hypertonia is common in leg extensors after stroke (Arene and Hidler, 2009) and may have negative effects on locomotor function, balance, the ability to perform daily life activities, which in turn compromises health-related quality of life (Arene and Hidler, 2009, Dietz and Sinkjaer, 2007).

Treatments aimed at controlling spastic hypertonia include pharmacological approaches, surgical intervention and conservative treatment (Bethoux, 2015, Gallichio, 2004). Although generally effective, antispastic medications and surgery may cause adverse effects such as muscle weakness, drowsiness and cognitive impairment and may lead to considerable financial burden (Bethoux, 2015, Gallichio, 2004), warranting the development of safe and cost-effective conservative treatment alternatives.

Whole-body vibration (WBV), a treatment modality involving the delivery of mechanical stimuli to the lower limbs via a vibration platform, has been suggested to have a therapeutic effect on spasticity (Huang, *et al.*, 2017). Vibration stimuli may reduce synaptic transmission of the Ia afferents by means of enhanced presynaptic inhibition (Gillies, *et al.*, 1969). In addition, muscle excitation induced by repetitive vibration may cause depletion of neurotransmitters within the presynaptic terminals thereby precipitating post-activation inhibition (Hultborn, *et al.*, 1996, Kipp, *et al.*, 2011). WBV has been shown to inhibit Hoffman's reflex (H-reflex) in healthy athletes and young adults (Apple, *et al.*, 2010, Armstrong, *et al.*, 2008, Cakar, *et al.*, 2014, Games and Sefton, 2013, Karacan, *et al.*, 2016, Kipp, *et al.*, 2011, Kramer, *et al.*, 2013, Krause, *et al.*, 2016, Ritzmann, *et al.*, 2013, Ritzmann, *et al.*, 2018). This suggests that WBV may have the potential to modify the reflex component of spastic hypertonia in people with stroke.

In young adults, WBV may also produce a training effect in muscle by increasing tissue oxygenation (Rittweger, *et al.*, 2010), blood flow in the femoral artery (Kerschan-Schindl, *et al.*, 2001, Lythgo, *et al.*, 2009), blood perfusion in the quadriceps and gastrocnemius (Kerschan-Schindl, *et al.*, 2001) and intramuscular temperature (Cochrane, *et al.*, 2010, Cochrane, *et al.*, 2008). WBV is also thought to modulate muscle stiffness by augmenting tissue temperature, thereby changing intrinsic mechanical properties (Bleakley and Costello, 2013, Noonan, *et al.*, 1993, Point, *et al.*, 2018). These findings suggest that WBV may have the potential to alter the non-reflex component of spastic hypertonia after stroke. Although WBV has the potential to modify both the reflex and non-reflex components of spastic hypertonia, its effect in people with central nervous system disorders (e.g., stroke,

cerebral palsy and spinal cord injury) is unclear (Huang, *et al.*, 2017). Among the scarce reports, most studies used the Modified Ashworth Scale (MAS) to measure hypertonia (Huang, *et al.*, 2017). However, the MAS cannot distinguish the reflex and non-reflex components of spastic hypertonia. Another limitation is that the MAS does not have the sensitivity to determine changes in hypertonia over time (Sunnerhagen, 2010). One method of investigating changes in the excitability of the spinal-reflex pathway is by recording an electrically induced H-reflex of Ia fibers (Voerman, *et al.*, 2005). Recording the H-reflex is an advantageous method for studying this pathway because it bypasses the muscle spindles and directly influences local change in motor neuron excitability and synaptic transmission (Voerman, *et al.*, 2005).

In addition to investigating the role of the reflex in modulating spastic hypertonia, examining the role of the mechanical properties and vascularity of muscle may also provide important insights. Ultrasound elastography is an established, non-invasive means of measuring these parameters. Supersonic shear wave ultrasound has been shown to be a valid and reliable tool to measure muscle stiffness (Lacourpaille, *et al.*, 2012). A link has also been established between muscle stiffness and spasticity (Gao, *et al.*, 2018, Lee, *et al.*, 2015). However, the effects of WBV on post-stroke muscle stiffness have not yet been determined. As previously stated, the vascularity of muscle tissue is also influenced by WBV. The vascularity index is generated from the Doppler ultrasound measurement that has been used to determine muscle blood perfusion (Chen, *et al.*, 2012, Kerschan-Schindl, *et al.*, 2001). To our knowledge, no studies have reported the use of these techniques to systematically quantify the effects of WBV on the mechanical

properties and vascularity of stimulated muscle tissue in individuals with chronic stroke.

A thorough mechanistic investigation into the physiological effects of WBV on spastic hypertonia may enhance our understanding of the potential benefits of this modality. This study therefore aimed to investigate the acute effect of WBV on the soleus H-reflex and the blood perfusion and stiffness of the medial gastrocnemius (MG) muscle in the paretic and non-paretic limbs of individuals with chronic stroke. It was hypothesized that WBV would result in inhibition of the H-reflex, increased muscle blood perfusion and decreased muscle stiffness in both paretic and non-paretic MGs muscle (Hypothesis 1). It was also hypothesized that the changes in the aforementioned outcomes would differ between the paretic and non-paretic sides (Hypothesis 2).

6.3 Method

6.3.1 Participants

People with chronic stroke were recruited from the community from May 2018 to September 2018 using convenience sampling. The inclusion criteria were (1) adult with a diagnosis of a hemispheric stroke >6 months, (2) medically stable, (3) able to stand independently for at least 1 minute and (4) MAS score >1 measured at the ankle plantar flexors. The exclusion criteria were (1) brainstem or cerebellar stroke, (2) other neurological condition, (3) serious musculoskeletal or cardiovascular disease, (4) metal implants or recent fractures in the lower extremities or spine, (5) fresh skin wound in lower extremities, especially popliteal fossa and (6) other severe illnesses or contraindication for exercise. The study was approved by the Human Subjects Ethics Sub-committee of the University and was

registered at ClinicalTrials.gov (NCT03015545). All of the participants provided written informed consent prior to data collection.

6.3.2 Experimental design and procedures

This was a single-blinded, randomized, split-leg, cross-over trial to investigate the acute effect of WBV on H-reflex, leg muscle blood volume and leg muscle elasticity. This design was chosen to reduce the effects of the confounding variables that may occur when comparing different subject groups (Pandis, *et al.*, 2017).

After being screened for eligibility, the participants underwent two laboratory assessment sessions (one to record H-reflex and another for ultrasound muscle elasticity and vascularity index measurements) in a randomized order generated by opening an opaque envelope containing a preassigned, computer-generated random sequence. Each session was separated by at least 24 hours but no more than 72 hours. During each session, all of the participants experienced four test conditions: (1) WBV intervention with measurement of paretic leg; (2) WBV intervention with measurement of non-paretic leg; (3) no-WBV condition with measurement of paretic leg; (4) no-WBV condition with measurement of non-paretic leg. Laboratory assessments were conducted immediately before the intervention (at t_0) and each minute for 5 minutes after the termination of the intervention (t_1, t_2, t_3, t_4 and t_5). The intervention and measurement sequences were randomly assigned (Figure 1). Based on the results of our pilot trial, a minimum of 15 minutes of rest between trials was given to ensure the wash-out period was sufficient. Each assessment session lasted for approximately 2.5

hours and was conducted in the same university laboratory with the temperature kept constant at 25 °C.

Demographic information was obtained through patient interviews during the initial assessment. Motor function of the paretic leg was assessed by a physiotherapist using the Fugl-Meyer Assessment for the lower limbs (FMA-LL), with higher scores indicating less impaired motor function (Sullivan*, et al.*, 2011). Ankle plantar flexor spasticity was rated using the MAS, with a higher score indicating more severe spasticity (Bohannon and Smith, 1987).

All of the measurements, including the H-reflex test, ultrasonography and clinical assessments, were performed by a researcher blinded to the intervention. The intervention was facilitated by a different researcher, who was not involved in the assessment of participants. The participants were required to refrain from strenuous exercise, stretching, alcohol, caffeine and any medications affecting the central nervous system for a period of 12 hours prior to the assessment (Armstrong*, et al.*, 2008).

6.3.3 WBV exercise protocol

The participants were required to stand barefoot on a vertical WBV platform (Fitvibe Excel, GymnaUniphy, Belgium) with knees flexed at 60° (i.e., in a squatting position) in both the WBV and no-WBV conditions. In the WBV condition, the WBV was set at a frequency of 30 Hz with an amplitude of 1.5 mm, which was validated using an accelerometer (Dytran Model 7523A5, Chatsworth, Canada). This WBV setting is considered adequate and safe because the transmissibility of the vibration stimulus to the head is low (transmissibility <0.2) but sufficient for transmission to the legs (transmissibility >0.6)

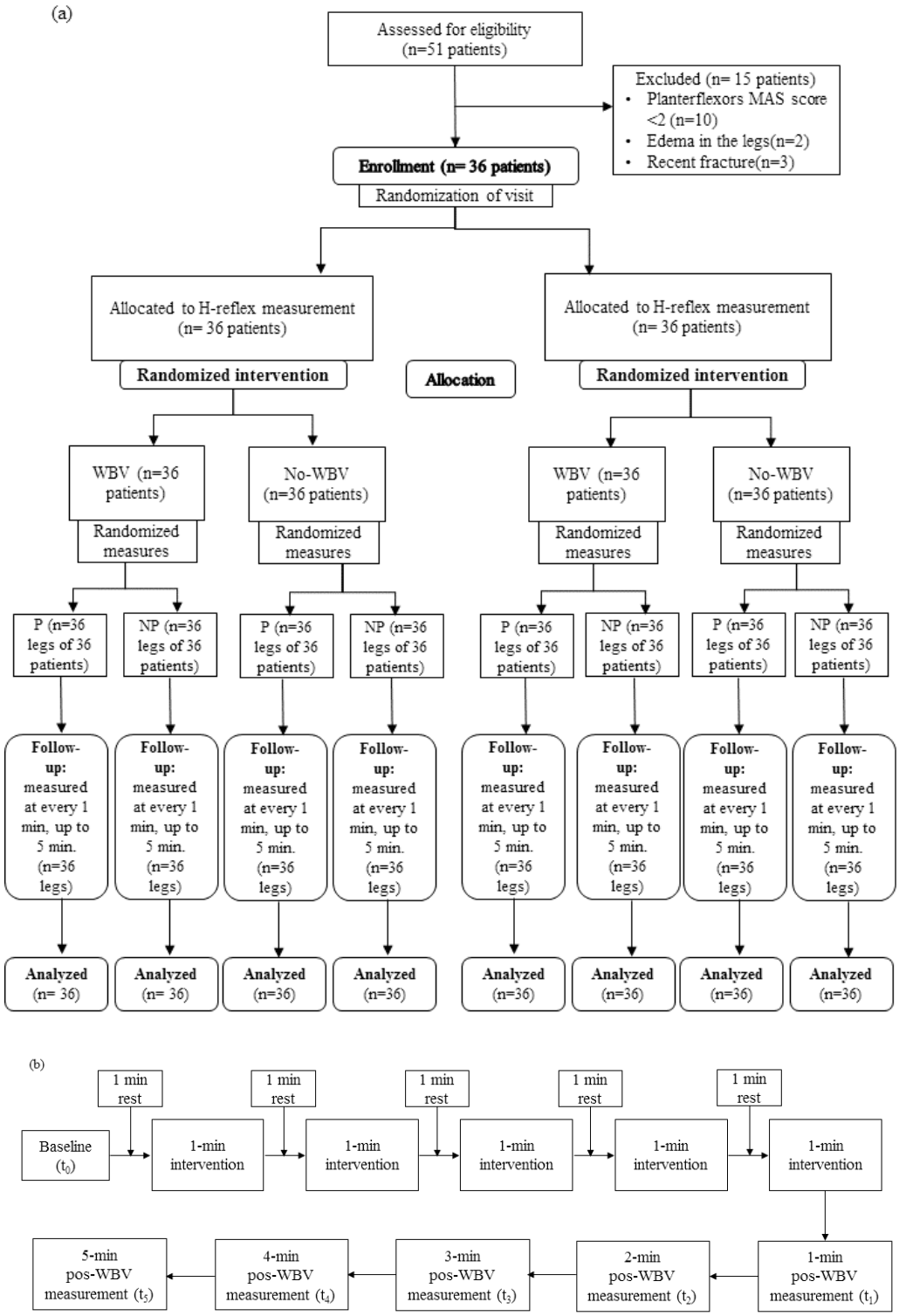


Figure 6-1 Experimental design

(a) Each participant underwent two assessment sessions, one for soleus H-reflex measurement and the other for ultrasonographic scanning of the medial gastrocnemius muscle. During each visit, the participants underwent two experimental conditions (with or without WBV). The above measurements were taken in both paretic and nonparetic legs. Thirty-six individuals with chronic stroke completed all assessment procedures.

(b) Each intervention included five 1-minute bouts with at least 1 minute of rest between intervals. Measurements were made before the intervention (i.e., t_0) and every minute after the termination of the intervention up to 5 minutes (i.e., t_1, t_2, t_3, t_4, t_5).

(Huang, *et al.*, 2018). In the no-WBV condition, the WBV device was turned off. Each condition consisted of five 1-minute bouts with at least 1 minute of rest between them. During each trial, the participants were asked to place their feet parallel a shoulder's width apart while distributing their body weight over each foot as evenly as possible. During each resting period, the participants were required to stand comfortably. A researcher provided standby supervision to ensure that safety and correct posture were maintained. The exercise was terminated immediately if adverse symptoms (e.g., fatigue or dizziness) were reported by the participant.

6.3.4 H-reflex measurement

The soleus H-reflex was measured using percutaneous stimulation of the tibial nerve while the participant assumed an erect standing position on the WBV platform (Hortobagyi, *et al.*, 2014, Ritzmann, *et al.*, 2013). After proper skin preparation, the receiving electrode (Nicolet Viking, Natus Medical Inc., Wisconsin, USA; 15 mm diameter) was positioned on the soleus muscle approximately 2 cm below the inferior margin of the two heads of the gastrocnemius muscle (Armstrong, *et al.*, 2008, Games and Sefton, 2013). The reference electrode was placed at the base of the Achilles tendon insertion at the approximate level of the medial malleolus. The ground strap (Nicolet Viking, Natus Medical Inc., Wisconsin, USA) was placed over the proximal tibial head. All of the electrodes were connected to the Nicolet Viking Select electrodiagnostic system (Nicolet Viking, Natus Medical Inc., Wisconsin, USA). Calibrated surface impedances were lower than 5 kΩ. The signals were sampled at rates of 10 kHz, amplified by 1000, band-passed filtered between 2 Hz and 5 kHz and the sweep time was 5 ms per division (Jabre, 1981). A bipolar electrode (Nicolet Viking,

Natus Medical Inc., Wisconsin, USA) was placed over the tibial nerve in the popliteal fossa (McBride*, et al.*, 2010), and the position of the probe was marked on the skin with semi-permanent pen to ensure a constant stimulation site for all trials.

The H-reflex was elicited using a constant current with a square-wave pulse of 1 ms duration every 5 s while increasing the stimulus intensity by 0.1 mV until the maximum M wave (M_{max}) of the soleus was determined (Games and Sefton, 2013, Hortobagyi*, et al.*, 2014). Peak-to-peak amplitudes of the H-reflex and M-wave were automatically detected and calculated by the Nicolet Viking Select Master Software program (Nicolet Viking, Natus Medical Inc., Wisconsin, USA). The stimulation intensity of the H-reflex was then set at 10% of that required to evoke the M_{max}. The M-wave was continuously monitored to ensure that the Ia afferents were excited to the same degree during each stimulation (Hopkins*, et al.*, 2009, Kipp*, et al.*, 2011, Sayenko*, et al.*, 2010). For each test condition, three soleus H-reflex responses were evoked for each time point. Average H-reflex, M wave and H/M ratio values for each time point were computed. During the stimulation, the participants were required to assume an erect standing posture and direct their gaze toward a fixed object placed at eye-level on the wall (Hortobágyi*, et al.*, 2014).

6.3.5 Ultrasound measurement: muscle stiffness and blood perfusion

Muscle stiffness and blood perfusion of the bilateral MG were assessed before and after WBV using an Aixplorer ultrasound scanner (Supersonic Imagine, Aix-en-Provence, France) coupled with a linear transducer array (4–15 MHz SuperLinear 15-4, Vermon, Tours, France). The supersonic shear imaging (SSI)

technique has been shown to be a reliable and valid tool for measuring the elasticity of the MG (Lacourpaille*, et al.*, 2012). As the elastic modulus of muscle (i.e., its stiffness) varies depending on joint position (Koo*, et al.*, 2014), we carefully controlled the position of the ankle and knee joints during all assessments. The participants sat comfortably on a high chair with the knee fully extended at 180° and the ankle fixed in a neutral position (i.e., at 90°) with a customized ankle stepping frame determined by the goniometer (Baseline HiRes Plastic 360 Degree ISOM, Fabrication Enterprises, White Plains, NY). Measurement points were marked on the skin to ensure that the ultrasound transducer was placed at the same site for all measures. Longitudinal and transverse points were marked at the proximal third of the tibial length between the crease of the popliteal fossa and the base of the Achilles tendon at the level of the medial malleolus (Kerschan-Schindl*, et al.*, 2001, Lacourpaille*, et al.*, 2012). As the orientation of the transducer in relation to the muscle fascicle influences the propagation of the ultrasound beam (Miyamoto*, et al.*, 2015), the transducer was placed parallel to the muscle fascicles. Gel was applied between the transducer and the skin surface to minimize impedance and compression.

Muscle stiffness was measured in SSI mode using the musculoskeletal preset of the Supersonic system (Supersonic Imagine, Aix-en-Provence, France). During the measurement, the transducer was placed parallel to the muscle fascicles as confirmed by the transposed B-mode images (Koo*, et al.*, 2014),because the transducer position in relation to the direction of fascicles may influence the elastography outcome (Miyamoto*, et al.*, 2015). Three images were captured within 10 s at every time point.

Using the directional color power Doppler (dCPD) mode (Supersonic Imagine, Aix-en-Provence, France), a dCPD sonogram of the MG was captured in the transverse plane to quantify intramuscular blood perfusion. The size of the color box was set to cover the entire cross-sectional area of the MG muscle. Doppler ultrasound settings were standardized for high sensitivity with a low wall filter to allow detection of vessels with low blood flow and low color noise (Ying, *et al.*, 2009). The color gain was first increased to a level that showed color noise and then progressively decreased until the color noise was no longer apparent (Ying, *et al.*, 2009). Color gain was kept constant for the same leg across all measurements. For each leg, three videos were captured at each time point.

6.3.6 Data processing

The magnitude of the H-reflex responses and M-wave were calculated as the means of the three responses at each time point for each participant. The H/M ratio was computed as the H-reflex response divided by the corresponding M-wave.

The shear modulus of the MG was measured over the region of interest (ROI) corresponding to the largest muscular region without visible intramuscular fascia (Point, *et al.*, 2018). The average values from three images at each time point were calculated.

The intramuscular blood perfusion volume was quantified by the vascular index (VI) (Chen, *et al.*, 2012, Ying, *et al.*, 2009), a computerized method analogous to Newman's grading scale (Chen, *et al.*, 2012, Newman, *et al.*, 1997). Data were processed using MATLAB2016a (Mathworks, Natick, MA, USA) with custom-written scripts. First, the dCPD videos were exported in "mp4" format from the Supersonic ultrasound system and sequenced in "jpeg" format. Next, the boundary of the MG muscle (i.e., the ROI) was manually outlined and extracted from the images. The total number of pixels in the ROI and the number of dCPD coded color pixels were then counted (Ying, *et al.*, 2009). The vascular index (VI) of the MG muscle was calculated as the number of color pixels within the ROI/total number of pixels within the ROI (Appendix 1) (Ying, *et al.*, 2009). Finally, for each of the three videos, the three frames (i.e., images) with the highest VI values were identified and the median value (VI_{video}) was computed. For each leg at each time point, the maximum VI (VI_{max}) was calculated based on the average value of the three VI_{video} results.

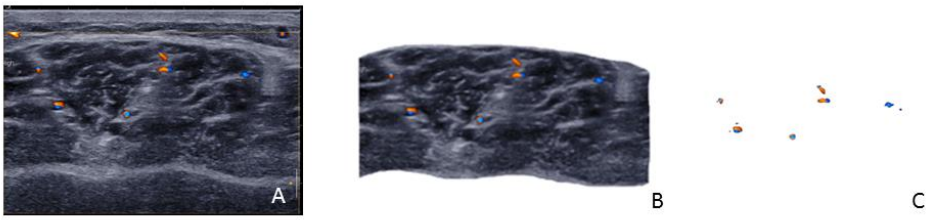


Figure 6-2 Sequential process of image analysis of the directional color power Doppler (dCPD) sonogram.
(A) Processing by the customized algorithm with Matlab. (B) The border of the medial gastrocnemius muscle (i.e., the region of interest [ROI]) was manually outlined and then extracted by trimming the unwanted area from the outlined area. The total number of pixels within the ROI was counted by the algorithm. (C) The color pixels coded by the dCPD were extracted by eliminating the gray-scale pixels, and the number of color pixels was counted by the algorithm. The vascular index (VI) of the medial gastrocnemius muscle was calculated by the following equation: VI of the MG = Number of color pixels within the ROI/Total number of pixels within the ROI. For this image, the VI value is 0.83%.

6.3.7 Statistical analysis and sample size calculation

All statistical analyses were conducted using SPSS 22 (IBM Corp., Somers, NY, USA). The dependent variables in statistical tests were soleus H/M ratio and the shear modulus and maximum vascular index (VI_{max}) of the MG. Data normality was verified using the Shapiro-Wilk test. The baseline values (i.e., at t_0) of all the dependent variables of the same leg were compared using paired-t tests. To ensure that the M-wave did not change over time in response to the intervention, paired t-tests were conducted to compare M-waves across trials.

To test Hypothesis 1, two-way repeated measures ANOVA (within subject factors: intervention (2 levels: with or without WBV) and time points (6 levels: t_0~t_5)) was used to compare each dependent variable for the paretic and the non-paretic legs. The results for the time × intervention interaction effect generated from the ANOVA models provide information about whether the changes in the outcome measures over time differed between the WBV and no-WBV conditions. When a significant time × intervention interaction was identified, post-hoc one-way repeated measures ANOVA analyses were conducted to examine the changes in outcomes over time for each experimental condition. To test Hypothesis 2, two-way repeated-measures ANOVA (within-subject factors: 2 sides and 6 time points) was used to compare each dependent variable between the paretic and non-paretic legs across time. In this ANOVA model, the time × side interaction provides information about whether the changes in outcome measures at each time point were different between the paretic and non-paretic sides. The sphericity assumptions of the ANOVA tests were verified using the Mauchly test. Greenhouse-Geisser adjustments were made if the sphericity assumptions were not met. Partial eta squared (η_p^2) values of 0.14, 0.06 and 0.01 represent large,

medium and small effect sizes, respectively (Levine and Hullett, 2002). A significance level of $p \leqslant 0.05$ was set for two-way repeated ANOVA models and a more stringent significance level of $p \leqslant 0.01$ was set for post-hoc one-way repeated-measures ANOVA. Bonferroni correction for multiple comparisons was performed when appropriate.

The sample size estimation was based on evidence from previous studies investigating the acute effect of WBV on H-reflex in people with stroke (Chan, *et al.*, 2012) and intramuscular blood perfusion in a young healthy population (Kerschan‐Schindl, *et al.*, 2001) using G*Power 3.1 (Faul, *et al.*, 2007). Chan et al. demonstrated that WBV could significantly reduce the H/M ratio in both legs with medium to large effect sizes (Cohen's d of 0.70–0.90) (Chan, *et al.*, 2012). Kerschan-Schindl et al. found that WBV could significantly increase the intramuscular blood volume based on Newman's score among young adults, with a large effect size (Cohen's d of 1.00) (Kerschan‐Schindl, *et al.*, 2001). Currently, no study has reported the effect of WBV on muscle elasticity. Thus, a conservative medium effect size (f = 0.25) was expected in this study. Based on ANOVA analysis, with an alpha value of 1%, power of 80% and an attrition rate of 10%, the minimum required sample size was estimated to be 36 participants for this study.

6.4 Results

6.4.1 Characteristics of participants

Thirty-six participants with chronic stroke (mean age: 61.4 ± 6.9 years) completed all assessments. No adverse effects were reported over the course of the study. The demographic results are summarized in Table 1. The median lower-limb FMA score was 27 out of 34 (interquartile range: 25–29), indicating mild to moderate impairment. The median MAS score for the ankle planter flexors was 2 out of 4 (interquartile range: 2–4), indicating mild to severe spasticity. There was no significant difference in the soleus H/M ratio, vascular index or shear modulus of the MG for each leg at baseline, irrespective of testing conditions ($p \geq 0.05$).

Table 6-1 . Characteristics of participants(n=36) *

Variable[a]	Value		p
Age, year	61.8 (7.0)		
Sex, men/women, n	26/10		
Body mass index, kg/m^2	25.7 (3.2)		
Total number of commodities, n†	2 (1-2)		
Total number of medications, n†	2 (1-4)		
Post-stroke duration, year	8.9 (5.0)		
Type of stroke, hemorrhagic/ischemic, n	13/23		
Side of paresis, left/right, n	18/18		
	Paretic side	**Non-paretic side**	
Fugl-Meyer Lower limb motor score (full score: 34) †	27 (25-29)	--	
Planterflexor Modified Ashworth Scale scores (range:0-5) †	3 (2-4)	--	
Planterflexor Modified Tardieu Scale scores (range:0-5)†	2 (2-3)	--	
Soleus H/M ratio	4.24 (2.24)	2.17 (1.47)	0.013‡
Vascular index of medial gastrocnemius	0.64 (0.40)	0.82 (0.63)	0.063
Shear modulus of medial gastrocnemius, kPa	25.05 (5.19)	25.14 (4.95)	0.298

* Mean (Standard deviation) indicated unless specified otherwise.

† Median (Interquartile range)

‡ Significant difference between the paretic and non-paretic side ($p<0.05$)

6.4.2 Acute effect of WBV on H-reflex

A significant time × intervention effect of soleus H/M ratio was found for both the paretic ($p < 0.001$, $\eta_p^2 = 0.234$) and non-paretic ($p < 0.001$, $\eta_p^2 = 0.268$) sides, indicating that the change in H/M ratio differed over time between the WBV and control conditions. On both sides, a significant change in H/M ratio over time was observed in the WBV condition (paretic side: $p < 0.001$, $\eta_p^2 = 0.249$; non-paretic side: $p < 0.001$, $\eta_p^2 = 0.231$) but not in the control condition ($p \geq 0.112$). Post-hoc analysis showed that the H/M ratio decreased significantly after WBV exposure (H/M ratio absolute change on paretic side: mean = 0.61 (95%CI: 0.31 to 0.91), p = 0.001; non-paretic side: mean = 0.34 (95%CI: 0.21 to 0.46), p = 0.001) and inhibition of H-reflex activity was sustained for 4 minutes in the paretic leg and 3 minutes in the non-paretic leg. A significant time × side intervention was observed in the WBV condition ($p < 0.001$, $\eta_p^2 = 0.231$), indicating that the absolute reduction in the H/M ratio was greater on the paretic side after the WBV intervention in comparison to the non-paretic side (Figure 2).

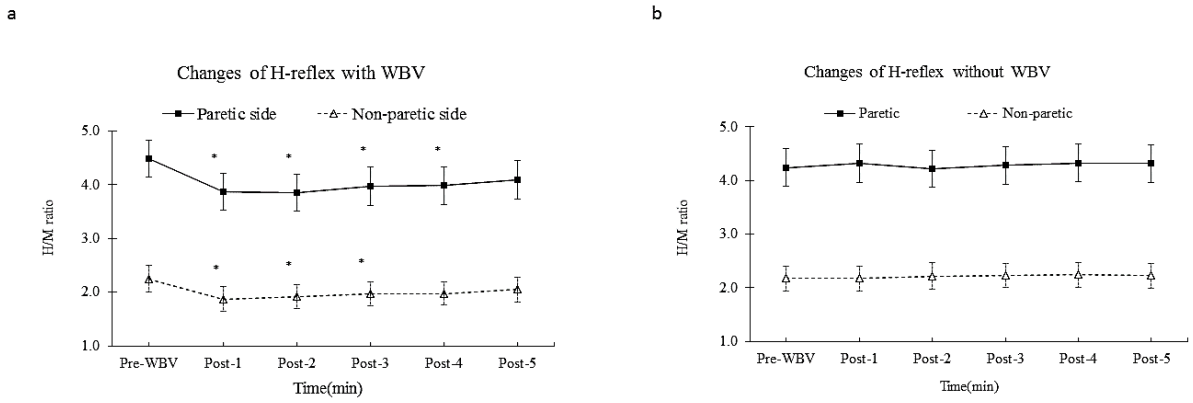
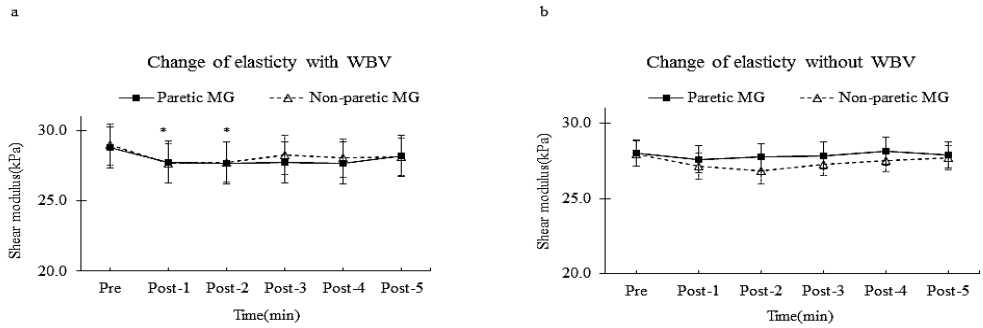


Figure 6-3 Acute effect of WBV on H-reflex
The soleus H-reflex immediately before and every minute after intervention with WBV (a) and without WBV (b). *Significant difference compared with baseline ($p<0.01$ with Bonferroni correction).

6.4.3 Acute effect of WBV on muscle stiffness

The time × intervention effect of the shear modulus of the MG was not significant for either the paretic or non-paretic sides (p = 0.307 and 0.513, respectively). The time × side effect was not significant for the WBV (p = 0.089) or control conditions (p = 0.400) (Figure 4).



3.1.1 Difference in WBV-induced muscle activation between the paretic and non-paretic side

There was no significant difference in WBV-induced muscle activation between the two sides, with the exception of the TA, where the EMG% was higher on the non-paretic than the paretic side (*P*=0.047).

effect of WBV on muscle stiffness

6.4.4 Acute effect of WBV on intramuscular blood perfusion

A significant time × intervention interaction effect for the vascularity index of the MG was observed in the non-paretic leg alone (p = 0.043, η_p^2 = 0.071). The same interaction effect in the paretic leg was marginal (p = 0.066). A significant time effect was observed in the WBV condition for the paretic side (p = 0.001, η_p^2 = 0.105) and non-paretic side (p <0.001, η_p^2 = 0.134), but not for the control condition (p ≥0.052). No significant time × side interaction was observed for either the WBV (p = 0.102) or control conditions (p = 0.180). Post-hoc analysis showed that the vascular index increased significantly after WBV exposure on both sides and was sustained for up to 3 minutes on the paretic side and 5 minutes on the non-paretic side (Figure 6-4).

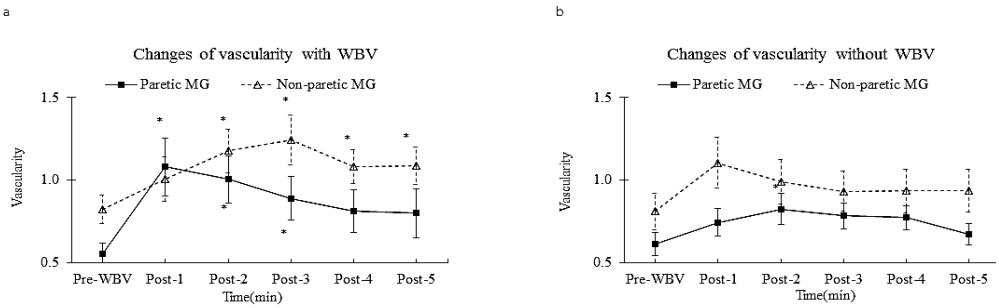


Figure 6-4 Acute effect of WBV on intramuscular blood perfusion
The vascularity index of the medial gastrocnemius muscle immediately before and every 1 minute after intervention with WBV (a) and without WBV (b). *Significant difference compared with baseline ($p<0.01$ with Bonferroni correction).

6.5 Discussion

To our knowledge, this is the first study to evaluate the acute effects of WBV on H-reflex, muscle blood volume and muscle stiffness in the MG in individuals with chronic stroke. Our results indicate that WBV can significantly inhibit the soleus H-reflex and increase the blood volume in the MG immediately after WBV. No significant changes in the shear modulus of the MG were observed.

6.5.1 Acute effect of WBV on H-reflex

The inhibition of the H-reflex was observed in the WBV condition but not the control condition. More specifically, the relative H/M ratio decreased by 14% and 17% from the baseline immediately following vibration and was sustained by up to 4 minutes on the paretic side and 3 minutes on the non-paretic side. These results are in general agreement with those previously reported for healthy young adults (Ahmadi, *et al.*, 2015, Apple, *et al.*, 2010, Armstrong, *et al.*, 2008, Cakar, *et al.*, 2014, Games and Sefton, 2013, Harwood, *et al.*, 2017, Hortobágyi, *et al.*, 2014, Kipp, *et al.*, 2011, Kramer, *et al.*, 2013, Ritzmann, *et al.*, 2013) and people with spinal cord injury (Sayenko, *et al.*, 2010) or stroke (Chan, *et al.*, 2012). These studies also described an immediate inhibition of the soleus H-reflex after WBV.

However, the degree and duration of suppression ranged from 6% to 60% and from 1 minute to 20 minutes across the studies. This may be due to methodological inconsistencies between studies with regards to WBV frequency, total exposure time, rest duration, type of vibration and discrepancies in H-reflex measurement procedures such as participant positioning and electrical stimulation intensity (Games and Sefton, 2013, Hortobágyi*, et al.*, 2014).

The study by Chan et al., which is the only other examination of the effect of WBV on H-reflex in people with stroke, reported that the H_{max}/M_{max} ratio decreased by more than 40% after a 20-minute WBV bout (frequency 12 Hz, amplitude 4 mm) (Chan*, et al.*, 2012). When compared with the control group, the WBV group showed a reduction in H_{max}/M_{max} on the non-paretic side rather than the paretic side (Chan*, et al.*, 2012). In contrast, the current study found a significant time × intervention effect on H/M ratio for both the paretic and non-paretic sides. It should be noted that the H-reflex measurement methodology used by Chan et al. was not described in detail. They also reported that several assessments, including the H-reflex of bilateral legs, MAS, timed up-and-go test,and 10-m walking test were conducted after only a single intervention. The time point and sequencing of these measurements were not clearly specified. If the H-reflex measurements were performed following the other assessments, any immediate effect of the WBV may have diminished at the time of measurement. In addition, the study by Chan et al. did not describe the participants' body position during the H-reflex measurement. Other studies suggest patient positioning is crucial during H-reflex testing (Palmieri*, et al.*, 2004, Voerman*, et al.*, 2005). In the current study, the H-reflex was measured in an erect standing position, which provides reliable readings (Voerman*, et al.*, 2005). Given the functional nature of

a weight-bearing assessment scenario, our results may provide a more clinically relevant interpretation of the effect of WBV on the H-reflex (Games and Sefton, 2013).

6.5.2 Acute effects of WBV on muscle elasticity

The results indicate no significant changes in muscle elasticity after WBV exposure. Although WBV has been shown to increase muscle blood volume and metabolic rate (Games and Sefton, 2013, Liao*, et al.*, 2015) leading to increased muscle temperature (Cochrane*, et al.*, 2010), this change may be negligible. A previous study showed that after 10 minutes of WBV (frequency 26 Hz, amplitude 3 mm), muscle temperature increased by only 1°C (Cochrane*, et al.*, 2010). Subtle changes in temperature over a short period may not be sufficient to induce changes in the mechanical properties of muscle tissue (Point*, et al.*, 2018). Ness et al. suggested that an eight-day WBV training protocol could significantly reduce quadriceps spasticity as measured by the pendulum test (Ness and Field-Fote, 2009). A randomized controlled trial by Pang et al. also provides preliminary evidence that 8 weeks of WBV training reduced quadriceps MAS score in people with chronic stroke (Pang*, et al.*, 2013a). Based on the findings of the current study, the reduction in leg muscle hypertonia following WBV training reported in previous studies is likely to be due to a reduction in the H-reflex rather than a change in muscle elasticity.

6.5.3 Acute effects of WBV on muscle blood volume

In the current study, a computation approach capable of detecting subtle changes in muscle blood volume was used to quantify the vascularity of the MG (Chen*, et al.*, 2012, Ying*, et al.*, 2009). People with chronic stroke may experience

reduced blood flow and decreased arterial diameter in the hemiparetic limb (Billinger, 2010). Among the participants in this study, baseline vascular indices tended to be higher on the paretic side compared with the non-paretic side ($p = 0.063$), suggesting reduced blood perfusion in the paretic MG.

The vascular index increased on both the paretic and non-paretic sides following WBV and did not increase during the control condition. WBV has been shown to increase oxygen consumption without any substantial changes in blood pressure or heart rate among individuals with chronic stroke (Liao*, et al.*, 2015). Moreover, vibration may lead to increased shear stress in the vascular endothelium due to blood flow inertia, thereby promoting the release of endothelial-derived vasodilators such as nitric oxide (Sackner*, et al.*, 2005). Thus, increases in both metabolic demand and vasodilatory factors may influence muscle blood volume after WBV. Similar results have been observed in young healthy adults (Games and Sefton, 2013, Kerschan-Schindl*, et al.*, 2001, Robbins*, et al.*, 2014) and people with spinal cord injury (Herrero*, et al.*, 2011). By using Doppler ultrasound with Newman's processing methods, Kerschan-Schindl et al. found a twofold increase in gastrocnemius muscle perfusion immediately following a 9-minute bout of WBV (frequency 26 Hz, amplitude 1.5 mm) among young adults (Kerschan-Schindl*, et al.*, 2001). A study by Games et al. utilizing near-infrared spectroscopy in young adults found an increase in total hemoglobin in the MG after a 5-minute WBV bout (frequency 50 Hz, amplitude 2 mm) (Games and Sefton, 2013). Robbins et al. reported that the median blood flow velocity of the dorsalis pedis artery increased twofold after 5 minutes of WBV (frequency 40 Hz, amplitude 1.9 mm) and the effect was sustained for 3 minutes (Robbins*, et al.*, 2014). In patients

with spinal cord injury, the mean blood velocity increased after a 3-minute WBV bout (frequency 30 Hz, amplitude 2.5 mm) and the effect was sustained for 1 minute after the termination of WBV (Herrero, *et al.*, 2011). Among the participants with chronic stroke recruited for the current study, the vascular index of the MG gradually increased twofold and was sustained for up to 3 minutes on the paretic side and 5 minutes on the non-paretic side. This is comparable with previous reports (Games and Sefton, 2013, Herrero, *et al.*, 2011, Kerschan-Schindl, *et al.*, 2001, Robbins, *et al.*, 2014). The difference in recovery duration between the paretic and non-paretic sides may be due to an altered vascular response to exercise (Billinger, 2010) and reduced arterial compliance in the paretic limb of chronic stroke survivors (Pang, *et al.*, 2013b). Nevertheless, these results demonstrate that the intramuscular perfusion of stroke survivors can be increased by WBV.

6.5.4 Clinical application

The inhibition of the H-reflex and the augmentation of blood flow in the ankle plantar flexors among individuals with chronic stroke demonstrated in this study may have important clinical implications. First, research has demonstrated that soleus H-reflex inhibition is associated with improved static (Koceja, *et al.*, 1995) and dynamic postural control (Kawaishi and Domen, 2016) in healthy adults. A meta-analysis revealed that WBV significantly improved balance ability and mobility among older adults (Lam, *et al.*, 2012). However, a previous study of WBV training for stroke survivors failed to identify any treatment effect on balance as measured by the Berg Balance Scale (Liao, *et al.*, 2014). Therefore, it is worth using other more sensitive measurement tools to evaluate the effect of

WBV training on balance performance among people with stroke. Second, our results show that WBV produced immediate motoneuronal excitability and muscle blood perfusion effects. Similarly, muscle spasticity has been shown to be associated with reduced blood perfusion in people with spinal cord injury (Dhindsa, *et al.*, 2011). Thus, WBV may have potential clinical applications in managing spasticity. Future research is needed to investigate the long-term effect of WBV in modulating spasticity after stroke. Third, impaired blood perfusion has been observed in the paretic limbs among chronic stroke survivors (Billinger, *et al.*, 2009, Ivey, *et al.*, 2004), which may contribute to metabolic dysfunction and functional decline (Billinger, 2010, Ivey, *et al.*, 2006). Arterial remodeling and increased basal blood flow has been shown to be induced by resistance training (Ivey, *et al.*, 2010). WBV had a comparable effect by increasing microcirculation in the skeletal muscles of young healthy adults (Beijer, *et al.*, 2015). Thus, WBV could be a substitute training modality to increase peripheral circulation and may be well tolerated compared with other forms of exercise, as it poses minimal risk to frail stroke survivors. Future research focusing on the clinical applicability of WBV may further elucidate the training effect and treatment periodization.

6.5.5 Study limitations

This study has several limitations. First, the H-reflex was used as the main outcome measure rather than clinical tests such as the MAS and visual analog scale (VAS) of spasticity. However, measuring the MAS after each WBV bout would require the participants to frequently change their body position. In addition, the MAS and VAS are gross measures of hypertonia (on an ordinal scale) and are somewhat subjective, whereas the H-reflex measurement provides an objective

and more precise estimate (being a continuous variable)(Platz*, et al.*, 2005). The MAS and VAS also do not differentiate between the reflex and non-reflex component of hypertonia, whereas the H-reflex specifically measures the reflex (neurological) component(Platz*, et al.*, 2005). Finally, only participants with mild to moderate stroke impairments were studied. Individuals with more severe motor impairment warrant further investigation. Nevertheless, as reflected by the MAS scores, our sample did include individuals with a wide range of severity of spasticity.

6.6 Conclusion

Whole-body vibration has a short-term effect on inhibiting the soleus H-reflex and increasing leg muscle blood perfusion volume in people with chronic stroke, but it has no immediate effect on leg muscle stiffness.

6.7 Acknowledgement

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6.8 Reference

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7 Chapter 7: Conclusions

Spastic hypertonia is a common phenomenon for people with chronic stroke. It has been suggested that, in patients with chronic stroke, spastic hypertonia has two components, namely, the reflex component (e.g., hyperreflexia) and the non-reflex component (e.g., changes in the mechanical properties of the affected muscles) (Katz and Rymer, 1989). This thesis shows that chronic stroke patients with spastic hypertonia had higher H-reflex amplitudes (Chapter 6) and alterations in the architectural properties (i.e., degrees of pennation and echogenicity) of the paretic leg muscles (Chapter 3). These changes in muscle properties may contribute to poor functional mobility (Chapter 3).

Whole-body vibration (WBV), which has gained its popularity in rehabilitation and sports practice and research, may have the potential in the management of spastic hypertonia, due to its reported effects on muscles and the nervous system. Thus, the general objective of this thesis was to investigate the acute effects of WBV on spastic hypertonia for people with chronic stroke. This purpose was achieved by settling two important questions: (1) outcome measures: to select appropriate outcome measures to examine the reflex and non-reflex component of spastic hypertonia; (2) intervention protocol: to devise a safe and efficient WBV training protocols.

Supersonic Shear Imaging, a most advance ultrasound elastography technique was used to investigate the passive muscle stiffness of medial gastrocnemius muscles (i.e. non-reflex component of spastic hypertonia) for chronic stroke survivors. The results in Chapter 3 suggests that this measure was

reliable and feasible for the medial gastrocnemius muscles in people with chronic stroke.

As the WBV is indirectly applied on the body parts, examination of the transmission and signal purity of WBV signals in the human body could provide valuable insights into the safety and efficacy of WBV application. The results generated from Chapter 4 suggested that vibration transmissibility and signal purity were influenced by the vibration amplitude, frequency, body postures, and their interaction for chronic stroke survivors. With the exception of bilateral ankles, increased vibration frequency, amplitude, or knee flexion angle led to lower the transmissibility. The transmissibility in the paretic side was comparable to the nonparetic sides, excepting that at the ankle during tip-toe standing. In a few conditions at the paretic ankle, knee, knee and hip, more-severe leg motor impairment was correlated with greater transmissibility. No significant association was observed between the leg muscle spasticity and WBV transmissibility.

Furthermore, understanding the mechanism by which WBV exerts its effects on neuromuscular activation is essential in informing the development of WBV intervention protocols. This thesis shows that the addition of WBV to exercise led to a significant increase in muscle activation in the medial gastrocnemius and the tibial anterior (TA) and medial hamstrings, but not the vastus medialis, on both paretic and nonparetic sides among individuals with chronic stroke. The degree of activation was dependent on the vibration amplitude, frequency, and body posture. The effect of WBV was similar on the two sides except the TA. Higher muscle activation was associated with larger attenuation of the signals at more proximal anatomical sites, which supports the muscle-tuning mechanism of WBV exercise

(Chapter 5). Collectively, to activate the leg muscles, WBV with frequency at 30~40Hz, amplitude at 1.5mm and squatting position would be safe and effective setting, which was used in the final study of this thesis.

In the final study of this thesis (Chapter 6), a randomized cross-over study was done to investigate the effect of 5-minute of WBV intervention on soleus H-reflex (i.e., reflex component of spastic hypertonia) and passive stiffness and blood perfusion of medial gastrocnemius muscle (i.e. non-reflex component of spastic hypertonia) for people with chronic stroke. The results showed that the brief period of WBV could inhibit the soleus H-reflex in the paretic leg by 14% and increase the vascular index of the medial gastrocnemius muscle in the same leg by two-fold, and the effect was sustained for 3 or 4 minutes. However, no significant changes were seen in the shear modulus of the medial gastrocnemius muscle in the paretic leg after the same WBV intervention.

Overall, for clinical application, the thesis indicates that WBV is a safe training modality for people with chronic stroke. WBV frequency, amplitude, body posture can influence the WBV transmissibility, signal purity and WBV-induced muscle activation. Muscle activation could damp the vibration during the WBV. Thus, specific WBV parameters should be carefully set to achieve the intended the therapeutic purpose.

WBV has potential applications in the management of spasticity hypertonia dominated by hyperreflexia and may be a substitute method of exercise to increase peripheral circulation, particularly for frail stroke survivors who cannot participate

in other forms of exercise training. However, these postulations will require further research (Figure 7-1).

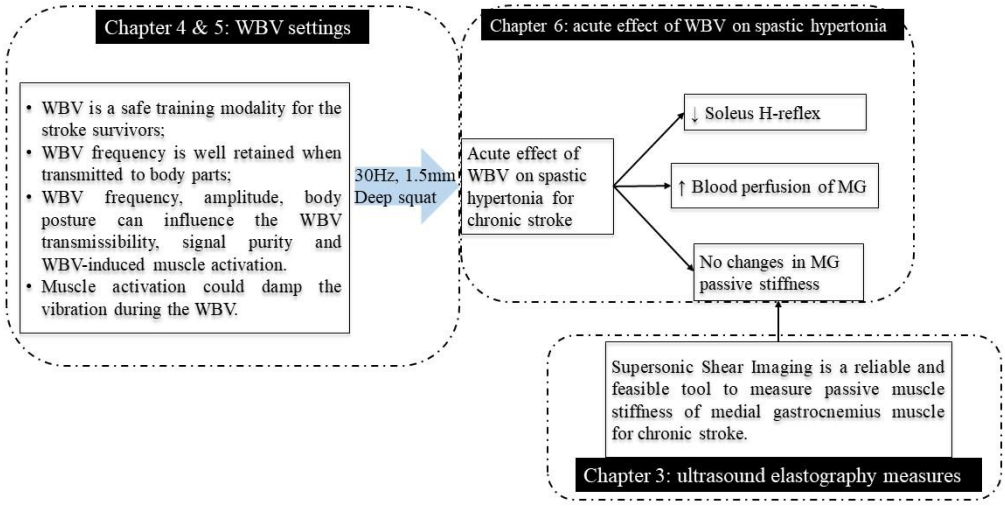

Figure 7-1 Study conclusions of each study in the thesis.

7.1 Reference

1. Katz RT, Rymer WZ: **Spastic hypertonia: mechanisms and measurement**. *Arch Phys Med Rehabil* 1989, **70**(2):144-155.

8 APPENDICES

8.1 Appendix 1. Summary of the study hypothesis and results of chapter 3-6.

Chapter	Hypothesis	Results summary
Chapter 3	1. Supersonic shear imaging is a reliable tool for measurement of the medial gastrocnemius muscle's elasticity in long-term stroke survivors;	• Shear wave ultrasound elastography is a reliable tool for the measurement of passive muscle stiffness in people with chronic stroke.
	2. No significant differences exist in passive muscle properties between the paretic and nonparetic sides among ambulatory long-term stroke survivors and between the nonparetic leg or the dominant leg of age-matched control subjects;	• Among *ambulatory chronic* stroke survivors with *mild to moderate spasticity levels*, No significant difference was found in slack angle, slack elasticity, or slope rate between the paretic side and nonparetic side in the stroke group or between the nonparetic side of the stroke group and the dominant side of the control subjects.
	3. The muscle architecture differs significantly between the paretic and nonparetic sides in ambulatory long-term stroke survivors and between the nonparetic leg of stroke survivors and the dominant leg of age-matched control subjects;	• Paretic MG demonstrated significantly lower pennation angles and greater echogenicity than the MG on the nonparetic sides of the stroke group. No significant difference was observed in these parameters between the nonparetic sides and the dominant legs of the control subjects. Individuals with stroke had significantly thicker subcutaneous fat, but no significant difference was found between the paretic and nonparetic sides.
	4. A significant association between measures of functional mobility and both passive mechanical and architectural muscle properties.	• No significant correlations were found between the parameters of elasticity–angle model and TUG. • The echogenicity of the paretic MG was significantly associated only with the duration of TUG ($r = 0.765$).
Chapter 4	1. WBV transmissibility and signal purity are influenced by vibration frequency and amplitude, body posture, and their interactions;	• The transmissibility decreased with increasing frequency in all sites except the ankles; • The transmissibility decreased with increasing amplitude in all sites except the ankles;

		• The significant frequency × posture interaction effect was found in all measured body sites. • The frequency × posture interaction effect was more prominent with high-amplitude WBV comparing to the low-amplitude WBV at the knee bilaterally; • Overall, vibration frequency and amplitude, body posture demonstrated a significant interactions effect on WBV transmissivity.
	2. Vibration signal purity are influenced by vibration frequency and amplitude, body posture, and their interactions;	• WBV signal purity showed no significant frequency × posture × amplitude interaction effects in all measured sites. • Frequency × posture interactions were significant at bilateral ankles, knees and hips. • Amplitude × posture interactions were significant in all measured sites.
	3. WBV transmissibility and signal purity demonstrate a significant difference between the paretic and nonparetic sides; and	• On the non-paretic side, there was significantly greater transmissibility in the ankle during most tip-toe standing conditions when compared with the corresponding values on the paretic side. • There was no significant difference between the paretic side and non-paretic in signal purity, regardless of the WBV conditions.
	4. WBV transmissibility is associated with the level of motor impairment or the muscle spasticity of the affected leg.	• There was no significant association of the MAS score of the knee flexors/extensors and ankle plantarflexors with transmissibility. • The FMA score was positively associated with transmissibility values measured at the paretic ankle during most tip-toe standing conditions (rho = 0.36–0.60). • The FMA score was also positively associated with the transmissibility (rho = 0.34–0.38) and signal purity (rho = 0.38–

		0.47) at the paretic knee and hip when performing a deep squat and tip-toe standing (40 Hz/high amplitude).
Chapter 5	1. Muscle activation of all tested leg muscles is significantly increased with the addition of WBV compared with the no-WBV condition;	• Adding WBV to exercise significantly increased muscle activation in the MG, TA, and MH on both the paretic and non-paretic sides of chronic stroke survivors.
	2. Muscle activation is increased when the vibration frequency or amplitude is increased under a given posture;	• The vibration higher amplitude leading to significantly greater increases in EMG for all muscle. • The higher vibration frequency lead to higher EMG for bilateral MG, bilateral MH, and bilateral TA.
	3. For a given vibration frequency and amplitude, the increase in muscle activation depends on body posture;	• A significant main effect of body posture was found in the bilateral MG, bilateral TA, and non-paretic VM. • The highest EMG ratio was found in the high squat position for the bilateral MG and TA, and the non-paretic VM
	4. Muscle activation is higher on the paretic side than on the nonparetic side during WBV;	• There was no significant difference in WBV-induced muscle activation between the two sides, with the exception of the TA, where the EMG ratio was higher on the non-paretic than the paretic side.
	5. Higher WBV-induced muscle activation is associated with lower WBV transmission in joints with more proximal locations.	• Significant negative associations were found between the transmissibility in the paretic knee and the EMG ratio of the paretic MG and TA. • Transmissibility measured at the paretic hip was significantly negatively associated with the EMG ratio of the paretic MG, TA, and MH. On the non-paretic side, the transmissibility in the knee was significantly negatively associated with the EMG ratio of the non-paretic TA, and the transmissibility in the hip was negatively correlated with the EMG ratio of the MH and VM.
Chapter 6	1. WBV would result in inhibition of the H-reflex, increased muscle blood perfusion and decreased muscle stiffness in both paretic and non-paretic MG muscle	• The inhibition of the H-reflex was observed in the WBV condition but not the control condition. More specifically, the relative H/M ratio decreased by 14% and 17% from the baseline

		immediately following vibration and was sustained by up to 4 minutes on the paretic side and 3 minutes on the non-paretic side. • The time × intervention effect of the shear modulus of the MG was not significant for either the paretic or non-paretic sides. • The vascular index increased on both the paretic and non-paretic sides following WBV and did not increase during the control condition. The vascular index of the MG gradually increased twofold and was sustained for up to 3 minutes on the paretic side and 5 minutes on the non-paretic side.
	2. The changes in the aforementioned outcomes would differ between the paretic and non-paretic sides.	• A significant time × side intervention was observed for H-reflex change in the WBV condition, indicating that the absolute reduction in the H/M ratio was greater on the paretic side after the WBV intervention in comparison to the non-paretic side. • The time × side effect of muscle stiffness was not significant for the WBV or control conditions. • No significant time × side interaction of vascularity was observed for either the WBV or control conditions.

8.2 Appendix II: Ethical approval for Chapter 3

THE HONG KONG POLYTECHNIC UNIVERSITY 香港理工大學

To	Pang Marco Yiu Chung (Department of Rehabilitation Sciences)		
From	TSANG Wing Hong Hector, Chair, Departmental Research Committee		
Email	rshtsang@	Date	20-Apr-2015

Application for Ethical Review for Teaching/Research Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following project for a period from 20-Apr-2015 to 19-Apr-2017:

Project Title:	Reliability and validity of supersonic elastography measurement in lower limb muscles
Department:	Department of Rehabilitation Sciences
Principal Investigator:	Pang Marco Yiu Chung
Reference Number:	HSEARS20150411001

Please note that you will be held responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project. In the case of the Co-PI, if any, has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Departmental Research Committee in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

You will receive separate email notification should you be required to obtain fresh approval.

TSANG Wing Hong Hector

Chair

Departmental Research Committee

8.3 Appendix III: Ethical approval for Chapter 4 and 5

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

To	Pang Marco Yiu Chung (Department of Rehabilitation Sciences)		
From	TSANG Wing Hong Hector, Chair, Departmental Research Committee		
Email	rshtsang@	Date	12-Jan-2015

Application for Ethical Review for Teaching/Research Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following project for a period from 09-Jan-2015 to 08-Jan-2017:

Project Title:	Transmission and neuromuscular effects of Whole Body Vibration (WBV) signals in people after stroke: influence of vibration frequencies, amplitudes and postures.
Department:	Department of Rehabilitation Sciences
Principal Investigator:	Pang Marco Yiu Chung
Reference Number:	HSEARS20141230001

Please note that you will be held responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project. In the case of the Co-PI, if any, has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Departmental Research Committee in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

You will receive separate email notification should you be required to obtain fresh approval.

TSANG Wing Hong Hector

Chair

Departmental Research Committee

8.4 Appendix IV Ethical approval for Chapter 6

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

To	Pang Marco Yiu Chung (Department of Rehabilitation Sciences)		
From	TSANG Wing Hong Hector, Chair, Departmental Research Committee		
Email	rshtsang@	Date	16-Dec-2016

Application for Ethical Review for Teaching/Research Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following project for a period from 01-Dec-2016 to 30-Nov-2018:

Project Title:	The effects of whole body vibration (WBV) on muscle stiffness and reflex activity in people after stroke.
Department:	Department of Rehabilitation Sciences
Principal Investigator:	Pang Marco Yiu Chung
Project Start Date:	01-Dec-2016
Reference Number:	HSEARS20161117007

You will be held responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project. In the case of the Co-PI, if any, has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Human Subjects Ethics Sub-committee in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

TSANG Wing Hong Hector

Chair

Departmental Research Committee

8.5 Appendix V: Journal's approval for reusing chapter 2 in the thesis

HUANG, Meizhen [Student]

From: PermissionsUK <PermissionsUK@
Sent: Tuesday, July 17, 2018 2:26 AM
To: HUANG, Meizhen [Student]
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Meizhen HUANG

Ph.D. candidate

Department of Rehabilitation Science

The Hong Kong Polytechnic University

Hong Kong

8.6 Appendix VI Journal's approval for reusing chapter 4 in the thesis

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Sent: Tuesday, July 10, 2018 9:41 PM
To: HUANG, Meizhen [Student]
Subject: Journal of Biomechanics

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1

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Journal - Volume	73
Journal - Issue	17
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Journal - Pages to	91
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8.8 Appendix VIII:Sample of search strategy for Chapter 2

Search strategy on Medline via Ovid

1. exp Central Nervous System Diseases/

2. ((central nervous system or cns) and (disorder? or disease?)).ab,kf,ti.

3. humans.sh.

4. ((cerebr* or brain or spin* or cerebel* or thalam* or basal ganglia) and (disorder? or disease? or accident? or damage? or trauma? or injur* or ischemi* or infarct* or h?emorrhag* or degenerat*)).ab,kf,ti.

5. "encephalopath*".ab,kf,ti.

6. stroke.ab,kf,ti.

7. apoplexy.ab,kf,ti.

8. ischemic attack?.ab,kf,ti.

9. ((multiple or lateral or disseminated) and sclerosis).ab,kf,ti.

10. "cerebral pals*".ab,kf,ti.

11. "Little* disease".ab,kf,ti.

12. (Parkinson* and (disease? or disorder?)).ab,kf,ti.

13. "lewy bod*".ab,kf,ti.

14. ((spin* or cord*) and (contus* or transect* or lacerat* or compress*)).ab,kf,ti.

15. "myelopath*".ab,kf,ti.

16. "polio*".ab,kf,ti.

17. "myeliti*".ab,kf,ti.

18. "encephalomyeliti*".ab,kf,ti.

19. "encephaliti*".ab,kf,ti.

20. "syringomyel*".ab,kf,ti.

21. (Morvan* and (disease* or syndrome)).ab,kf,ti.

22. chorea.ab,kf,ti.

23. (dystonic and (disorder? or disease?)).ab,kf,ti.

24. Huntington Disease?.ab,kf,ti.

25. "dement*".ab,kf,ti.

26. "Alzheimer*".ab,kf,ti.

27. (Down* and syndrome*).ab,kf,ti.

28. (myoton* and dystroph*).ab,kf,ti.

29. "neuroaxonal dystroph*".ab,kf,ti.

30. atax*.ab,kf,ti.

31. 1 or 2 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

32. "Vibration/tu [Therapeutic Use]".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

33. whole body vibration.ab,kf,ti.

34. whole-body vibration.ab,kf,ti.

35. (vibrat* and (exercis* or therapy)).ab,kf,ti.

36. 32 or 33 or 34 or 35

37. exp Reflex/

38. exp Neurologic Manifestations/

39. exp Diagnostic Techniques, Neurological/

40. exp Electrophysiological Processes/

41. exp Biomechanical Phenomena/

42. exp Muscle contraction/

43. "muscle ton*".ab,kf,ti.

44. "neurophysiolog*".ab,kf,ti.

45. "electrophysiolog*".ab,kf,ti.

46. "biomechanic*".ab,kf,ti.

47. "neuromusc*".ab,kf,ti.

48. motoneuron?.ab,kf,ti.

49. motor neuron?.ab,kf,ti.

50. motor unit?.ab,kf,ti.

51. "myograph*".ab,kf,ti.

52. "electromyograph*".ab,kf,ti.

53. muscle torque.ab,kf,ti.

54. "hyperton*".ab,kf,ti.

55. "hypoton*".ab,kf,ti.

56. "dyston*".ab,kf,ti.

57. "reflex*".ab,kf,ti.

58. "rigid*".ab,kf,ti.

59. "spasm*".ab,kf,ti.

60. "spastic*".ab,kf,ti.

61. "stiff*".ab,kf,ti.

62. "tight*".ab,kf,ti.

63. "flaccid*".ab,kf,ti.

64. "resilien*".ab,kf,ti.

65. "pliabl*".ab,kf,ti.

66. "cramp*".ab,kf,ti.

67. "myoton*".ab,kf,ti.

68. "fasciculation*".ab,kf,ti.

69. "tetan*".ab,kf,ti.

70. "flopp*".ab,kf,ti.

71. "atonic*".ab,kf,ti.

72. "inotrop*".ab,kf,ti.

73. "elast*".ab,kf,ti.

74. "synap*".ab,kf,ti.

75. "tens*".ab,kf,ti.

76. "complian*".ab,kf,ti.

77. "hyperreflex*".ab,kf,ti.

78. "hyporeflex*".ab,kf,ti.

79. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78

80. 3 and 31 and 36 and 79

8.9 Appendix Ix Fugl-Meyer Assessment (Lower Limbs)

Position	TEST	Item	Fugl-Meyer	SCORING CRITERIA
Supine	Flexor Synergy *請將你嘅膝頭哥移向胸口並將腳趾指向頭(X3)*	Hip flexion		0-Cannot be performed at all 1-Partial motion 2-Full motion
		Knee flexion		
		Dorsiflexion		
Side-lying	Extensor Synergy *請伸直腿并向後踢（X3）* *Marking!*	Hip extension		0-Cannot be performed at all 1-Partial motion 2-Full motion
		Adduction		
		Knee extension		
		Ankle plantar flexion		
Sitting	Reflex Activity *(X3)*	Patellar		0-No reflex activity can be elicited 2-Reflex activity can be elicited
		Achilles		
	Movement combining synergies *(著襪)X3*	Knee flexion beyond 90 *(成只腳向後放)*		0-No active motion 1-From slightly extended position, knee can be flexed, but not beyond 90° 2- Knee flexion beyond 90°
		Ankle dorsiflexion *(腳踭唔離開地，腳趾向上)*		0-No active flexion 1-Incomplete active flexion 2-Normal dorsiflexion
	Normal reflex (Only do when all others are maximum. Otherwise, 0)	Patellar		0-At least 2 of the 3 phasic reflexes are markedly hyperactive 1-One reflex is markedly hyperactive, or at least 2 reflexes are lively 2-No more than one reflex is lively and none are hyperactive
		Achilles		
		knee flexor		
	Coordination/speed - Sitting: Heel to opposite knee (5 repetitions in rapid succession) *(將腳踭沿著對側腿骨向上向下滑，越快越好)*	Tremor		0-Marked tremor 1-Slight tremor 2-No tremor
		Dysmetria		0-Pronounced or unsystematic dysmetria 1-Slight or systematic dysmetria 2- No dysmetria
		Speed Left: _____s Right: _____s		0-Activity is more than 6 seconds longer than unaffected side 1-(2-5.9) seconds longer than unaffected side 2-Less than 2 seconds difference
Standing	Movement out of synergy *(X3)*	Knee Flexion *(大脾唔郁，腳踭踢向臀部)*		0-Knee cannot flex without hip flexion 1-Knee begins flexion without hip flexion, but does not reach to 90°, or hip flexes during motion 2-Full motion as described
		Dorsiflexion *(膝頭哥伸直，腳踭踩地，抬起腳尖)*		0-No active motion 1-Partial motion 2-Full motion

8.10 Appendix X: Modified Ashworth Scale (MAS)

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

8.11 Appendix XI: Modified Tardieu Scale (MTS)

Score	Description
0	No resistance throughout passive movement
1	Slight resistance throughout
2	Clear catch at a precise angle
3	Fatigable clonus (<10secs) occurring at a precise angle
4	Unfatigable clonus (>10secs) occurring at a precise angle
5	Joint Immobile