ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 May 26; 11(15): 3369-3663

Published by Baishideng Publishing Group Inc

WJCC

World Journal of
Clinical Cases

Contents   Thrice Monthly Volume 11 Number 15 May 26, 2023

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 15 May 26, 2023

Contents

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

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PUBLICATION DATE
May 26, 2023

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World J Clin Cases 2023 May 26; 11(15): 3434-3443

DOI: 10.12998/wjcc.v11.i15.3434

ISSN 2307-8960 (online)

MINIREVIEWS

Effectiveness and safety of subthreshold vibration over suprathreshold vibration in treatment of muscle fatigue in elderly people

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Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bernardes A, Portugal; Dye DC, United States

Received: February 4, 2023
Peer-review started: February 4, 2023
First decision: March 28, 2023
Revised: March 29, 2023
Accepted: April 20, 2023
Article in press: April 20, 2023
Published online: May 26, 2023

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Abstract

Muscle fatigue is common in many populations, particularly elderlies. Aging increases the incidence of muscle fatigue and delays its recovery. There is a huge debate about the current treatments for muscle fatigue, particularly in elderlies. Recently, it has been discovered that mechanoreceptors have an important role as a sensory system in sensing muscle fatigue which could enhance the body's response to muscle fatigue. The function of mechanoreceptors could be enhanced by applying either suprathreshold or subthreshold vibration. Although suprathreshold vibration improves muscle fatigue, it can cause desensitization of cutaneous receptors, discomfort, and paresthesia, which are barriers to clinical use. Subthreshold vibration has been approved as a safe and effective method of training for mechanoreceptors; however, its use and effectiveness in muscle fatigue have never been tested or explained. Possible physiological effects of subthreshold vibration in the treatment of muscle fatigue include: (1) Enhancing the function of mechanoreceptors themselves; (2) Increasing the firing rate and function of alpha motor neurons; (3) Increasing blood flow to fatigued muscles; (4) Decreasing the rate of muscle cell death in elderlies (sarcopenia); and (5) Driving motor commands and allow better performance of muscles to decrease fatigue incidence. In conclusion, the use of subthreshold vibration could be a safe and effective treatment for muscle fatigue in elderlies. It could enhance recovery from muscle fatigue. Finally, Subthreshold Vibration is safe and effective in treating muscle fatigue in comparison to suprathreshold vibration.

Key Words: Subthreshold; Vibration; Muscle; Fatigue; Elderly people

Core Tip: Subthreshold vibration may be a safe and effective treatment in the treatment of muscle fatigue. this review discusses the possible effects of subthreshold in treatment of muscle fatigue which include: (1) Enhancing the function of mechanoreceptors themselves; (2) Increasing the firing rate and function of alpha motor neurons; (3) Increasing blood flow to fatigued muscles; (4) Decreasing the rate of muscle cell death in elderlies (sarcopenia); and (5) Driving motor commands and allow better performance of muscles to decrease fatigue incidence. In conclusion, the use of subthreshold vibration could be a safe and effective treatment for muscle fatigue in elderlies. Also. It could enhance recovery from muscle fatigue. Finally, Subthreshold Vibration is safe and effective in treating muscle fatigue in comparison to suprathreshold vibration.

Citation: Mohamed AA, Khaled E, Hesham A, Khalf A. Effectiveness and safety of subthreshold vibration over suprathreshold vibration in treatment of muscle fatigue in elderly people. *World J Clin Cases* 2023; 11(15): 3434-3443

URL: https://www.wjgnet.com/2307-8960/full/v11/i15/3434.htm

DOI: https://dx.doi.org/10.12998/wjcc.v11.i15.3434

INTRODUCTION

Muscle fatigue is common among elderly people. Muscle fatigue usually begins at the age of 40 years and continues to increase afterward[1]. Muscle fatigue in elderly people commonly arises due to prolonged abnormality in their neuromuscular systems, which disrupts the capability of elderly people to resist muscle fatigue. These abnormalities happen in all regions of the neuromuscular system. Also, muscle fatigue in elderly people can occur due to a depletion in adenosine triphosphate (ATP) and calcium ions (Ca^{2+})[2]. Muscle fatigue has a close relationship to the rate of sarcopenia. The rate of muscle loss ranges from 1 to 2% per year past the age of 50 years. Thus, 25% of people under the age of 70 years and 40% of those over the age of 80 years have sarcopenia[3].

Existing rehabilitative procedures to decrease the incidence of or treat muscle fatigue are few and their attribute is minimal. Thus, it is difficult to make clear decisions on the effect of these procedures to reduce the incidence of muscle fatigue[4]. The existing rehabilitative procedures to reduce the incidence of muscle fatigue were built on the basis that muscle fatigue arises due to dysfunction in the neuromotor system. This dysfunction can happen in any region in the motor control system, involving, actin-myosin links, neuromuscular junction coupling in muscle, signals from motoneurons to muscle, signals from cortex to motoneurons, or motor cortex[5].

Existing rehabilitative procedures developed to enhance the fatigability and decrease the occurrence of muscle fatigue, focused mainly on increasing the rest periods[6], using mild training intensity[7], or grading the exercise intensity[8] to recover muscle force or allow more amount of Ca^{2+} ions and ATP. Other studies reported that usual participation in physical activity and grading the exercise have little effect on decreasing the occurrence of muscle fatigue or enhancing fatigability in seniors[9,10].

Numerous studies demonstrated that sensory receptors play a critical role in the development and perception of muscle fatigue[11-15]. Interestingly, muscle fatigue also has sensory receptors, which are the mechanoreceptors and metaboreceptors[5,16]. Mechanoreceptors are the most important receptors of muscle fatigue and they are sensitive to variations in muscle strain[11,16]. Metaboreceptors are the secondary receptors of muscle fatigue and they sense fluctuations in the number of metabolites produced by muscle contraction[11,16].

A large change in strain sensation in working muscles and/or joints, accumulation of muscle metabolites, and depletion of substrates during physical activity are the triggers of sensing muscle fatigue[16-20]. These peripheral changes are mainly sensed by the mechanoreceptors[21,22] and to a lesser extent by the metaboreceptors[23,24]. This sensory data then reaches the brain, informing it about the exertion or fatigue level in working muscles[11], which in turn could help in improving body response to muscle fatigue.

The sensory system has a vital role in driving motor signals[25], thus any exercise or intervention that targets the proprioception (sensory receptors of muscle fatigue) may have a superior role over the previous interventions that focused only on improving the motor system. Changing the temperature applied to the foot affected the balance and hyperemia[26]. Different walking speeds affects plantar pressure patterns at the sole[27]. Proprioceptive training accomplished significant enhancements in neuromotor function in almost conditions applied in[28-32]. Vibration is a type of proprioceptive training that directly trains the mechanoreceptors. Vibration can be either suprathreshold or subthreshold. The effect of suprathreshold vibration is still in debate and could have harmful effects. Some studies found that suprathreshold vibration has a positive effect on decreasing the incidence of muscle fatigue[33-35]. Other studies found that suprathreshold vibration has a nonsignificant effect[36, 37] and may lead to harmful effects. Furthermore, a recent meta-analysis reported that the available studies on suprathreshold muscle tendon vibration after stroke are low in their methodological qualities and additional studies of high methodological quality are required to achieve a strong agreement concerning muscle tendon vibration intervention protocols and their recommendation in clinical settings[38]. Another systematic analysis reported that the studies that used focal mechanical suprathreshold vibration have several constraints[39]. Other studies found that prolonged exposure to high vibration is not safe and causes adverse effects. Adamo *et al*[40] reported that local suprathreshold vibration can cause a decrease in muscle force and the early development of muscle fatigue and musculoskeletal disorders. Also, long-term exposure to suprathreshold vibration causes an increased health risk to the spine and the peripheral nervous system[41]. Furthermore, suprathreshold vibration applied for 7 d or more causes significant damage to peripheral nerves when no recovery time was given[42]. Furthermore, high-frequency whole-body vibration may result in harmful effects, including intervertebral disc shift, visual impairment, and hearing loss[43].

Subthreshold vibration was applied in several studies and produced significant positive effects on neuromotor function in almost all of them with no recorded harmful effect; however, its effect in decreasing the incidence of muscle fatigue in elderly people is unclear yet. Thus, this review summarizes the possible physiological effects of subthreshold training in decreasing the incidence of muscle fatigue as an attempt to advance the rehabilitation of muscle fatigue. The goal of any rehabilitative intervention is to be applied safely and effectively for prolonged periods. Thus, this review discusses the effectiveness of subthreshold vibration in treating muscle fatigue and its safety over suprathreshold vibration for prolonged use. This review includes seven main sections including what is the subthreshold vibration, the effect of subthreshold vibration on the mechanoreceptors themselves, the effect of subthreshold vibration on alpha motor neurons, the effect of subthreshold vibration on blood flow to working muscles, the effect of subthreshold vibration on muscle cell death rate (sarcopenia), the effect subthreshold vibration as a sensory stimulation in driving motor commands, and the safety of subthreshold vibration in treating muscle fatigue in elderly people.

WHAT IS THE SUBTHRESHOLD VIBRATION

Subthreshold vibration can be defined as the application of vibration below the conscious level. Most studies used a 75% to 90% subsensory threshold. They used 90% subsensory amplitude and their rationale was decreasing the subsensory threshold by 10% to achieve the term of subsensory amplitude [44]. Sensory feedback is crucial in driving various motor commands including posture, balance, muscle action, gait, muscle spasm, *etc*[5].

Subsensory vibration depends on stochastic resonance theory. In the clinical field, stochastic resonance theory was used to train somatosensory systems. The stochastic resonance theory states that if the optimal low level of noise was applied, signal detection enhances[45,46]. The noise was accidentally discovered by Albert Einstein in 1905 when he noticed that atoms move consistent with the Brownian molecular motion[45]. After his detection, several studies, related to noise, were conducted in biological and physical systems, without identifying its vital influence on these systems[45]. However, this noise is frequently observed as an undesirable component or trouble to a system. Nowadays, targeting the optimal low level of noise for biological tissues offers incredible effects on numerous aspects of medicine[45]. Stochastic resonance theory arises in both artificial and naturally occurring non-linear systems. For example, paddlefish were shown to use stochastic resonance theory to locate and catch their targets[47]. It was found that using this small noisy input can improve the firing patterns of squid axons[48], the breathing stability in preterm infants[49], the postural control in older adults, stroke or peripheral neuropathy[44,46,50].

EFFECT OF SUBTHRESHOLD VIBRATION ON THE MECHANORECEPTORS THEMSELVES

Subthreshold vibration is a proprioceptive training that can improve the function and sensitivity of mechanoreceptors themselves. Subthreshold vibration could improve the function and sensitivity of mechanoreceptors both neurologically and morphologically[51]. Subthreshold vibration could improve fatigability by improving neural signals that arise from muscle spindles and other mechanoreceptors [52]. Subthreshold vibration could produce morphological modifications in muscle spindles themselves. These morphological modifications can happen as a result of both micro-adaptations including changes in intrafusal muscle fibers as a result of metabolic modifications, and macro-adaptations including a decrease in the response latency of the stretch reflex and an increase in its amplitude[53-55]. Also, it can enhance the firing rate of α-motoneurons and reduce the disruption of the function of α-motoneurons *via* increasing the sensitivity of mechanoreceptors[5].

Subthreshold vibration could produce central modifications. Subthreshold vibration as a proprioceptive training can enhance the muscle spindle signals, causing plastic modifications in the central nervous system (CNS), such as improving synaptic network strength and/or normalizing the structure and numbers of networks amid neurons. Consequently, plastic modifications in the cortex occur leading to an enhancement in cortical maps of the body, and cortical representation of the joints[51].

The effect of subthreshold vibration can extend to remote areas from the application site. Plater *et al* [56] investigated the effect of subsensory vibration applied away from the testing site. They applied subthreshold vibration at the posterior thigh and measured the vibrotactile threshold at the calf. Also, they applied subthreshold vibration at the calf and measured the vibrotactile threshold at the sole. They found that subthreshold vibration can enhance the perception of vibrotactile inputs in hairy skin in neighborhood areas. The effect of subthreshold vibration on the mechanoreceptors themselves is shown in Figure 1.

EFFECT OF SUBTHRESHOLD VIBRATION ON ALPHA MOTOR NEURONS

Subthreshold vibration can adjust and normalize motor neurons firing rate[5]. Normalization of motor neurons' firing rate subsequently helps in normalizing calcium secreted from calcium networks in the sarcoplasmic reticulum causing a decrease in the incidence of muscle fatigue[5]. Subthreshold vibration can decelerate the decline in the function of α-motoneurons[57-59].

This previous suggestion could be reinforced by Hospod *et al*[60]'s study, who found that Ia afferents significantly enhanced after proprioceptive attention task. These significant enhancements in Ia afferents occurred in the form of an enhancement in the adaptability of discharge, a reduction in neural modulation depth, and an adjustment in random activity. These previous changes caused a renormalization in the firing of α-motor neurons which consequently produced an increase in muscle performance and a reduction in the incidence of muscle fatigue.

Renormalization of α-motor neuron's firing rate can improve the secretion of Ca^{2+} from its channels. In-depth, it is well-established that the activation of muscle spindles happens because of increased muscle strain. Thus, the increase in muscle spindle signals causes an increase in α-motor neuron firing rate *via* a reflex action mediated by Ia nerve afferents. Finally, activation of extrafusal muscle fibers and muscle contraction occur[2,5]. The contraction of muscle fibers begins with acetylcholine secretion at the neuromuscular junction which extends to the synaptic cleft and activates nicotinic acetylcholine receptors within the endplate. These nicotinic acetylcholine receptors stimulate the release of calcium and the influx of cations (sodium and calcium) leading to a depolarization of the muscle cell membrane and the occurrence of muscle contraction[2]. Thus, subthreshold vibration could improve the secretion of Ca^{2+} ions in the neuromuscular junction, which significantly helps in decreasing the incidence of muscle fatigue[2].

Several studies found that there is a strong effect of subthreshold vibration on alpha motor neurons. Sharma *et al*[61] investigated the effect of applying subthreshold vibration to the sole on the cutaneous reflex generation of the lower limb. They used varying subsensory intensities (0%, 20%, 40%, 60%, 80%, or 100%) for 120 s each. They found that subthreshold vibration improved cutaneous reflex generation of the lower limb and the intensity of 20% was the best intensity among them. Seo *et al*[62] investigated the effect of subthreshold vibration applied to the wrist joint on the sensorimotor activity of the cortex and grip-associated desynchronization. They found that subthreshold vibration applied to the wrist joint at rest reduced electroencephalogram power and transcranial magnetic stimulation short-interval intracortical inhibition (*i.e.*, disinhibition) compared with no vibration. Also, subthreshold vibration applied to the wrist joint at rest increased grip-associated desynchronization during vibration, compared to no vibration. The effect of subthreshold vibration on alpha motor neurons is shown in Figure 2.

EFFECT OF SUBTHRESHOLD VIBRATION ON BLOOD FLOW TO WORKING MUSCLES

To the best of our knowledge, the effect of subthreshold vibration on blood flow to working muscles has not been demonstrated yet. The effect of subthreshold vibration on blood flow to working muscles may occur through two main mechanisms. First, muscle spindles have a connection with the sympathetic nervous system (SNS). Strong proof exists on the effect of stimulation of high threshold skin mechanoreceptors sensitive to noxious stimuli and its influence on heart rate, blood pressure, and efferent sympathetic outflow to skeletal muscle[5,63]. Thus, improving the sensitivity and function of muscle spindles might cause a decrease in the sympathetic blood flow; this would improve blood flow. Afferents from muscle spindles provide low-threshold information on muscle length. The influence of the SNS on muscle spindle receptors has been studied and concluded that stimulation of SNS decreases the activity of muscle spindles[64]. Cutaneous mechanoreceptor feedback from feet and hands can decrease the sympathetic nerve activity of muscles, causing an improvement in the blood flow to the muscle. Second, muscle spindle and Golgi tendon organs have a strong control over extrafusal muscle extrafusal muscle fibers. Proper function and sensitivity of muscle spindles cause a better contraction of the extrafusal muscle fibers, which in turn causes an increase in blood flow to working muscles (muscle

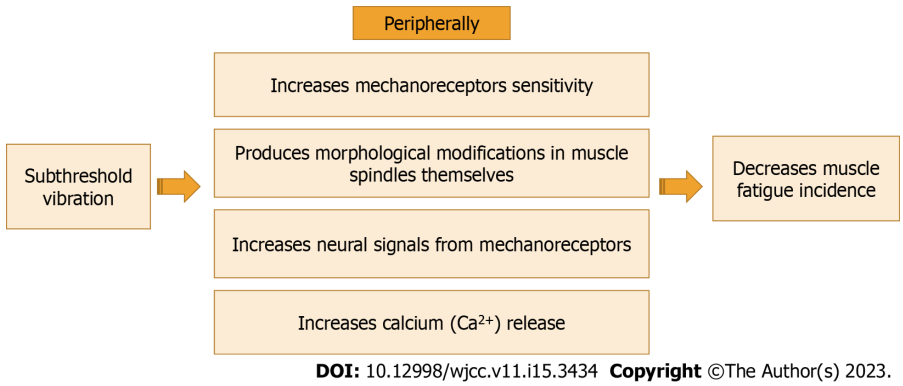


Figure 1 Effect subthreshold vibration on the mechanoreceptors themselves.

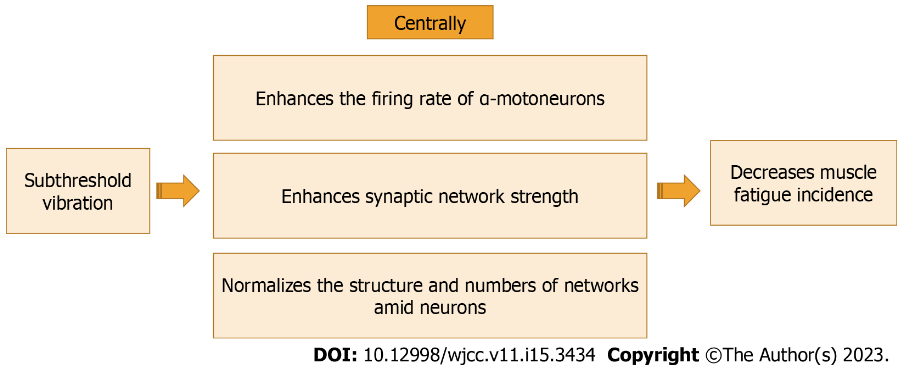


Figure 2 Effect subthreshold vibration on alpha motor neuron.

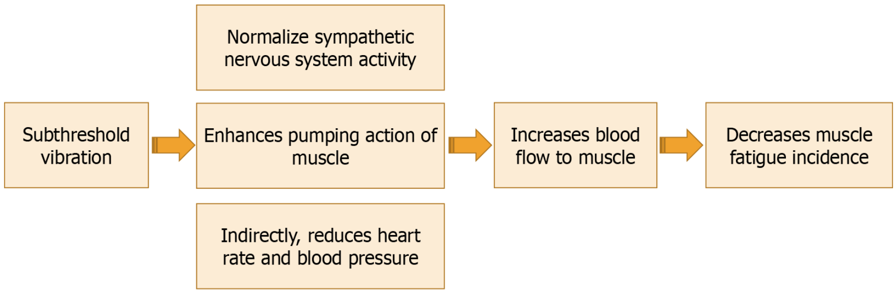
pumping effect)[65,66]. Muscle spindles and Golgi tendon organs are sensitive to changes in muscle strain. Enhancing the function of muscle spindles and Golgi tendon organs functions could enhance muscle response and their pumping role in increasing the blood flow to muscles.

Studies on the effect of subthreshold vibration on blood flow to muscle are very lacking. One study conducted by Hidaka *et al*[67] investigated the effect of noise on heart rate and sympathetic nerve reactions to oscillatory lower body negative pressure in normal people. They found that noise significantly improved heart rate, cardiac interbeat interval, and total muscle sympathetic nerve activity. Future studies are strongly recommended to investigate this effect in both animals and humans. The effect of subthreshold vibration on blood flow to working muscles is shown in Figure 3.

EFFECT OF SUBTHRESHOLD VIBRATION ON MUSCLE CELL DEATH RATE (SARCOPENIA)

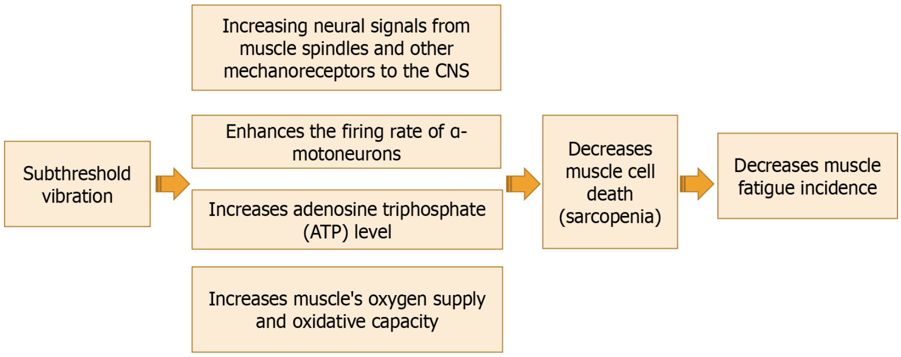
Decreased activity of muscle spindles is one of the primary mechanisms that cause a decrease in the firing rate of α -motor neurons. Subthreshold vibration as a proprioceptive training can improve the activity of muscle spindles to renormalize the firing rate of group Ia muscle afferents, presynaptic inhibition, and the firing rate of α-motor neurons[21,68,69]. Subthreshold vibration may improve fatigability and slow sarcopenia progression by improving neural signals from muscle spindles and other mechanoreceptors to the CNS leading to an increase in the firing rate of α -motor neurons and a reduction in muscle fibers loss (sarcopenia).

To the best of our knowledge, rare studies have been conducted to study the effect of subthreshold vibration on muscle strength. Kim *et al*[70] demonstrated that subthreshold stimulation with motor training improves functional recovery after stroke through normalizing neural reconstruction, showed by advanced neurite expression in the activated areas and associated alteration in behavior and neural spike firing rate throughout the rehabilitation after stroke. Previously, we reported that proprioceptive training might be an efficient treatment in reducing the progression rate of sarcopenia and improving the fatigability within elderly people[2]. The effect of subthreshold vibration on muscle cell death rate (sarcopenia) is shown in Figure 4.



DOI: 10.12998/wjcc.v11.i15.3434

Figure 3 Effect subthreshold vibration on blood flow to muscle.



DOI: 10.12998/wjcc.v11.i15.3434

Figure 4 Effect subthreshold vibration on muscle cell death rate (sarcopenia).

EFFECT OF SUBTHRESHOLD VIBRATION AS A SENSORY STIMULATION IN DRIVING MOTOR COMMANDS

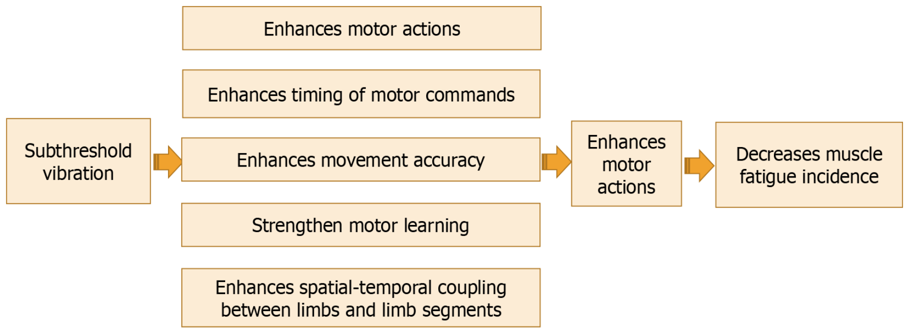
According to the theory of motor control, sensory information has a key role in controlling motor actions[71,72]. The muscle spindle is the most important source of proprioceptive information to the CNS about limb position, movement, and velocity, as well as a sense of effort[5]. Proprioceptive feedback influences motor actions and movement accuracy in several ways, including the timing of motor command onset and coordination[73].

The research documented the important role of improving proprioceptive training in improving motor function and learning. Barbieri *et al*[74] explained the role of proprioception in controlling posture and spatial-temporal coupling among limb segments. Wong *et al*[75] reported that there is a connection between sensory function and motor learning and adding proprioceptive training can strengthen motor learning. Recently, Winter *et al*[76] demonstrated that proprioceptive training can cause significant enhancements in proprioceptive and motor function in several healthy and clinical individuals, and rehabilitative programs that aim to improve active motion are most effective in improving sensorimotor performance. A previous systematic analysis conducted by us[30] to investigate the effect of adding proprioceptive exercise to balance training in elderly people with diabetes mellites. We found that proprioceptive exercise is a crucial element in balance training to achieve short-term enhancement of balance control in elderly people with diabetes mellites. The effect of subthreshold vibration as a sensory stimulation in driving motor commands is shown in Figure 5.

SAFETY OF SUBTHRESHOLD VIBRATION IN TREATING MUSCLE FATIGUE IN ELDERLY PEOPLE

The optimal role of any rehabilitative technology is to be both effective and safe[77]. Seo *et al*[78] reported that prolonged application of vibration for hours and days, as in rehabilitative settings, might cause modification of mechanoreceptors' sensitization, which requires to be investigated before application of vibration in a prolonged rehabilitation setting.

Almost all studies reported no harmful effects for subthreshold vibration. Subthreshold vibration is a safe rehabilitative method that can be applied for hours and days because it is subsensory and the patient will not feel it. Regueme *et al*[79] investigated the effect of subthreshold vibration insole on



DOI: 10.12998/wjcc.v11.i15.3434

Figure 5 Effect subthreshold vibration as a sensory stimulation to drive motor actions.

postural stability in elderly people with Type 2 Diabetes mellites. They demonstrated that there were no adverse reactions connected to vibrating insoles. Seo *et al*[78] investigated the effect of subsensory vibratory vibration conducted to the skin of the wrist joint on fingertip touch evoked potentials. they used a 500 Hz, and 60% intensity of participants' sensory threshold at the wrist. They reported no harmful effects for the immediate application of subthreshold vibration. Child *et al*[80] investigated the effect of prolonged subthreshold stimulation applied to subdural cortical stimulation. They use a constantly implantable 4 × 4 grid with 4-contact electrodes. They reported no harmful effects for subthreshold stimulation.

CONCLUSION

The use of subthreshold vibration could be a safe and effective treatment for muscle fatigue in elderly people over suprathreshold vibration. Subthreshold vibration could enhance the function of mechanoreceptors themselves, increase the firing rate and function of alpha motor neurons, increase blood flow to fatigued muscles, decrease the rate of muscle cell death in elderly people (sarcopenia), and drive motor commands. Subthreshold vibration also could enhance recovery from muscle fatigue.

FOOTNOTES

Author contributions: Mohamed AA wrote and revised the manuscript; Khaled E participated in writing the manuscript; Hesham A revised the manuscript; and Khalf A drew the figures and participated in writing the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Egypt

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S-Editor: Liu XF
L-Editor: A
P-Editor: Chen YX

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