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GRACE ANNE DUGINSKI
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BY THE COMMITTEE CONSISTING OF

Dr. Yuan Yang, Chair

Dr. Sarah Breen

Dr. Andrew Fagg

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Abstract of the Thesis

Stroke is the fifth leading cause of death and a leading cause of disability in the state of Oklahoma and the United States. Although there are several approaches to stroke rehabilitation, most stroke survivors live with upper limb impairments, which causes difficulties for independent living and social participation. One promising method for rehabilitation of the upper limb following stroke is focal muscle vibration, thought to work by activating the Ia afferent muscle spindle fibers for somatosensory and motor cortex stimulation. In this thesis, I describe the development of a novel wearable focal vibration device, called FoVi. Then, I report the findings from a pilot study of the feasibility and efficacy of the FoVi device in a short-term intervention. The FoVi device was developed according to design criteria specified through a focus group, including being comfortable and easy to use, having vibration motor pods controlled by an app on the user's smartphone, and recording usage logs for real-time communication with therapists. Short-term interventions with FoVi show promise in increasing upper limb mobility and function, evidenced through non-significant increases in Fugl-Meyer Upper Extremity score, Chedoke Arm-Hand Activity Inventory score, and grip strength. In conclusion, the FoVi device could be a helpful treatment method in stroke rehabilitation, and future long-term intervention studies with larger sample sizes and more robust outcome measures may show significant improvements in upper limb function. Combination with other treatment modalities, such as transcranial direct current stimulation, may enable a more effective treatment of the upper limb in stroke patients.

Chapter 1. Introduction and Background

This chapter introduces the motivation for this thesis work and some key background information for understanding the problems being addressed by this research. The primary objectives and aims of the thesis are also presented.

1.1 Motivation

Stroke is one of the leading causes of death and disability in the world. Nearly 800,000 people in the United States have a stroke each year. In Oklahoma, more than 1800 people died from stroke in 2014, and stroke was the fifth leading cause of death in the state from 2014-2017 (Centers for Disease Control and Prevention, 2018; Oklahoma State Department of Health, 2022). In 2014, Oklahoma ranked 9th in the nation for death rate from strokes (Oklahoma State Department of Health, 2022). Although many therapies exist to assist patients to recover function in the affected side of the body, the reality is that up to 65% of patients will still have minor to severe impairments throughout their lives (American Stroke Association, 2019). Conventional methods of rehabilitation such as physical, occupational, and speech therapy, as well as newer treatment methods like constraint induced movement therapy (Gitendra Uswatte *et al.*, 2006; Morris, Taub and Mark, 2006; Kwakkel *et al.*, 2015), electrical or magnetic stimulation of the brain (Schlaug, Renga and Nair, 2008; Hoyer and Celnik, 2011), mirror therapy (Dohle *et al.*, 2009; Carvalho *et al.*, 2013; Hoffman, 2019), virtual reality (Saposnik and Levin, 2011; Laver *et al.*, 2017), robot-assisted therapy (Chang and Kim, 2013), tele-rehabilitation (Sarfo *et al.*, 2018; Chang and Boudier-Revéret, 2020), and vibration therapy (Noma *et al.*, 2012; Caliandro *et al.*, 2012; Tavernese *et al.*, 2013; Murillo *et al.*, 2014; Paoloni *et al.*, 2014; Casale *et al.*, 2014; Constantino,

Galuppo and Romiti, 2014; Saggini *et al.*, 2016; Go and Lee, 2016; Calabrò *et al.*, 2017; Celletti *et al.*, 2017; Choi, 2017; Costantino, Galuppo and Romiti, 2017; Jung, 2017; Annino *et al.*, 2019; Li *et al.*, 2019; Toscano *et al.*, 2019; Wang *et al.*, 2020) have all shown promising gains for patients recovering from stroke. Vibration therapy includes whole-body and focal vibration, but it needs further study to determine which vibration parameters are most effective. In this thesis project, a new focal vibration device is tested in chronic stroke patients to measure the feasibility of the focal vibration device design, collect participant feedback, and assess whether the device improves the mobility and function of the upper limb after a short-term intervention.

1.2 Background

Stroke is an umbrella term referring to an injury of the brain resulting from the occlusion or hemorrhage of the blood vessels supplying the brain (Lo, Dalkara and Moskowitz, 2003). One type, an ischemic stroke, occurs when there is blockage to a blood vessel in the brain. This could be due to either a blood clot, called thrombosis, or plaque buildup, called atherosclerosis. Another type of stroke, a hemorrhagic stroke, occurs when a blood vessel in the brain ruptures, causing internal hemorrhagic bleeding in the brain. This could be caused by the rupture of a brain aneurysm, which experiences higher stresses from irregular blood flow. Transient ischemic attacks, known as mini-strokes, are another type of stroke in which blood vessels are blocked for five minutes or less. These are often a warning sign for future, more severe strokes. Ischemic strokes make up 87% of all strokes (Virani *et al.*, 2021). Stroke ranks fifth among all causes of death in the United States, behind only cancer, heart disease, chronic lower respiratory disease, and unintentional injuries/accidents (Virani *et al.*, 2021). Some factors that put a person at higher

risk for a stroke include high blood pressure and cholesterol, obesity, and history of smoking (Oklahoma State Department of Health, 2016).

The extent of the effects of this disability on a person's life can be understood in terms of the International Classification of Functioning, Disability, and Health (ICF). The ICF model of disability describes the interaction between health conditions and contextual factors, taking into account both environmental and personal factors (OMS, 2002). It describes disability as dysfunction at one or more levels of human functioning: impairment of a body part, activity limitations on a person, and/or participation restrictions on the person in their social context. Strokes may be debilitating at each of these levels. Depending on the area of the brain affected and the severity of the stroke, several different body parts may be impaired. There is usually some degree of hemiparesis, where only one side of the body is impaired with muscle weakness and lack of control. The side of the body that is impaired is contralateral to the side of the brain where the stroke occurred. Upper limb impairments can prevent people from movements such as reaching, gripping, or grasping objects. Paresis of the upper limb affects up to 95% of stroke patients in the acute phase, and even after rehabilitation 89% of patients still have some deficits in upper extremity function (Jørgensen *et al.*, 1999). Lower limb impairments may affect the ability to walk or balance without assistance. Some patients also have hyperactive reflexes or reduced sensation and feeling after a stroke. There are often also speech impairments and cognitive effects after a stroke, such as aphasia that makes it difficult to remember words or understand them, memory problems, or cognitive deficits (Al-Qazzaz *et al.*, 2014). At the level of activity limitations, loss of function in the arms and legs can prevent stroke patients from completing activities of daily living (ADLs) like eating and drinking, dressing themselves, or

cooking meals. The ability to perform tasks like these is initially decreased in 75% of stroke patients (Jørgensen *et al.*, 1999). Many people require help from a family member or full-time caregiver in all of these daily tasks and more. Finally, at the level of social participation, the inability to complete daily tasks, move about unassisted, and speak or understand speech can all contribute to social isolation of the stroke patient. This social isolation, in combination with cognitive deficits, may contribute to post-stroke depression, which affects about 55% of stroke survivors (Towfighi *et al.*, 2017).

Stroke rehabilitation refers to the methods used with stroke patients to improve the function of impaired body parts, increase their ability to complete ADLs on their own, and engage in greater social participation. Improving all three of these levels of human functioning will reduce their overall disability and help them live life closer to how it was before the stroke. There are many rehabilitation methods that can help accomplish this, and these will be discussed in greater detail in the following chapter.

1.3 Objective

The objectives of this thesis are to describe the development of a focal vibration device for stroke rehabilitation, and to test this device in patients with stroke to determine its initial efficacy and feasibility. In Chapter 2, a review of stroke rehabilitation methods and clinical assessments of upper limb function is presented. Chapter 3 describes the development of a wearable focal vibration device for upper limb rehabilitation after stroke. In Chapter 4, my study of the efficacy and feasibility of this novel focal vibration device is presented. Finally, Chapter 5 concludes the thesis and presents some potential future directions for this research on the novel focal vibration device and the field of focal vibration as a whole.

Chapter 2. Literature Review

This chapter presents a review of stroke rehabilitation. The chapter begins with a discussion of clinical assessments of upper limb function and continues with a review of common methods for stroke rehabilitation. Several different standard and experimental methods are presented, with a focus on focal muscle vibration.

2.1 Overview of Clinical Assessment for Stroke Rehabilitation

When discussing stroke rehabilitation, it is necessary to first understand how one can measure the patient's functional gains. Quantitative measurements can help doctors and therapists determine how much a certain treatment has helped patients. This type of assessment can also help researchers develop more effective therapeutic methods. Of course, functional gains may look different from one patient to the next, so it is important to be thorough in evaluating recovery and account for possible subjectivity. There are a variety of stroke evaluation methods that are currently used in clinics, varying from an interview style like the Motor Activity Log (Taub *et al.*, 2011), to evaluation of movement such as the Fugl-Meyer Upper Extremity Assessment (Fugl-Meyer *et al.*, 1975), to functional activity performance such as the Action Research Arm Test (Lyle, 1981) or the Chedoke Arm-Hand Activity Inventory (Barreca *et al.*, 2004). These methods are discussed in greater detail in this section.

There are many standardized methods of evaluation of upper limb function available, and it can be beneficial to include more than one in a study to better capture the patient's range of abilities. Some of the tests have a significant floor or ceiling effect, where patients may score the minimum or maximum possible score. Including multiple tests increases the amount of data

collected for each patient and contributes to an overall better understanding of their abilities, especially when they might score the minimum or maximum on one particular assessment.

In addition to understanding the purpose and scope of an outcome measure, it is also important to examine its reliability and validity. This can be accomplished through the use of psychometric properties, such as inter- and intra-rater reliability or internal consistency. Some commonly used psychometric properties and their definitions are as follows. The intra-rater reliability refers to the ability of the test to provide the same score over multiple testing sessions, assuming the condition being tested is stable. The inter-rater reliability refers to the ability of more than one rater to obtain the same score for the same subject. The minimum detectable change refers to the smallest score necessary to indicate a real change in function and not a change due to randomness. Internal consistency is a measure of how well different items measuring the same thing can produce the same scores. A floor effect occurs when a participant scores the minimum possible score, since it's impossible to differentiate between two different minimum scores, and a ceiling effect occurs when a participant scores the maximum possible score, since it's impossible to differentiate between two maximum scores.

2.1.1 Motor Activity Log

The Motor Activity Log is a standard method of assessing patient function outside of the laboratory setting (Taub *et al.*, 2011). It takes the form of an interview, where the patient is asked a series of questions about the activities they are able to do at home. Questions involve object manipulation tasks like turning a key in a lock, writing with a pen, or eating with a fork; or gross motor activities like getting out of a car, or pulling a chair in to sit at a table. There are two scales for this test, the Amount Scale and the How Well Scale. The Amount Scale refers to how much

the subject uses their affected arm for each activity, as compared to before the stroke, and the How Well Scale assesses the quality of movement. The patient is asked to score from 0 to 5 both how often they do the activity and how well they do it. It is important that they answer based on how much they actually do the activity, not how much they think they might be able to. If the patient responds that they never do the given activity with their affected arm, the test administrator tries to determine why: perhaps someone else always helps them with this task, or perhaps they simply haven't had a chance to do the task in the past week.

The standard version of this test has 30 questions and the total score for each scale is divided by the number of questions asked for a maximum score of 5 points on each of the scales and a minimum score of zero. The intra-rater reliability for this assessment is 0.79 for the Amount Scale and 0.82 for the How Well Scale (G. Uswatte *et al.*, 2006). The inter-rater reliability is not possible to calculate since the subject assigns their own ratings. The minimum detectable change has been reported as 0.5 points, or 10% of the range of the scale (Van Der Lee *et al.*, 1999). The internal consistency of this test is 0.88 for the Amount Scale and 0.91 for the How Well scale (Van Der Lee *et al.*, 2004). The MAL has been reported to have a floor effect of 17.3%, and these authors did not report a ceiling effect (Chuang *et al.*, 2017).

2.1.2 Fugl-Meyer Upper Extremity Assessment

The Fugl-Meyer Assessment of Motor Recovery after Stroke for the Upper Extremity (FMA-UE) determines what movements of the upper extremity the patient is able to perform (Fugl-Meyer *et al.*, 1975). The patient is asked to move their arm, wrist, and fingers in a variety of ways (*e.g.*, shoulder flexion and abduction, wrist flexion, extension, or circumduction, grasping a pencil, cylindrical object, or spherical object, etc.). Additionally, their reflexes, coordination and

dysmetria, sensation and proprioception, passive range of motion, and joint pain are assessed. The tasks start with actions within synergies and progress to actions with little to no synergy. For each task, the patient is given a score of 2, meaning that they can fully complete the task; 1, meaning that they can partially complete the task; or 0, meaning that they cannot complete the task. The subsections of this test, which were used in this thesis work together (upper extremity, sensation and proprioception, passive range of motion, and joint pain), have a maximum score of 126 points and a minimum score of zero.

The Fugl Meyer Assessment is the gold standard assessment of upper extremity function because it thoroughly assesses each joint motion and has been extensively validated. The intra-rater reliability of this test is 0.99 as calculated using Spearman's *R* and intraclass correlation coefficient (ICC), and the inter-rater reliability is 0.97 as calculated using Spearman's *R* and 0.99 as calculated using ICC (See *et al.*, 2013). The minimum detectable change of the FMA-UE is 5.2 points (Wagner, Rhodes and Patten, 2008). This test has an internal consistency of 0.94-0.98 (Lin *et al.*, 2004). The floor and ceiling effects for the upper extremity subsection have been reported as 4% and 4% at admission, respectively, and as 0% and 18% at discharge, respectively; however, the sensation subsection tends to have higher ceiling effects (Lin *et al.*, 2004; Hsueh *et al.*, 2008).

2.1.3 Action Research Arm Test

The Action Research Arm Test (ARAT) is another test of upper extremity function (Lyle, 1981). It has a greater focus on functional tasks, like handling objects, rather than on isolated arm or wrist movements. There are four subsections of this test: grasp, grip, pinch, and gross movement. The patient is scored from 0-3 points on each task. The tasks are given in a hierarchical order. The subject is asked to begin with the hardest task in the subsection, and if

they complete it with the maximum score, it is assumed they would achieve the maximum score for the other items in the subsection and they can move on to the next subsection. If they do not achieve the maximum score on the hardest task, they are next asked to perform the easiest task in the subsection. If they score 0 on this task, it is assumed they would score 0 on all the tasks in the subsection and they can move on to the next subsection. Otherwise, they perform the rest of the intermediate tasks in the subsection and are scored accordingly. In this way, the test may be expedited for a patient who has very high or very low functionality. The materials for this test are very standardized and include wooden blocks of various sizes, a marble, ball bearings, cricket ball, and a standard sized box that both holds all the materials and is part of the test (for example, the patient is asked to move the wooden block to the top of the open box lid in one of the grasping tasks).

This test has a maximum score of 57 points and a minimum score of zero. In one study, the intra-rater reliability was 0.94 if the two ratings were from different sources (one in the laboratory and one videotaped) and 1 if the two ratings were from the same source (both videotaped) (Van der Lee *et al.*, 2001). The inter-rater reliability is 0.93 (Van der Lee *et al.*, 2001). The minimal clinically important difference for the ARAT has been defined as 5.7 points, or 10% of the range of the scale (Van der Lee *et al.*, 2001). The internal consistency is 0.985 (Nijland *et al.*, 2010). The floor effect and ceiling effect have been reported as 12.5% and 17%, respectively (Nijland *et al.*, 2010).

2.1.4 Chedoke Arm-Hand Activity Inventory

The Chedoke Arm-Hand Activity Inventory (CAHAI-7) also focuses on functional activities, with an even greater focus on activities the patient may encounter in daily life. The activities were

chosen based not only on their clinical validity and ability to demonstrate patient functionality with a variety of grasping and pinching motions, but also based on what areas were important to stroke patients in their daily lives (Barreca *et al.*, 2004). The tasks consist of everyday activities like opening a jar lid, dialing a phone, pouring a glass of water, and fastening buttons on a vest. The patient is asked to perform each task using both hands, and the test administrator records on a scale from 1 to 7 how well the patient's affected arm could contribute to the task – from complete independence to total assistance. The affected arm may be used either to stabilize or manipulate during the tasks, with more points given if it can contribute to manipulation of the test materials.

The maximum score for this assessment is 49 points, and the minimum score is 7 points. The test-retest reliability is 0.96 (Barreca *et al.*, 2006). The inter-rater reliability using ICC is 0.98 (Barreca *et al.*, 2005). The minimum detectable change for this test, calculated by multiplying the standard error of measurement by the *z*-value associated with a 90% confidence level is 6.3 points (Barreca *et al.*, 2005). The internal consistency is 0.97 (Barreca *et al.*, 2006). The floor and ceiling effects have not been reported.

2.1.5 Psychometric Properties

The psychometric properties of the four stroke evaluation methods discussed above are summarized in Table 1. These properties include the intra- and inter-rater reliability, the minimum detectable change, the internal consistency, and any reported floor or ceiling effects. Some measures did not have information about all the properties available.

Table 1. Psychometric properties of four clinical assessments of upper extremity function.

	MAL	FMA-UE	ARAT	CAHAI-7
Minimum possible score	0	0	0	7
Maximum possible score	5	126	57	49
Score calculation method	average	sum	sum	sum
Intra-rater reliability	0.79-0.82	0.99	0.94-1	0.96
Inter-rater reliability	-	0.97	0.93	0.98
Minimum detectable change	0.5	5.2	5.7	6.3
Internal consistency	0.88-0.91	0.94-0.98	0.985	0.97
Floor effect	17.3%	0-4%	12.5%	-
Ceiling effect	0%	4-18%	17%	-

2.2 Stroke Rehabilitation

The clinical assessments discussed above can be used as outcome measures in a variety of contexts within stroke rehabilitation. There are many different methods for stroke rehabilitation that have been studied and used with patients. An overview of some of these methods is the subject of this section.

After a person has a stroke, they enter the acute phase of recovery, which can last from two weeks up to six months. Functional gains that occur during this phase are due to physical improvements such as a reduction of swelling and inflammation. After the acute phase is the chronic phase of stroke recovery, from about six months after the stroke onward. In this phase, functional gains are made as the patient retrains their brain how to perform tasks that have become difficult for them. Previously, it was assumed that functional gains in the chronic phase of stroke would plateau after 3-6 months of therapy. However, this has more recently proven not to be the case, as functional gains may continue long after 6 months of therapy (Dobkin, 2004). Regardless of when therapy is begun, there are many types of treatments that can help patients regain the use of their upper limb after having a stroke. Routine treatment includes physical

therapy, during which exercises are done to increase the patient's range of motion, muscle strength and precision, and balance. Occupational therapy is another routine treatment that uses similar principles to physical therapy, but with a greater focus on everyday tasks the patient will need to do to be independent, such as eating, drinking, and using the bathroom. Constraint-induced movement therapy is currently regarded as the best treatment for stroke rehabilitation. Several other emerging treatment methods have also shown promise, including electrical or magnetic stimulation, mirror therapy, and even virtual reality. Vibration therapy is another promising therapeutic tool that can be applied to stroke rehabilitation.

2.2.1 Constraint-Induced Movement Therapy

The gold standard for stroke rehabilitation of the paretic upper limb is constraint-induced movement therapy (CIMT). CIMT consists of restraining a patient's unaffected arm to force them to relearn how to use the affected arm and address learned non-use. It has good outcomes but does require that the patient already has some mobility in their wrist and fingers. This therapy is based on the work of Dr. Edward Taub *et al.* and has shown very positive results in stroke patients (Morris, Taub and Mark, 2006). The main features of this therapy are a combination of elements that are applied for many hours a day for several weeks to encourage the patient to use their affected arm. This is based upon the idea of learned non-use: that during the recovery from a stroke, patients learn not to use their affected arm, and this prevents them from making the fullest possible recovery. The three key elements of CIMT are (1) constraining the less affected arm with a sling or mitt, (2) repetitive, task-oriented training, and (3) a transfer package to integrate the training into everyday activities (Morris, Taub and Mark, 2006).

The constraint is the most easily recognizable element of CIMT. During treatment, the patient will wear a sling or mitt on their unaffected arm for 90% of waking hours, reminding and forcing them to use their affected arm for most tasks. A sling is often used to restrain the entire unaffected arm, but a safety mitt may also be used. The safety mitt is sometimes preferred in patients with balance instability or higher risk for falls, since it still allows them to use their unaffected arm for support in case of a loss of balance. Regardless of the type of constraint, the patient is encouraged to use their more affected arm for as many tasks as possible. Even tasks that were previously performed by the unaffected arm (such as writing when the unaffected arm is also the dominant hand) are required to be performed by the affected arm. When a task requires two hands, the task may be modified or a caregiver might serve as the second hand, to maximize the amount of practice with the affected arm of the patient. Although this is a unique element of CIMT, the constraint itself does not provide functional outcomes without the other elements of the therapy. Some studies have used other elements of CIMT without a physical restraint, relying only on patient commitment and interventionist reminders to use the affected arm for most activities (Gitendra Uswatte *et al.*, 2006). These patients also saw functional gains, but they were less long-lasting than studies that used the physical restraint, potentially because of the overwhelming urge to use the less affected arm even with reminders. On the other hand, in 6 randomized controlled trials that studied forced use – physical constraint of the unaffected arm only, without the other elements of CIMT like task-oriented training – no functional benefit was added at all (Kwakkel *et al.*, 2015).

Repetitive, task-oriented training is the main effective element of the therapy. Patients train with an interventionist for 3-6 hours per weekday of the training period, usually 2-3 weeks.

They practice shaping activities and task practice. In shaping activities, a small task such as placing a block on top of a box is performed repeatedly. The task can be made more difficult as appropriate as the patient improves, for example by moving the target further away from the patient or requiring them to complete the task more frequently in a given time frame. In task practice, the patient completes more functional, less structured activities, like folding towels. In both types of activities, the patient is given feedback and encouragement from the interventionist. This repetitive, task-oriented training makes up the majority of the CIMT treatment and has been shown to be essential for the functional gains the therapy offers.

The third element of CIMT is the transfer package, which consists of behavioral methods used to enhance adherence to the protocol and transfer the functional gains made in the clinic to the patient's real-life activities. There are several methods used to achieve this, including a behavior contract, activity log or diary, problem-solving, and home-skill assignment (Morris, Taub and Mark, 2006). The behavior contract identifies the activities which are to be done with the affected arm, and may even suggest activities to do during idle time (such as turning the pages of a magazine with the affected arm occasionally during time spent watching TV). Entering into a formal agreement helps increase adherence to the protocol. Monitoring or recording daily activities in an activity log or diary can also increase adherence. In problem-solving sessions, patients may be asked why they did not do a certain task with their affected arm, and alternate solutions like using an assistive device or modifying the task to make it easier will be discussed. Home-skill assignment asks the patient to spend about 30 minutes per day at home doing tasks with their affected arm that they might not normally try. The patient may be asked to choose

tasks from a list, and to pick some that they think will be easy for them and a few that they think will be challenging for them.

In a review of CIMT, one large randomized controlled trial (RCT) using the original CIMT protocol was found, and 44 other smaller RCTs using a modified version of CIMT were investigated (Kwakkel *et al.*, 2015). The modified CIMT protocols used the same foundational principles of CIMT, but adjusted treatment duration, the amount of time that the unaffected arm was restricted, or to the transfer package. Even the wide variety of modified CIMT protocols produced significant positive results after training and at follow-up. Overall, this treatment method has been shown to be very effective, but it does require that patients already have some voluntary function in their wrist and fingers. This metric alone has been shown to be a very strong indicator for whether a patient will be able to recover from a stroke (Kwakkel *et al.*, 2015).

2.2.2 Neuromodulation for Rehabilitation

Neuromodulation refers to the targeted delivery of a stimulus with the aim of alteration of nerve activity in nervous tissues such as the brain and spinal cord. Trans-cranial direct current stimulation (TDCS) is one method for directly stimulating the brain. In this treatment method, surface electrodes are placed on the scalp, and a constant current stimulator provides current directly to the brain. The direction of current flow determines whether the excitability of the area of the brain the electrodes are applied to is increased or decreased (Schlaug, Renga and Nair, 2008). In this way, the likelihood that neurons will fire can be modulated. For example, the ipsilesional sensori-motor cortex could be activated, which correlates with good recovery and increased neuroplasticity (Schlaug, Renga and Nair, 2008). On the other hand, it is uncertain whether a contralesional activation pattern is a positive phenomenon of reorganization or a

maladaptive phenomenon that may get in the way of recovery. This could be examined further by using TDCS to suppress activation in the contralesional side of the brain during therapy.

TDCS may have advantages over other brain stimulation methods because of its ease of use, its portability which makes it possible to combine with other types of therapy simultaneously, and its capability of influencing a wider region of the brain (Schlaug, Renga and Nair, 2008). It also has a sham mode where the current is turned off after about a minute, which feels the same to the patient as applying current for longer than one minute. However, it is limited by poor temporal resolution, anatomical localization, inter-individual variation, and undetermined safety of prolonged stimulation (Schlaug, Renga and Nair, 2008).

Transcranial magnetic stimulation (TMS) works in a similar way to TDCS, except it uses magnetic field pulses to induce electrical activity in the brain (Hoyer and Celnik, 2011). TMS can be used to directly stimulate the brain in a therapeutic manner, or it can be employed to study causality of phenomena that have been observed using fMRI. Like TDCS, TMS can be used to modulate cortical excitability, and make specific areas of the brain either more or less likely to be activated. In combination with other training exercises, this can enhance the neuroplasticity and the motor gains induced by the training (Hoyer and Celnik, 2011). TMS can also be used at the primary motor cortex to elicit motor evoked potentials (MEPs) of contralateral muscles, which causes these muscles to contract and serves as a quantification of cortico-spinal excitability (Bestmann and Krakauer, 2015). The amplitude and latency of the MEPs can be useful outcome measures in studies of stroke rehabilitation, especially those that target the excitability of the cortico-spinal tract, as with TDCS.

2.2.3 Assistive and Rehabilitative Technologies

In addition to traditional treatment methods like physical and occupational therapy and CIMT, some more experimental treatment methods like mirror rehabilitation, virtual reality, tele-rehabilitation, robotic-based rehabilitation, etc. have shown promising results in stroke patient rehabilitation.

2.2.3.1 Mirror Therapy

Mirror therapy was developed in the 1990s to treat chronic pain associated with phantom limb syndrome in amputees (Hoffman, 2019). The general principle of the treatment is to create an illusion that the impaired limb is functioning and activate the mirror neuron system, which in turn activates the somatosensory cortex and promotes neuroplasticity in the patient. During a mirror therapy session, a mirror will be placed to separate the affected and unaffected arms. The patient will do exercises with their unaffected arm like flexing and extending their fingers, manipulating objects, or walking their fingers across the surface of the mirror. Meanwhile, the affected arm is hidden from view, which can trick the brain into thinking both hands are performing the tasks. After learning the therapy protocols, the patient can perform the tasks on their own at home, ideally in 30-minute daily sessions for at least 6 weeks. This type of therapy may not be suitable for patients who do not have the cognitive abilities to perform the therapy on their own at home. Patients who have visual or physical impairments that prevent the illusion from working or the unaffected arm from carrying out the tasks properly also may not benefit. Studies of this therapy have shown promising results – one study of mirror therapy in 36 patients found that the group receiving mirror therapy showed improvements in function compared to the control group (Dohle *et al.*, 2009). While there were several functional improvements found in this study, many did not achieve statistical significance. This therapy works because of the

mirror neuron system, which was first discovered in rhesus monkeys but has also been evidenced in humans (Carvalho *et al.*, 2013). Mirror neurons are found in the motor cortex and are activated by observing an action, not just by doing it.

2.2.3.2 Virtual Reality

Virtual reality (VR) is another emerging treatment method, defined as "computer-based technology that allows users to interact with a multisensory simulated environment and receive 'real-time' feedback on performance" (Saposnik and Levin, 2011). The virtual reality system can involve patients in rehabilitation through engaging video games that help them with task-oriented practice and can provide real-time feedback and/or an illusory effect like in mirror therapy. There is some evidence that VR induces neuroplasticity in patients, but in most of the studies reviewed, the sample sizes were relatively small and there was not evidence of a statistically significant improvement over conventional therapy approaches (Laver *et al.*, 2017). There is evidence that functional activities prior to VR activated the contralesional hemisphere, while activities after VR training activated the ipsalesional hemisphere (Laver *et al.*, 2017). This is important because recovery of movement requires some reorganization of the cortical index, recruiting nerves from the opposite side to accommodate for what was lost in the injury. Virtual reality is still a promising treatment method in combination with other more conventional therapies, but further investigation is warranted.

2.2.3.3 Robotic Rehabilitation

Robotic-based therapy is another promising new treatment option. In addition to assistive robots which help patients compensate to complete tasks they would not be able to on their own, therapeutic robots can help with task-specific training to rehabilitate the patient and

improve motor function (Chang and Kim, 2013). There are two main types of therapeutic robots: end-effector and exoskeleton robots. End-effector robots provide forces at the distal end of the patient's limb, but this may produce unnatural movement patterns; on the other hand, exoskeleton robots have axes aligned with the anatomical axes of the user, but these are more expensive (Chang and Kim, 2013). Several studies of end-effector type robot therapy in upper limb motor function have been effective at high intensities of treatment. Although there was less improvement compared to conventional therapy in the first couple weeks of treatment, patients with robot-based therapy kept making gains in the last couple weeks of treatment when conventional therapy methods had plateaued (Chang and Kim, 2013). Exoskeleton robot-based therapy for upper limb function has proved to be comparable or slightly better than conventional therapy, but there have been few significant improvements.

2.2.3.4 Tele-Rehabilitation

Recovery and rehabilitation after a stroke involves many hours of multidisciplinary therapy, including speech therapy, physical or occupational therapy, and psychiatric therapy to address post-stroke depression. It may be a challenge for the patient to get transportation to the clinic or for these resources to be available often enough for maximum recovery. Home-based tele-rehabilitation is a promising solution for therapists to provide support from a distance and evaluate or treat patients from home. A 2018 review on tele-rehabilitation therapies found them to be as effective as in-person therapies, if not better, in 18 studies of motor function (Sarfo *et al.*, 2018). In-clinic rehabilitation also resulted in more expenses for patients than tele-rehabilitation did.

Of course, since the beginning of the COVID-19 pandemic, there has been a rise in the use of tele-rehabilitation, especially for patients who are at a high risk of complications if they contract the virus. Patients with a history of stroke are about 2.5 times more likely to progress to a severe stage of COVID-19, and existing psychological conditions like depression or anxiety are likely to be exacerbated by the pandemic, resulting in a greater need for care (Chang and Boudier-Revéret, 2020). Tele-rehabilitation is especially important to protect these high-risk patients from infection while still allowing them to make improvements from therapeutic interventions, especially in the first 6 months after the stroke which are especially critical for recovery.

2.2.3.5 Vibration Therapy

Another method for stroke rehabilitation that can be combined with conventional physical and occupational therapy for improved results is vibration therapy, which is the focus of the rest of this review chapter. Vibration therapy includes whole-body vibration and focal vibration, where a vibratory stimulus is applied to a specific limb or muscle. Vibration therapy works to stimulate the patient's muscles and is thought to activate the Ia muscle spindle fibers.

2.3 Vibration Therapy

Vibration first emerged as a therapeutic tool in the 1880s, when French neurologist Jean-Martin Charcot noticed that his Parkinson's patients showed improvement in tremor after a train or horseback ride. He created a chair that would vibrate the patient's whole body for 30-minute sessions. Since then, the use of vibration in neurorehabilitation has expanded to include treatment for many other pathologies like multiple sclerosis, age-related muscle loss, myofascial pain syndrome, and stroke (Saggini *et al.*, 2016). Methods for whole-body vibration (WBV) treatments have also become more refined – they now usually take the form of a platform that

the patient stands on to deliver the vibration at a frequency of 15-60 Hz (Saggini, Bellomo and Cosenza, 2017). Vibration was first used to treat stroke patients in the late 1960s, around the same time that the tonic vibration reflex (the phenomenon that muscle vibration elicits agonist contraction and antagonist relaxation) was discovered. Vibratory stimuli were used to decrease muscle spasticity in stroke patients. Vibration therapy has benefits of being non-pharmacological and non-invasive as a treatment method.

WBV studies in stroke patients have had somewhat varied results. One review compared the methods and results from eight different WBV studies on stroke patients (Celletti *et al.*, 2020). They found a wide range of study parameters, like frequency ranging from 5 to 40 Hz, vibration duration from 30 seconds to 2.5 minutes, and number of sessions from 1 to 30. The effects of whole-body vibration in these studies seem to be equally varied. Some studies saw significant improvements in balance, muscle strength, and spasticity, and other studies did not see improvements even though they measured the same outcomes. Similarly, another review of WBV mentions that one study they reviewed showed patient improvement in both paretic and non-paretic limbs after WBV at 20 or 30 Hz, but a similar study did not show quite as positive results after WBV at 50 Hz, possibly due to patient fatigue (Saggini, Bellomo and Cosenza, 2017). A meta-analysis of the effect of WBV on stroke patients as evidenced by changes in motor functions and body structures found that WBV had only a small effect size (Park, Park and Lee, 2018). However, they found that WBV has a larger effect on the spasticity that causes gait impairments than the gait impairments themselves (Park, Park and Lee, 2018). Ultimately, WBV studies could benefit from more standardized protocols to control for possible differences in frequency, duration, number of sessions, outcome measures, and several other parameters.

Additionally, larger sample sizes would lend more confidence to the results – most of the studies cited had sample sizes of less than 30 patients per group (Celletti *et al.*, 2020). A greater number of studies using WBV can help understand the effects especially according to the timing after stroke (Park, Park and Lee, 2018).

Another form of vibration therapy in neurorehabilitation is focal muscle vibration (FMV) therapy. In this type of treatment, the vibratory stimulus is applied not to the whole body but to a specific limb or muscle. This therapy has several advantages, including a greater range of possible frequencies: while WBV has a maximum frequency of about 60 Hz before adverse effects would take place, FMV can utilize frequencies of up to 300 Hz (Saggini *et al.*, 2016). Different frequencies have been shown to have different advantages. Low frequencies up to 50 Hz target muscle relaxation, medium frequencies from 80-100 Hz improve proprioception and spasticity, and high frequencies from 200-300 Hz can strengthen muscle fibers (Saggini *et al.*, 2016). By applying vibration directly to the affected limb of the patient, higher frequencies may be used than are possible using WBV, and improvements in spasticity and proprioception may be made. FMV is also more localized and targeted to the specific muscles of interest, as opposed to WBV which is applied generally to the whole body without specific targeting.

FMV also has the advantage of being more portable than WBV. Where WBV treatment apparatuses usually consist of a platform the patient stands on that applies vibration to their whole body, FMV can take the form of a much smaller device that can be held in the hand of the therapist or patient, worn on the affected limb, and even used outside of a hospital or clinic setting. Wearable FMV devices can allow for at-home treatment, so the patients do not have to

travel to the clinic every time they are scheduled for a vibration session. The portability and wearability of FMV devices is more convenient for patients and their caretakers.

FMV is thought to work by inducing activation of the Ia afferent spindle fibers in the muscles, as evidenced by the suppression of the H reflex during vibration (Murillo *et al.*, 2014). There are also effects at the cortical level since the central nervous system receives proprioceptive signals from the peripheral nervous system. The afferent muscle spindle fibers carry the vibratory signal to the somatosensory cortex via the dorsal column-medial lemniscus pathway. Vibration has been shown to lead to an increase in neuronal excitability, and perhaps a decrease in the excitability of the antagonist muscle. This may enable reorganization at the cortical level, which is important for regaining motor function of the affected limbs when that part of the motor cortex is damaged. Activity in response to vibration occurs not only in the somatosensory cortex but also in the motor cortex, premotor cortex, and supplementary and cingulate motor areas (Murillo *et al.*, 2014). This activity in motor areas of the brain is the main reason FMV is thought to help patients strengthen and control their muscles after treatment. Activating these areas of the brain is key in helping patients to retrain their brain and recover lost function.

Focal vibration is used throughout neurorehabilitation in general to reduce spasticity, to facilitate muscle contraction for functional activities, to stimulate the proprioceptive system, to obtain better motor control, and to provide proprioceptive training and restore sensorimotor organization (Celletti *et al.*, 2020). Studies tend to vary with respect to several important parameters, such as amplitude and frequency of vibration, number and duration of treatment sessions, muscles targeted, and outcome measures assessed (Wang *et al.*, 2020). For example, in

studies of focal vibration for upper limb rehabilitation after stroke in the past decade, there were many differences in these key parameters among 15 different studies (Noma *et al.*, 2012; Caliandro *et al.*, 2012; Tavernese *et al.*, 2013; Paoloni *et al.*, 2014; Casale *et al.*, 2014; Constantino, Galuppo and Romiti, 2014; Go and Lee, 2016; Calabrò *et al.*, 2017; Celletti *et al.*, 2017; Choi, 2017; Costantino, Galuppo and Romiti, 2017; Jung, 2017; Annino *et al.*, 2019; Li *et al.*, 2019; Toscano *et al.*, 2019). Among these studies, the amplitude of vibration ranged from 0.01 mm to 2 mm, a difference of two orders of magnitude. The frequency of vibration ranged from 30 to 300 Hz, a difference of one order of magnitude. Since there is evidence that different frequencies of focal vibration have different effects, these studies may have actually had different effects on their participants, ranging from muscle relaxation to strengthening muscle fibers (Saggini *et al.*, 2016). Number and duration of treatment sessions also varied greatly: one study only performed one session of focal vibration (Noma *et al.*, 2012), while another study had 40 different sessions over the course of 8 weeks (Calabrò *et al.*, 2017). Most studies fell in the middle of this range, with about 10-12 sessions total (Tavernese *et al.*, 2013; Casale *et al.*, 2014; Constantino, Galuppo and Romiti, 2014; Paoloni *et al.*, 2014; Go and Lee, 2016; Choi, 2017; Costantino, Galuppo and Romiti, 2017). The vibration sessions also varied in duration, from 3 minutes (Li *et al.*, 2019) to 1 hour (Calabrò *et al.*, 2017), with the majority of studies performing 30 minutes of focal vibration (Tavernese *et al.*, 2013; Casale *et al.*, 2014; Constantino, Galuppo and Romiti, 2014; Paoloni *et al.*, 2014; Go and Lee, 2016; Costantino, Galuppo and Romiti, 2017; Jung, 2017; Toscano *et al.*, 2019). Target muscles varied greatly, with the most common muscles being the biceps, triceps, flexor carpi radialis and ulnaris. Other target muscles included the pectoralis minor, deltoid, wrist flexors, and hand and finger muscles. The outcome measures

chosen were different from each study to the next. Some common measures included grip strength, Modified Ashworth Scale (MAS), FMA-UE, and the Box and Block Test (BBT), but numerous others were chosen by different groups.

Although most of the studies saw significant improvements in their chosen outcome measures after focal vibration, all of them were limited by small sample sizes – none of the experiments had a sample size larger than 30 in the experimental group, and 67% of the studies reviewed had a sample size of 15 or less in the experimental group. Almost all of the studies explicitly recommended future studies to include a larger sample size, longer follow-up time, and/or more standardized protocols. Thus, according to the repeated recommendations from those researching focal vibration, there is a pressing need for more studies with randomized trials and larger sample sizes, with aims of determining which parameters produce the best results. This will lead to a greater understanding of the effects of FMV on stroke rehabilitation. Standardized, validated protocols will benefit patients and ensure the most effective treatment regimen.

2.4 Problem Statement

One potential problem with many stroke rehabilitation treatments is that of under-dosage. It is not certain how much treatment is necessary to produce the best results and the greatest functional gains. One benefit of a focal vibration device is that the patient could take the device home and continue to use it as long as it is helping improve function, for weeks, months, or beyond after the beginning of treatment. Another aspect many of the other stroke rehabilitation methods, especially CIMT and conventional physical therapies, have in common is the large number of hours required to be in the clinic working with a therapist. This can be a

burden on patients who may have trouble getting transportation to a clinic site every day for several weeks. Costs of travel and in-person care can also be a barrier to receiving enough rehabilitative care. Especially during the COVID-19 pandemic, there are additional risks associated with leaving the home and going into a clinic for treatment. Thus, there is a need for more home-based rehabilitation methods, that can help patients make significant functional gains without requiring travel or face-to-face hours with a therapist.

The specific FMV treatment parameters and ideal amount of dosage represent gaps in the field that need to be examined before FMV can be widely used or accepted as a rehabilitation method. The potential functional gains from this treatment also need to be thoroughly quantified. First, however, it is important to develop appropriate focal vibration devices that will be of use not only to patients, but also to the therapists who are assigning treatment and monitoring functional gains. The goals of this research are to describe the development of one such focal vibration device, and to test the device with stroke patients to gather information about its efficacy and feasibility for use in the clinic.

Chapter 3. Focal Vibration Device Design

This chapter focuses on the development of a novel focal vibration device (FoVi device). The device was developed by other members of the Technology for Occupational Performance Laboratory (TOPL) with input from a focus group of physical therapists, occupational therapists, and stroke patients (Wang *et al.*, 2022). Focus group meetings and prototype design sessions occurred from spring 2019 to spring 2020. This work was done before I began studying in Dr. Wang's lab. My main contributions to the manuscript cited throughout this chapter were revising and proofreading the writing. The information discussed in this chapter is included to provide further context and details behind the work I did in the short-term intervention study described in Chapter 4. An iterative design process was used for the development of the device, including the presentation of initial design plans and prototypes to the focus group to get feedback from therapists and patients. Their feedback was then used to refine and rework the design to ensure it meets patient and therapist needs as intended.

Previous focal vibration studies have used a variety of focal vibration devices to deliver the vibration intervention to their participants. Some examples are CroSystem (Caliandro *et al.*, 2012; Toscano *et al.*, 2019), VIBRA (Casale *et al.*, 2014), ViSS (Constantino, Galuppo and Romiti, 2014; Costantino, Galuppo and Romiti, 2017), Vibraplus (Calabrò *et al.*, 2017), and Thrive MD-01 (Choi, 2017; Jung, 2017). These have a variety of mechanisms and procedures for usage: CroSystem is rigidly anchored to the floor and a mechanical arm is moved with an electromechanical transducer (Caliandro *et al.*, 2012; Toscano *et al.*, 2019), VIBRA and Vibraplus work via a pneumatic vibrator that delivers compressed air (Casale *et al.*, 2014; Calabrò *et al.*,

2017), ViSS depends on the action of a mechano-acoustic square wave (Constantino, Galuppo and Romiti, 2014; ViSS Manufacturing Company, 2015; Costantino, Galuppo and Romiti, 2017), and Thrive MD-01 is available for commercial purchase and works like a massage gun, but limited technical specifications for this device were available (Choi, 2017; Jung, 2017). These devices have limitations that prevent them from being useful for home-based rehabilitation. Since the CroSystem is attached to the floor for stability, it is not portable and must be used in the clinic. Patients using this system would have to travel to the clinic each time they need treatment. Although other systems like VIBRA, Thrive MD-01, and ViSS are more portable or even handheld, they still require someone to hold the device on the targeted location for the duration of the treatment. If the target location is at an awkward angle, this can be difficult for the patient to do themselves and may require a caretaker to hold the device the entire time. These inconveniences may lead to reduced compliance to the given treatment protocols and schedules.

Although none of the devices used in previous focal vibration studies were wearable, there are a few commercially available wearable focal vibration devices: Myovolt (Myovolt, Christchurch, New Zealand), VibraCool (Pain Care Labs, Atlanta, Georgia), and Equistasi (Equistasi, Gorgonzola, Italy). However, these have some other challenges in that even though they are wearable, there is still some awkward reaching involved in turning on the device using a switch, and they do not record a log of usage. It would be easier for patients if the wearable focal vibration device could be put on, taken off, and turned on with one hand, and if a usage log was created and sent in real-time for better compliance and communication with therapists.

The goals of creating this device in comparison to other commercially available focal vibration devices were to develop something easy for patients to use even with limited

functioning in one arm, and to send reminders and track their usage in real time rather than depending on the patient alone to follow a schedule and log their usage. Greater communication with the therapist through the app could help make sure protocols and schedules are being followed as prescribed, ensure complete usage data, and allow for real-time changes and adjustments to treatments.

To achieve these goals, the FoVi device was developed with two control electronics boxes that control 2-3 motor pods each. The motor pods apply vibration to the desired muscles. The electronics boxes and the motor pods are all housed in a sleeve with adjustable straps that is easy for the patient to put on and remove. An app was also developed that can communicate with the device via Bluetooth. Therapists can put protocols and schedules onto a patient's profile; the app will be used to remind patients when it is time for a treatment and to control the motor pods according to the protocol.

From the iterative design process, a working prototype was developed according to the final device design. This chapter describes the methods used in assembling a focus group and going through the iterative design process. Then, the final device design is described in detail. Finally, after the working prototype was developed, I performed a feasibility study using the working prototype with patients – that study is the focus of the next chapter.

3.1 Methods

3.1.1 Focus Group

To begin to design the FoVi device, it was necessary to first understand what design criteria would be most useful and beneficial to the intended users of the device: stroke patients and therapists. To help better understand user needs, develop appropriate design criteria, and

prioritize system capabilities, a focus group was consulted. The focus group consisted of occupational therapists (OTs), physical therapists (PTs), and stroke patients. To participate in the focus group, therapists were required to be over 18 years of age and to have clinical experience working with stroke patients for at least three years. Stroke patients were required to be in the chronic phase of stroke recovery (at least two years after the stroke), have some ongoing hemiparesis of the upper limb, and be in a medically stable condition. The focus group met either in the research laboratory or remotely four times to provide their opinions on the device design and give their feedback. This focus group was approved by the University of Oklahoma Institutional Review Board (IRB), and formal consent was obtained from the focus group participants before the sessions began. During focus group sessions, there were discussions about previously existing focal vibration devices and the aims and objectives of the current project. Questions were asked about what features would be most useful, and what method of putting on and controlling the device would be most convenient. Later, the concept and initial prototype for the device was presented to the focus group, and members provided feedback about the ideas.

3.1.2 Initial Device Design

The goal of this work was to develop a working prototype of a focal vibration device to assist in upper limb rehabilitation after a stroke. With feedback and input from the focus group, it was clear that the device should be easy to put on, take off, and set up, and it should be comfortable to wear without interfering with normal movements or function. To fit the requirements, five key initial design criteria were identified:

1. The device should be a wearable device with six independently controlled focal vibration pods to deliver vibratory stimuli to different muscles,
2. The device should have configurable vibration protocols, including the capability for frequencies between 60-300 Hz and amplitudes between 0.1 and 10 mm,
3. The device should permit controllable activation and deactivation of each vibration motor using a wireless remote-control interface,
4. The device should be comfortable, easy to wear, affordable, and flexible,
5. The device should include an interface for therapists to track the device usage, monitor compliance, and remotely adjust the vibration intensity and dosage (Wang *et al.*, 2022).

Other design criteria included the ability for the device to be put on and taken off one-handed, since most stroke patients have very limited use of one arm and full use of the other arm. It would be most useful to patients if they are able to put on and take off the device on their own, without help from someone else. The device should also be rechargeable. For therapists, it would be most useful if the device logged usage information of the vibration protocols and allowed therapists to view and edit protocols remotely as needed.

The device will target muscles associated with reaching and grasping with the upper limb. For reaching, these muscles are the triceps brachii, the common extensor tendon origin on the lateral epicondyle of the humerus, and the tendons of the dorsal wrist (Figure 1). For grasping, these muscles are the biceps brachii, the common extensor tendon origin on the lateral epicondyle of the humerus, and the common flexor tendons on the palmar surface of the wrist (Figure 1). These muscle locations were chosen based on recommendation from therapists and evidence from previous research. One previous study applied vibration to the triceps brachii and

the extensor carpi radialis longus and brevis, and they found that the intervention improved grip strength and hand function and decreased spasticity (Costantino, Galuppo and Romiti, 2017). This informed our decision to target the triceps brachii and the common extensor tendon origin to improve reaching. Another study applied focal vibration to the biceps brachii and flexor carpi radialis, and they saw increased grip strength and dexterity as measured with the Box and Block Test (Jung, 2017). This informed our decision to target the biceps brachii and the common flexor tendons of the wrist to improve grasping.

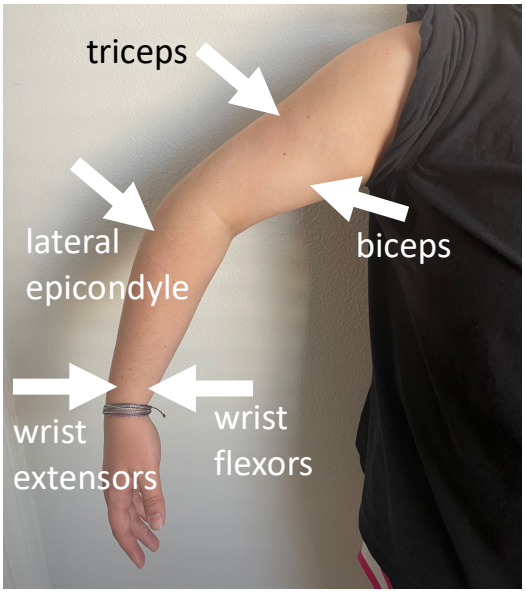

Figure 1. Targeted muscles associated with reaching and grasping.

To address design requirements of being easy for the patient to use and control the device, and for the therapist to view and edit vibration protocols and schedules, a smartphone app was planned to conveniently control the device. Design requirements for this app included a display of the vibration information including frequency, amplitude, and which motors were active; data collection running as a background program, with vibration motors accessed from

the background program; recording and monitoring of usage information in the background, without interfering with other smartphone functions such as phone calls and text messages; safety warnings and reminders about scheduled vibration sessions; and a website portal for therapists to access information about usage, user compliance rates, safety warnings, and reminders (Wang *et al.*, 2022). The remote-control interface should communicate with the user's smartphone using Bluetooth 4.0, and commands should be sent in binary for optimal microcontroller and data transmission efficiency. The InsightTM platform was used through the Mobile Health (mHealth) Shared Resource and the Stephenson's Cancer Center to develop, customize, test, and launch the user phone app and therapist web portal.

3.1.3 Iterative Design Approach

As the prototype of the focal vibration device was developed, modifications were made to some of the original device design criteria to reflect further insights gained from the focus group and adjust the design to make the device more feasible (Wang *et al.*, 2022).

Firstly, although the original design requirement stated that each vibration motor pod should be independent from other electronic components, after testing of the original prototype, this criterion was changed. It was more feasible to have independent electronics boxes that each control up to four vibration motors. The electronics boxes still met the rest of the design requirement of being rechargeable and wirelessly controlled. Instead of having independent, wireless, rechargeable vibration pods, several pods are controlled by one electronics box that receives the wireless commands and sends them to the appropriate vibration motor pod. This new design was a manageable middle ground between having too many wireless components,

which would become too bulky, or having too many wired components which would also be difficult to work with.

Secondly, the original design of the device was intended to have commands in binary for maximum data transmission and microcontroller efficiency. However, through working with the Android app development team, the design was changed to include string commands instead of binary commands. The tradeoff with this change was that microcontroller programming became more complicated, but development of the Android app became easier.

Thirdly, feedback from the focus group indicated that all the intended users of the focal vibration device may not be smartphone users. So, instead of a smartphone app being the only option for controlling the device, a new design requirement was added to include a non-smartphone, microcontroller-based wireless remote to control the device, which could be used in place of the smartphone app if the patient prefers not to use a smartphone. This remote control should have the same firmware as the rest of the device, and should also be rechargeable and record the date and time of commands.

Finally, more feedback from the focus group revealed that patients would prefer to be able to wash the device sleeve at home, especially if treatment schedules indicated that they would be wearing the device for long periods of time between lab or clinic visits. The original prototype of the device included a wearable sleeve that would be discarded or washed only when the patient returned the device, with the intention that the patient would use disinfectant spray at home if they wanted to clean the sleeve. This way, the device would only be removed from the sleeve by the engineers or therapists. The new design requirement is for a sleeve with a removable device, allowing the patient to wash the sleeve at home. However, this also means

that the device needs to be reinforced so patients cannot accidentally damage it during removal from the sleeve. Currently, adjustments are still being made to protect the device while still meeting the new design requirement of the device being removable from the sleeve.

3.2 Final Device Design

3.2.1 Sleeve Design

The final device is planned to have two sleeves with embedded motor pods and electronics boxes, which will be in pockets for security and easy removal by the patients if they want to wash the pockets (Figure 2). Each sleeve will have one control electronics box and several vibration motor pods which are controlled by the box. The sleeve will be made of Micromodal fabric, which is breathable, wicks moisture, and is comfortable for prolonged close contact with the skin. Velcro straps are located around the motor pod, which can be closed and tightened to secure the sleeve to the arm. The end of the strap can be looped around while holding the other end of the strap down with the thumb of the same hand, making it ideal for one-handed operation. Some members of the focus group suggested using hook-and-loop cinch straps such as the straps found on some shoes. However, our in-lab testing demonstrated that in this context, pulling on this type of strap caused the whole sleeve to rotate around the arm. Due to this finding, a simple strap design was chosen instead (Wang *et al.*, 2022).

Figure 2. Sleeve design with vibration pods and control electronics box in pockets. Velcro straps are looped around the vibration pods and can be tightened with the other hand. (Wang *et al.*, 2022)

3.2.2 Vibration Pod and Electronics Design

The vibration pods house 3V eccentric rotation mass (ERM) motors (14 mm length, 6 mm diameter). The pods are disk-shaped (28 mm diameter, 10 mm thickness), and they are 3D-printed from polylactic acid (PLA) and sealed using epoxy (Wang *et al.*, 2022).

The electronics box hardware includes a custom printed circuit board (55x30 mm) with a Microchip ATmega328 microcontroller (3.3 V, 8 MHz). This microcontroller can independently control up to four vibration motor pods with up to 500 mA each. The box is powered by a rechargeable 500 mAh battery, which is expected to last at least one hour per charge. The microcontroller is able to monitor its own battery voltage, which changes as the battery is discharged. There is a status LED light which turns on to indicate that the battery needs to be recharged. The change in battery voltage is accounted for when setting the pulse width modulation for the motors, to maintain a constant vibration intensity.

Commands are sent from the user to the microcontroller wirelessly, using Bluetooth through the Android app or a radio module for the wireless remote control. The Android

smartphone app or wireless remote control serves as the “controller device”. Each electronics box (also called a “responder device”) controls up to four motor vibration pods in its sleeve (Figure 3). A command packet string is sent from the controller device to the responder device and contains commands for all four motors connected to the responder device.

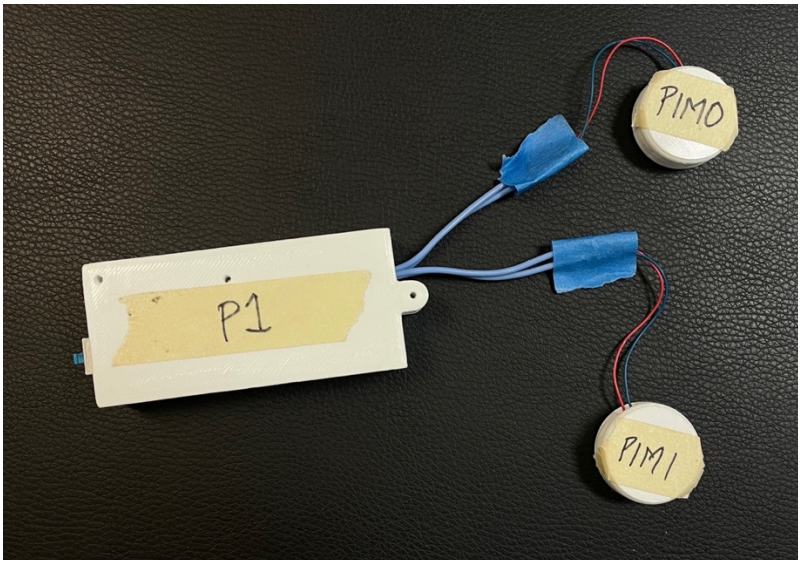

Figure 3. Control electronics box (P1) with two vibration motor pods (P1M0 and P1M1) attached.

3.2.3 User Interface

The user interface encompasses the parts of the app and device control that the various intended users will interact with, namely therapists and patients. The therapist interface is used to define focal vibration therapy protocols and assign them to patients, create patient portals, and distribute schedules to patients. This is all done using a web-based portal, which receives information such as device usage logs from the app, and can send patient schedules and therapy session protocols to the app. The therapy session protocols consist of vibration sessions with specific motors, with optional breaks in between. Patient schedules are defined as the assignment of protocols to the patient over a defined calendar period, *i.e.,* the number of days

per week and number of weeks the patient should complete the protocols. The usage log includes all the commands sent to the sleeves and the time-stamped acknowledgement packets given in response.

The patient interface includes protocol and scheduling information, which are downloaded to the phone when the patient profile is set up. The app will generate a push notification to the smartphone when it is time for the vibration therapy to begin, and reminders can also be set prior to the scheduled time for the treatment. Tapping on the push notification will launch the app and prompt the user to tap the “go” button when they have put on the device and are ready to begin. Once the patient confirms they are ready to start, the app will begin to send the pre-assigned protocol commands for the vibration motors to the electronic boxes. The app will log all commands sent to the electronic boxes, all the received acknowledgements, and any reminders or safety warnings, with their respective timestamps. When there is an internet connection, these logs are sent to the therapist web portal, or if there is no internet connection for the entirety of the patient’s at-home treatment the uploading can be done at a follow-up visit when the device is returned. If the patient is using the wireless remote control instead of the smartphone app, then protocol commands are programmed directly into the microcontroller. They will have a printed schedule that they need to follow, since the remote is only turned on when it is time for a session, with no reminders. The remote has a single start/stop button and LEDs to display status information. It runs on three AA batteries rather than a battery that would need to be recharged. The remote has a Real Time Clock that records the timestamped transmitted commands and received acknowledgements, and enough memory to record four

weeks' worth of treatments. The logs are uploaded using USB when the device is returned by the patient.

3.3 Discussion

This portion of the project focused on developing a prototype of the FoVi device that could be used to apply focal vibration to the muscles of the affected upper limb of stroke patients. We succeeded in creating a prototype that consists of electronics control boxes and motor pods to apply the focal vibration. An app was also created that works with the device using Bluetooth to send reminders and control the vibration pods according to a protocol and schedule that has been programmed into the app for the specific patient. This prototype is expected to meet the design criteria outlined. Other commercially available vibration devices like Myovolt are not able to record patient usage logs or send reminders when it is time for treatment. Additionally, the Myovolt device has three preset vibration frequencies, but the FoVi device can have more specific adjustments to frequency and amplitude. Using the app to communicate information directly with therapists is another benefit to the FoVi device compared to other focal vibration devices.

3.3.1 Limitations

Some limitations of this work include delays in the design process which have prevented the final device prototype from being ready for long-term, at-home use at this time. For example, when the design criteria were changed to allow the sleeve to be washable, that caused delays in preparing the sleeve since the device needed to be reinforced for user handling. The sleeves are currently manufactured by hand, and this process needs to be simplified to improve the speed and accuracy of manufacture and allow for different sleeve sizes. Additionally, the Android app and software are currently still in the final stages of being tested for user readiness and reliability.

Although the hope was to have the sleeve and app ready for patients to take home and use in a long-term intervention study, because laboratory personnel can control the device directly and use Velcro straps without the sleeve to secure the device to the patient's arm, a short-term intervention feasibility study was possible.

3.3.2 Future Work

After the working prototype was developed, the next step was to test it out in a feasibility study. The goals of the feasibility study are to continue to get patient feedback about the device design. Specifically, we want to know if the device meets the design requirements of being comfortable, flexible, and easy to wear, put on, and take off. We also want to know if the vibration parameters are appropriate for treating the upper limb of patients affected by hemiplegia from stroke. Finally, we want to learn whether the device has an effect on mobility and functionality of the upper limb.

Another possible future direction from this work would be to ask other potential consumers for more opinions. A survey could potentially be sent out to stroke patients and therapists outside the community. This survey could ask therapists if a device with an app like this would be useful to them in their practices, and could ask other patients if a device like the one we have developed would help meet their needs. This way, a broader diversity of opinions could be considered to make sure this device would be useful to those outside the group that participated in the focus group and iterative design process.

The phone app created for this project could likely also be applied to other at-home interventions or rehabilitation therapies. Giving therapists direct access to add or change treatment schedules, doses, and protocols allows for flexibility in a rehabilitation program.

Allowing them to see usage information in real time is also beneficial and allows for more complete information than the patient could log on their own. In future studies, more feedback from therapists can be gathered to get their opinions on how useful and understandable the app is, and if there are any other features that may be useful to them.

Chapter 4. Focal Vibration Short-Term Study

This chapter focuses on the short-term intervention study that I performed to test out the FoVi device discussed in the previous chapter. The FoVi device consists of two electronics control boxes, each of which connects to and controls two to three vibration motor pods. The sleeve component of the design was not ready for use at this point in the study, so the FoVi device was secured to the upper limb using three to five Velcro straps (Baixt Group Limited). Additionally, the app designed for patients was still undergoing reliability testing, so the FoVi device was controlled on the smartphones of the research personnel using the Bluefruit Connect app (Adafruit, New York City, New York). These factors contributed to the decision to collect short-term feasibility data before designing a long-term study for the participants to test out the device in an at-home setting.

The goals of this short-term study were to determine if the FoVi device met the design criterion of being comfortable and easy to use, to gather participant feedback in a qualitative manner, and to collect initial quantitative results on whether the FoVi device improves upper limb mobility and function. The remainder of this chapter discusses the methods used to conduct this short-term study, including participant selection, outcome measures, and the focal vibration treatment. Then, the quantitative and qualitative results of the study are summarized and discussed. The chapter concludes with some final discussion, limitations, and future directions for this research.

4.1 Methods

4.1.1 Participants

This study was done with five patients with chronic stroke. Four of the patients came from the focus group discussed in the previous chapter, so they were familiar with the design of the device and had some additional interest in experiencing how the device worked. The other patient was recruited after being excluded from a different stroke rehabilitation study. To be included in the study, participants were required to have a history of ischemic or hemorrhagic stroke and hemiparesis of the upper limb, be over 18 years of age, and have the ability to provide consent to the study. Participants with a history of fractures or dislocations in the shoulder, elbow, or wrist from which they had not fully recovered, and participants who were simultaneously participating in another research study for stroke rehabilitation were excluded.

4.1.2 Outcome Measures

For assessment of the effects of the focal vibration intervention on the mobility and function of the upper limb, a variety of outcome measures were chosen with the intent of broadly assessing functioning to determine what aspects of arm function and mobility were affected by the device. Each visit began with the patient signing the informed consent form, followed by the researcher asking the questions from the Motor Activity Log (MAL) to assess what their normal level of functioning at home was. Next, we measured the participants' grip strength on both sides using a dynamometer (North Coast Medical, Morgan Hill, California). One participant's grip strength was measured first with the dynamometer, and then with a Squegg device (Squegg, Plantation, Florida). Then, we conducted the FMA-UE, the ARAT, and CAHAI-7. The ARAT was not conducted at two of the visits, for reasons that will be discussed later. The main outcome

measures for this study were grip strength, FMA-UE score, and CAHAI-7 score, while the MAL and ARAT provided additional context and information about the participants' upper limb function.

4.1.3 Focal Vibration Intervention

After the pre-intervention baseline testing, focal vibration was applied using the FoVi device. The device was placed onto the patient's arm and secured using Velcro straps (Figure 4). The vibration pods were placed on the muscle belly of the biceps brachii and triceps brachii, the lateral epicondyle, and on the distal wrist flexors and extensors. We took care to put the motor pods on locations away from bony parts of the elbow and wrist, focusing on the muscle belly. The electronics control boxes that send commands to the vibration pods were also secured to the arm in convenient locations away from the vibration pods. After securing the device using Velcro straps, the device was turned on and connected to the test administrator's phone via Bluetooth. Then, we showed the patient what the different vibration intensities (low, medium, and high) felt like at the lateral epicondyle location to determine which intensity was most comfortable for them. The low intensity setting had a frequency of 152 Hz and an amplitude of 0.07 mm, the medium intensity had a frequency of 213 Hz and an amplitude of 0.07 mm, and the high setting had a frequency of 277.3 Hz and an amplitude of 0.06 mm. After deciding on an intensity, we began the intervention protocol. The vibration motor was turned on at each location, one at a time, in sequence, for ten minutes each. We started with the biceps brachii, then triceps brachii, then lateral epicondyle, then wrist flexors, then wrist extensors. Patient comments were recorded throughout the intervention time, including what they thought of the device, if they felt the device was comfortable, and other opinions about the device or treatment.

Figure 4. FoVi device secured to participant's arm using Velcro straps.

4.1.4 Post-intervention Testing

After the vibration intervention was complete, we repeated the outcome measures to determine if there were changes in the patient's upper limb mobility and function after the short-term vibration intervention. The test of grip strength, FMA-UE, and CAHAI-7 were repeated. We chose not to repeat the MAL because the interview focuses on how much and how well the patient has used their upper limb at home over the past week, so it would be impossible to assess changes in this test after a one-hour treatment in the clinic. We also did not repeat the ARAT after the intervention, to help limit the total study session time to a reasonable length and because the muscle locations we applied focal vibration to were not expected to improve scores of this test. For a more detailed description of the protocols used in this treatment, see the Appendix.

4.2 Results

4.2.1 Qualitative Results

Overall, participant comments about the device were positive. Participants noted that the device was comfortable on their arm, and all had neutral or positive impressions about the way the treatment felt while the device was turned on. Some participants mentioned that they felt like they could move their hand or flex their fingers a little better during the vibration treatment. After removing the device, participants had some impressions or indentations on the skin from the edges of the control box and vibration motor pods. These were not painful, but the way the Velcro straps pushed the device into the skin caused some redness and indentations when the device was removed. One participant commented that they preferred the chamfered, rounded edges of the vibration motor pods over the unchamfered, sharper edges of the electronics control box. This is one detail we could change about the device design, to make sure all edges are rounded off to be more comfortable. Once the sleeve is ready to house the electronics control boxes and vibration motor pods, this problem will likely be lessened, since the sleeve will be in direct contact with the skin rather than the device. The sleeve will also make the device much quicker and easier to put on to the upper limb, and the patient should be able to put it on and remove it unassisted.

Four of the participants preferred the high intensity vibration setting, and one participant preferred the medium intensity vibration setting. None of the participants preferred the low intensity vibration setting, either because the intensity was too low to feel or because they thought the medium or high intensity was more comfortable. Several participants noted that the high intensity setting could be felt not only at the location it was applied to, but also further down

to the fingertips and/or further up into the shoulder. In some cases, researchers could also feel the vibration at other locations, but other times this was something that only the patient could detect. This may indicate that at higher settings, the focal vibration treatment became less localized. Some participants also said that they could not feel the vibration when it was at the lowest setting. This could be due to sensory impairments that were noted in some patients. One participant commented that it might be helpful to include a "cool-down" period at the end of the treatment session, instead of stopping abruptly. They suggested that at the end of a treatment session, the motor pod could switch to the next-lowest intensity for a few seconds, and repeat this until the motors stop at the end of the treatment session.

4.2.2 Quantitative Results

The quantitative results from the outcome measures of this short-term intervention study are summarized in Table 2.

Our first participant came for two separate visits. These visits were five months apart from each other, so there was plenty of washout time for any potential effect of the device to fade. The participant returned because during their first visit, we did not collect grip strength data, and we wanted a complete set of data from this participant. The MAL scores from the first visit were 21 points on the Amount scale, and 16.5 points on the How Well scale. At the second visit, the MAL scores were 17.5 points on the Amount scale, and 22.5 points on the How Well scale. This participant preferred the high intensity setting for the focal vibration intervention at both visits. Participant #1 scored 81 points on the FMA-UE before the intervention, and this increased to 82 points after the intervention. At the second visit, the FMA-UE score was 82 points before the intervention, and this increased to 90 points after the intervention. At the first visit, the

participant scored 0 points on the ARAT. At the return visit, we did not perform the ARAT. The CAHAI-7 scores for this participant were 22 points before the intervention and 24 points after the intervention, at the first visit. At the second visit, the participant scored 29 points on the CAHAI-7 both before and after the intervention. As mentioned previously, we did not collect grip strength data for this participant at the first visit. At the second visit, grip strength was assessed first with the dynamometer, and then with the Squegg device. The dynamometer showed 0 lbs of force both before and after the intervention. However, the Squegg showed an average of 11 lbs of force before the intervention, and 12.33 lbs of force after the intervention.

Participant #2 had MAL scores of 50 on the Amount scale and 54 on the How Well scale. They preferred the high intensity setting. This participant had an FMA-UE score of 105 points before the intervention, which increased to 106 points after the intervention. Their ARAT score was 31 points. The participant's CAHAI-7 score before the intervention was 30 points, and after the intervention this score increased to 36 points. Their average grip strength on the affected side before the intervention was 23.33 lbs of force, and after the intervention the grip strength decreased to an average of 11.67 lbs of force.

Participant #3 dropped out of the study after completing the focal vibration intervention and only some of the post-intervention testing. Their MAL score was 52 points on the Amount scale, but the test was discontinued before collecting How Well scale data because the scores were not reliable based on comments from the participant's spouse and the observed function of their upper limb. They preferred the high intensity setting for the focal vibration intervention. This participant had an FMA-UE score of 75 points before the intervention, and after the intervention this score increased to 80 points. They had an ARAT score of 43 points. The CAHAI-

7 score for participant #3 before the intervention was 33 points, but they dropped out of the study before completing the CAHAI-7 post-treatment. Their grip strength before the intervention was 27.17 lbs of force on average, and after the intervention the grip strength increased to 31.67 lbs of force.

Participant #4 had MAL scores of 5 points on the Amount scale and 18.5 points on the How Well scale. They preferred the high intensity setting. This participant's FMA-UE score remained unchanged at 71 points before and after the intervention. Their ARAT score was 3 points. Before the intervention, the CAHAI-7 score was 13 points, but after the intervention it increased to 15 points. Their average grip strength before the intervention was 22 lbs of force, and after the intervention it decreased slightly to 21 points.

Lastly, participant #5 had MAL scores of 0 points for both scales, because they did not use their affected arm for any of the 30 listed activities at home. This participant preferred the medium intensity setting. Their FMA-UE score remained unchanged at 44 points before and after the intervention. We did not conduct the ARAT with this participant. Their CAHAI-7 score remained unchanged at 7 points (the minimum score) both before and after the intervention. Finally, the grip strength measurements with the dynamometer were 0 lbs of force both before and after the intervention.

Table 2. Summary of results from short-term intervention.

OCAST Patient		#1	#2	#3	#4	#5	#1.2
MAL (max 5)	Amount scale	0.7	1.67	1.73	0.17	0	0.58
	How Well scale	0.55	1.8	-	0.62	0	0.75
FMA-UE (max 126)	pre	81	105	75	71	44	82
	post	82	106	80	71	44	90
ARAT (max 57)		0	31	43	3	-	-
CAHAI (max 49)	pre	22	30	33	13	7	29
	post	24	36	-	15	7	29
Grip strength (lbs) (affected arm)	pre	-	23.33	27.17	22	0	0 (11 with Squegg)
	post	-	11.67	31.67	21	0	0 (12.33 with Squegg)

4.3 Discussion

4.3.1 Key Findings

Across the five participants, we saw a wide variety of MAL scores. These often correlated with scores from the other outcome measures – that is, participants with higher MAL scores also tended to have higher scores on the FMA-UE or CAHAI-7. There also seemed to be some differences based on whether the affected arm was also the dominant arm. For example, participant #4 had hemiparesis on the nondominant side, so they tended to use their dominant side for most activities, much like they would have before the stroke. Therefore, their MAL score was quite low due to disuse of the affected arm. On the other hand, participant #2 had hemiparesis on the dominant side, and although they compensated with their nondominant, unaffected arm for some activities, they used their dominant, affected arm for more activities which contributed to a higher score.

Overall, we saw little change in the FMA-UE scores after the focal vibration intervention (Figure 5). At two of the visits, there was no change in the score before and after the intervention,

and at two other visits, the score only increased by one point. One participant showed a larger change of five points, but the minimally detectable change for this assessment is 5.2 points (Wagner, Rhodes and Patten, 2008). So, it is not possible to say that the increase in score was due to the vibration treatment; it could be simply a random fluctuation in scores from one test to another. However, when participant #1 returned for a second visit, there was an increase of eight points, which is greater than the minimally detectable change. This indicates that the increase in mobility is more likely due to the effects of the intervention. Although the increase was larger than the minimally detectable change of 5.2 points, none of the participants' scores increased more than the minimum clinically important difference of 12.4 points (Hiragami, Inoue and Harada, 2019). One potential reason for the improvement in participant #1's second visit as compared to the first visit is that during the second visit, the participant spent the time during the intervention stretching their fingers, hand, and wrist while the vibration was being applied to muscles including the wrist flexors and extensors. It is possible that the stretching combined with the focal vibration treatment produced better results than vibration treatment while resting the arm muscles. This is supported by comments from this participant that it felt like the focal vibration treatment was helping relax the muscles of the upper limb and alleviate some of the abnormal spasticity and muscle tone. Further research would need to be done to determine whether stretching combined with focal vibration produces better outcomes than focal vibration alone, and whether the focal vibration treatment improves muscle spasticity and tone.

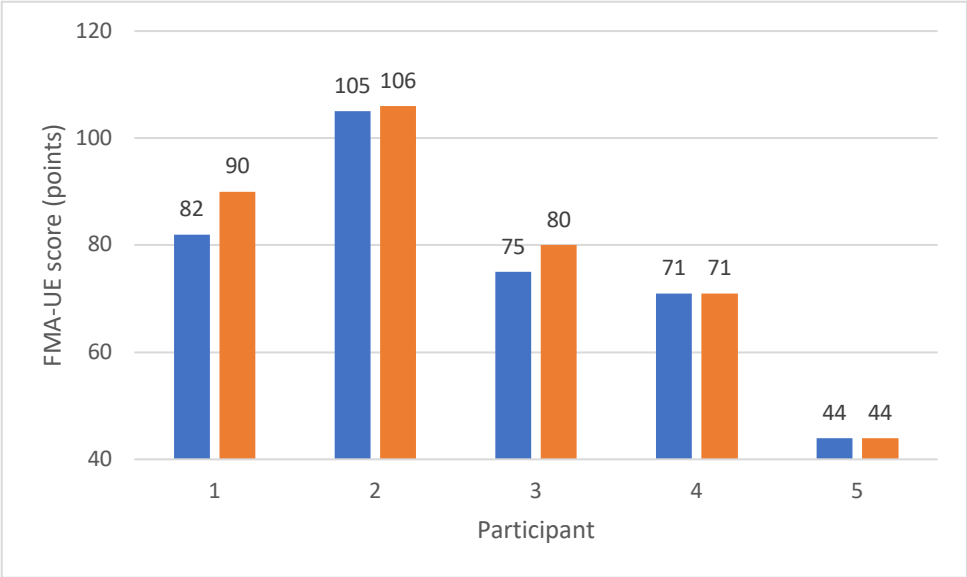

Figure 5. FMA-UE scores for each participant before (blue) and after (orange) focal vibration.

When conducting the ARAT, we saw two participants had very low scores (0 or 3 points), and two other participants had moderate scores (31 or 43 points). We did not repeat the ARAT after the focal vibration intervention, because we noted that many tasks in this test involve using the shoulder muscles to lift the arm up to the top of a box. None of the muscles we targeted during the focal vibration treatment included shoulder muscles that would help with these types of reaching tasks, so we did not expect to see an improvement in shoulder function after the vibration treatment. The primary reason we chose not to repeat the ARAT after the intervention was this expectation that there would not be a change in the shoulder mobility or function, but the length of the total testing session was also a concern. Since the total session time was quite long with all the planned outcome measures and tests, we decided to remove the ARAT after the intervention to help shorten the post-intervention testing. For our last two participant visits, we removed the ARAT altogether to help simplify the testing procedures and shorten the session time further. Participant #5 had the most limited upper limb function as shown by their MAL,

FMA-UE, and CAHAI-7 scores, and participant #1 had an ARAT score of 0 for their first visit, and these factors also contributed to our removal of the ARAT from the protocols.

During this short-term intervention study, there were very small changes in the CAHAI-7 scores, and some participants had no change at all after the intervention (Figure 6). The largest change was in participant #2's scores, which had a difference of six points. However, the minimum detectable change for this outcome measure is 6.3 points (Barreca *et al.*, 2005), so it is not possible to say whether this improvement was truly due to the focal vibration intervention or due to random differences from one test to another. The CAHAI-7 scores indicate that short-term focal vibration treatment may not improve upper limb function. This test assesses functional activities rather than only testing mobility of the upper limb. It is possible that with more than one treatment, participants would make more functional gains. Further studies could include more repeated treatments or longer treatments with the goal of affecting not only upper limb mobility but also arm function and ability to complete functional tasks.

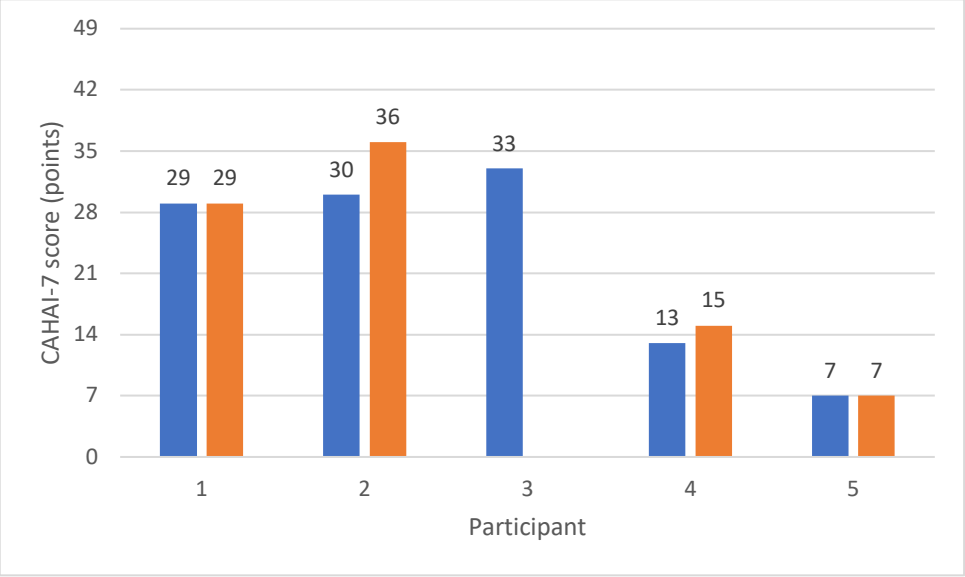

Figure 6. CAHAI-7 scores for each participant before (blue) and after (orange) focal vibration.

The grip strength outcome measure revealed some interesting results in this short-term study. Some participants had increases in grip strength after the focal vibration intervention, while others had decreases in grip strength (Figure 7). Prior to the study, I hypothesized that focal vibration would improve the upper limb mobility and function, and therefore it would increase grip strength after treatment. However, the results show conflicting trends in grip strength from one participant to another. It is possible that the vibration treatment increased grip strength in some participants. One potential explanation for the decreases in grip strength is participant fatigue. Since the pre-treatment grip strength measurement was collected first, before the other baseline tests, the participant was unlikely to have fatigue of the upper limb. The post-treatment grip strength measurement occurred first of all the post-intervention testing, but at that point the participant had not only undergone approximately one hour of focal vibration, but also the pre-intervention FMA-UE and CAHAI-7, and the ARAT in some cases. It is possible that the decrease in grip strength was due to fatigue of the muscles in the arm and hand after all this testing. Another potential explanation for the decreases in grip strength is that the focal vibration intervention may have decreased some abnormal muscle tone in the upper limb. If the initial grip strength measurements were augmented by some of the abnormal muscle tone of the upper limb, and then the focal vibration device reduced some of that tone, then we might expect to see a decrease in grip strength after the intervention rather than an increase. This explanation is supported by participant comments that the intervention seemed to help with some spasticity and abnormal tone, but further investigation would have to be done to confirm whether the treatment actually helps with these issues and whether the reduction in grip strength is associated with reduction of spasticity.

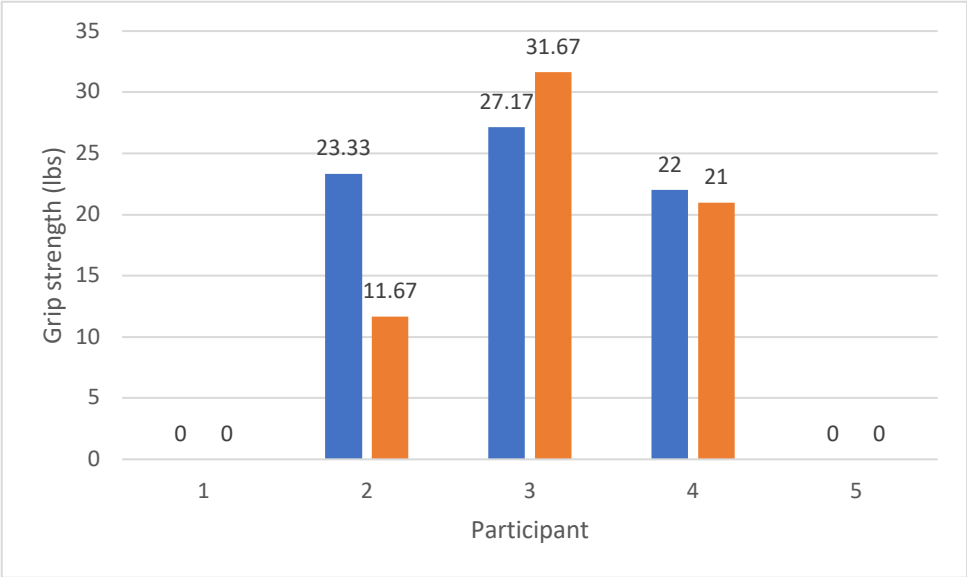

Figure 7. Grip strength in pounds before (blue) and after (orange) focal vibration.

Another interesting result of the grip strength outcome measure is the difference between the dynamometer and Squegg measurements in the one participant who used both. The dynamometer showed grip strength as 0 lbs of force both before and after the intervention, but the Squegg device showed a slight increase from 11 to 12.33 lbs of force before and after. This could be because the Squegg is more sensitive than the dynamometer to small forces. The Squegg does measure forces to the nearest lb of force, while the dynamometer only has marks for every 5 lbs of force. Additionally, although these two devices measure grip strength of the same muscles, the hand position is slightly different between the two (Figure 8). While using the dynamometer, the first knuckle is extended and only the more distal finger joints are used to squeeze the bar (Figure 8a). While using the Squegg device, all the finger joints are used to squeeze the Squegg in the hand, using more of a fist shape (Figure 8b). So, using the Squegg may allow for greater force from the fingers to be applied than using the dynamometer. Further comparisons should be made between the dynamometer and the Squegg to determine if the

Squegg truly is more sensitive to changes in grip strength. If it is, this may be a better method of measuring grip strength than a normal dynamometer, especially in participants with reduced hand function and strength.

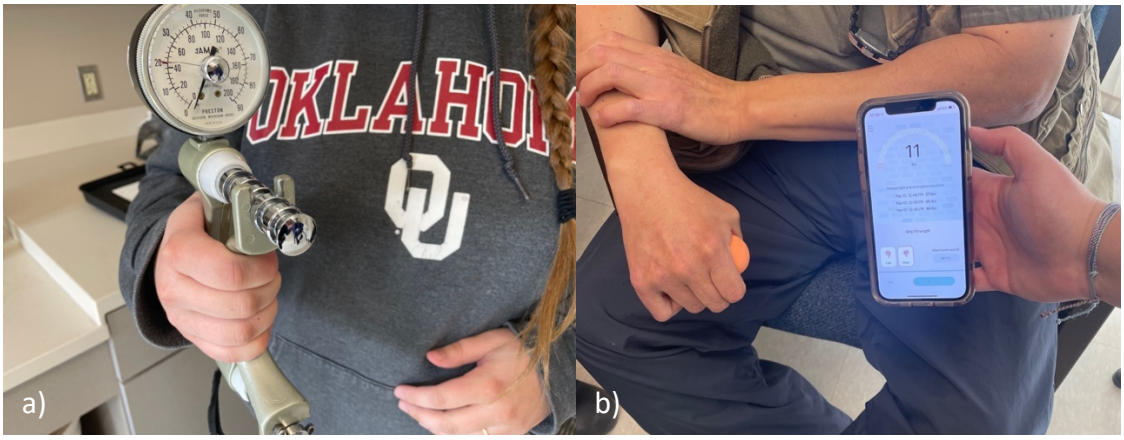

Figure 8. Grip strength measurement using a) the dynamometer, and b) the Squegg device.

One final point of discussion is the reason for the incomplete data from participant #3. This participant completed the baseline testing and the focal vibration intervention but asked to leave before completing all the post-intervention testing. Prior to the participant asking to leave, the MAL test at the beginning of the session was discontinued before the How Well scale questions were asked. This is because for the Amount scale, the participant's self-reported activities did not seem to be reliable. They often rated their activity as a higher amount than seemed possible based on their ability to move their affected upper limb. This was confirmed by their spouse, who shook their head or otherwise indicated that the participant's responses were not accurate to their actual activities at home. For these reasons, the test was determined to be unreliable, and it was discontinued before asking the How Well scale questions. This could be due either to the participant not fully understanding the questions being asked or the meaning of the scale, or perhaps they simply misrepresented their abilities and at-home activities.

Participant #3 also dropped out of the study before completing the CAHAI-7 after the vibration treatment. The main factors that contributed to this dropout were participant fatigue and a long total session time. At the point they asked to leave, the session had been going on for over four hours. The reason for the incomplete CAHAI-7 scores for this participant is the dropout prior to the completion of this test.

4.3.2 Limitations

One limitation of this study was that the total time of the baseline testing, focal vibration intervention, and post-intervention testing combined was quite long, often around four hours. This led to participant fatigue, especially since most of the testing involved using the weaker upper limb. This fatigue may have affected the results of the outcome measures, especially towards the end of the session after several hours of testing. Additionally, the long session length caused one participant to drop out of the study before completing all of the post-intervention tests. This participant completed the test of grip strength and the FMA-UE after the focal vibration intervention but asked to leave before completing the CAHAI-7.

The choice of outcome measures may have been a limitation as well. For example, we did not include an outcome measure related to spasticity, like the Modified Ashworth Scale. Therefore, it is uncertain whether the vibration intervention from this study had an effect on spasticity or abnormal muscle tone. Some participants commented that they felt the intervention was alleviating some of the abnormal muscle tone, but we did not include an outcome measure that would quantify this. During initial participants' sessions, we discovered that the ARAT test was a less helpful measure than expected – we saw some floor effect from patients who scored 0 points on the test, and the types of movements required to complete the tasks often involved

the shoulder, which we did not target with the intervention. We included many different outcome measures to quantify changes in both mobility and function but adding so many outcome measures increased the total time of the session overall, which may have increased participant fatigue.

Another limitation of this study was the short duration of the focal vibration and the fact that participants only received one session of focal vibration before the post-intervention testing. It seems that applying focal vibration for 10 minutes on each target muscle was not enough to produce a statistically significant change in outcome measures. However, it is possible that with longer sessions or more sessions spread out over several days, a greater effect would be seen. Because the sleeve to house the FoVi device was not ready for participants to take home, and the smartphone app was still undergoing final testing for reliability, we were limited to conducting the intervention in the laboratory. Without these limitations, we could have sent the FoVi device home with the participants and asked them to complete several vibration treatment sessions at home before returning to the lab for follow-up testing.

This study was also limited by subjectivity in the outcome measures. Other than grip strength, most of the outcome measures involved scoring the participant on a scale based on their movement ability or functional activities. These scales always involve some discretion from the test administrator in choosing which score to assign. Bias could be introduced since the same test administrator scored the participant before and after the intervention, so the score of the participant before the intervention was known when giving the test afterwards. Additionally, the MAL involves asking the participant about their own activities at home, so if the questions or scales are not fully understood the scores will not be accurate. Additionally, it is possible the

person will overestimate or underestimate their activities, which will also skew the results of this test.

Finally, a limitation of this research was a small sample size. With only five participants, it is difficult to perform statistical analysis on the data. With more participants, we could get a clearer picture of any effects of the focal vibration intervention on mobility and function, and we could also gather more participant feedback about the device and the intervention methods. Also, all the participants we had happened to be male, so in the future it is important to get feedback from female patients and a greater diversity of participants in general.

4.3.3 Conclusion

This research focused on testing the feasibility of the FoVi device and investigating preliminary efficacy on upper limb rehabilitation using a short-term intervention. With regards to feasibility, I showed that the design of the device works well for our participants with stroke. This was demonstrated through the success of the experimental setup – we were able to set the device up on the upper limb and send commands to it over Bluetooth using our smartphones. The feasibility was also supported by the comments from participants that the intervention was comfortable or felt good. This indicates that stroke patients would be willing to use the device for treatment and would likely comply with a prescribed treatment schedule. Further research should continue to study aspects of feasibility that we were not able to examine in this study, like the ability to put the device on one-handed with the sleeve, or the usability of the app. My own observations in addition to the participant comments contributed to the goal of testing the feasibility of the FoVi device.

The goal of investigating the preliminary efficacy of the FoVi device was achieved through the quantitative data that I collected. Although I was not able to show statistical significance in the results due to the small sample size and small changes in outcome measures, in general the trends showed positive improvements in upper arm mobility and function. Again, we would need to perform further study with a larger sample size and perhaps a longer treatment time to fully quantify the efficacy of the FoVi device. However, the preliminary data from using the FoVi device shows promise of its effectiveness at improving upper limb mobility and function. This is demonstrated through the quantitative data from the FMA-UE, the CAHAI-7, and grip strength, as well as participant comments about the feeling of muscles relaxing and being easier to move. These comments warrant further investigation of the effects of the FoVi device on muscle spasticity. Although there were only a few gains in upper limb mobility and function during this study, a long-term intervention with more participants may show greater improvements. Future directions arising from this work will be discussed in more detail in the next chapter.

Chapter 5. Future Directions and Conclusion

In this chapter, I present some future directions for further research with the FoVi device and in the field of focal vibration as a whole. I also briefly describe another ongoing stroke rehabilitation study using a different method to try to improve the function and mobility of the upper limb. This ongoing study combined with focal vibration treatment could be a powerful tool for stroke rehabilitation.

5.1 Future Directions

Future studies should be done using the FoVi device, and using focal vibration treatments in general, to fully determine the effects of this treatment on upper limb rehabilitation after stroke. Further investigations with the FoVi device would allow researchers to better understand the effects of this specific device on the function of the upper limb, and to further refine the design of the device and the smartphone app for patients and therapists. Focal vibration in general would also benefit from further study, to determine the ideal treatment parameters and assess the effects of this treatment modality compared to other therapeutic tools.

In future studies with the FoVi device, it would be beneficial to include a test for spasticity, like the Modified Ashworth Scale (MAS), to investigate if this device improves abnormal spasticity and muscle tone. In our short-term study, some patients commented that they felt like they had less spasticity and abnormal muscle tone during the intervention, and this is one possible explanation for some of the results we saw, like decreased grip strength after the intervention. Further investigation needs to be done to determine if there were changes in spasticity due to the focal vibration intervention, and to quantify any changes that may have occurred.

A long-term intervention study would be another important future study using the FoVi device. Ideally, participants would take the FoVi device and sleeve home with them and use it with the smartphone app daily for one or two sessions per day for a few weeks. Then, they could come back to the lab for follow-up testing and to provide feedback about the treatment, the device design, and the smartphone app or remote control. This would not only provide an opportunity for participants to test out the whole device system themselves, it would also allow therapists to try out the user interface of the patient portal and the real-time usage log. Then, we could also determine if repeated focal vibration sessions in the long term provide more improvements to upper limb mobility and function than a single short-term session. Even though we did not see much change with the short-term intervention, it is possible that several repeated intervention sessions would promote functional improvements over time. A long-term study would help us determine the effectiveness of focal vibration and the appropriate dosage for maximum functional gains.

Another addition to future studies with the FoVi device would be a study design that includes a control group that does not receive focal vibration, and a randomized double-blind study design, so that test administrators do not know whether the participant they are assessing has received focal vibration treatment. A larger sample size will also add greatly to the quality of the study and the data collected. Adding these elements will make the study design more robust for more reliable results. With a larger sample size, statistical analysis can be done on the results to determine if any effects are truly due to the focal vibration intervention rather than to random error from one testing session to another. I would recommend that the primary outcome be the FMA-UE, with secondary outcome measures of grip strength and MAS. This study could be

statistically analyzed with a paired sample, one-tailed *t*-test to determine if the FMA-UE score increases more than the minimal clinically important difference of 12.4 points. The minimal clinically important difference should be chosen instead of the minimum detectable change, because it is more important to see a change that is large enough to impact the patient's function rather than just a change that can be detected by the outcome measure.

In general, focal vibration studies that include different vibration intensities, session durations, and number of sessions would greatly add to the body of knowledge about focal vibration. Currently, it is unknown what vibration parameters or treatment regimens provide the greatest functional gains or improvements to upper limb mobility. By performing more research on the different aspects of a focal vibration treatment plan, greater benefits to patients with stroke can be achieved.

5.1.1 Transcranial Direct Current Stimulation

One future avenue of study by our research group is an investigation of transcranial direct current stimulation (TDCS) for upper limb rehabilitation for stroke. Rather than focusing on the muscles of the upper limb like focal vibration does, the goal of TDCS is to apply electrical current directly to the areas of the brain that are affected by the stroke. Current is directly applied to the motor cortex, with the goal of modulating the neurons so they are either more or less excitable. For example, one may wish to make the neurons of the primary motor cortex on the side affected by the stroke more excitable using anodal stimulation, so the corticospinal tract will be more likely to engage and send a motor signal to the muscles (Schlaug, Renga and Nair, 2008). On the other hand, the patient may benefit from cathodal, inhibitory signals on the premotor cortex on

the opposite side of the brain, so the neurons will be less likely to fire (Schlaug, Renga and Nair, 2008).

In our current study, participants visit the lab three times, spaced two weeks apart, and have one of three interventions at each visit. The treatments are administered in a random order, in a double-blinded fashion, and include 1) an excitatory treatment on the ipsilesional side of the brain, 2) an inhibitory treatment on the contralesional side of the brain, or 3) a sham treatment. Before and after the intervention, the FMA-UE score, Erasmus modified Nottingham Sensory Assessment (EmNSA) test for sensation, the motor evoked potentials (MEP) as measured with electromyography (EMG), and brain symmetry index as measured with electroencephalogram (EEG) are recorded. The aims of this study are to determine the effects of these treatments on the motor function, sensation, and brain function of stroke patients. We hypothesize that applying anodal TDCS to excite the ipsilesional side of the brain or cathodal TDCS to inhibit the contralesional side of the brain will improve the FMA-UE and EmNSA scores, reduce the time for the MEP, and improve the brain symmetry index. Data is still being collected for this double-blinded study, so preliminary results are not available yet.

Depending on the results of this current study, it may be beneficial to design a study that combines TDCS with the focal vibration treatment from my research. Focal vibration is thought to activate the somatosensory cortex, the motor cortex, premotor cortex, and supplementary motor area. TDCS can be applied directly to the motor cortex or supplementary motor area. Focal vibration may also work directly at the muscles to help alleviate tone and spasticity. In combination, these two interventions together could act as a powerful treatment for the entire affected side of the brain and body. A study could be done comparing the effects of focal

vibration and TDCS separately and in combination, to determine whether these treatments work more effectively together than they each do on their own.

5.2 Conclusions

Overall, this thesis research met the initial goals of describing the novel wearable focal vibration device developed for rehabilitation of the upper limb after stroke, and of conducting a pilot study with five chronic stroke patients to test the preliminary efficacy and feasibility of the device. The FoVi device shows promise as a treatment for stroke based on the positive comments from participants during the intervention and the minor improvements observed for some of the outcome measures. However, most of these improvements were not statistically significant and the sample size was very small, so further study needs to be done with a larger sample size, more treatment groups, and a double-blinded randomized controlled study design to truly understand the extent of the benefits of this focal vibration treatment. Future work with the FoVi device should include the finalized sleeve design, and the smartphone app for patients and therapists to track real-time usage and protocols. Future work with focal vibration could also include studies of optimal treatment parameters and investigations in combination with TDCS for a robust, multi-faceted stroke rehabilitation regimen.

This research sets a foundation for contributing to the gaps in knowledge in the area of focal vibration for stroke rehabilitation. Previous focal vibration research was limited by devices that were not wearable and needed to be held at sometimes awkward angles by the patient or therapist. Even wearable devices could not be controlled remotely or through an app, so they also required difficult maneuvering for patients to be able to reach the on switch and use them on their own. The FoVi device will be able to be used by patients independently and at home,

because it is possible to put it on, take it off, and operate it one-handed and because therapists will be able to update patient protocols and track-real time usage through the app. This will hopefully lead to greater user compliance and better communication between therapists and patients. With this device, investigations into the optimal treatment parameters will be easy and more accurate. The FoVi device can facilitate focal vibration research for better patient outcomes and upper limb functioning.

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Appendix

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RESEARCH PROTOCOL

Development and Evaluation of Vibration-based Wearable Upper Limb Rehabilitation Device

Principal Investigator: Shirley James, PhD, Department of Rehabilitation Sciences

Abstract

Stroke often leads to significant impairment of upper limb function and is associated with decreased quality of life. Change in muscle activation is the key underlying factor. Despite study results from several interventions for muscle activation and motor coordination, wide-scale adoption remains largely elusive due to the lack of sustainability of those interventions. The aims of this study are to design, develop and evaluate the usability and feasibility of a novel vibration- based wearable device for upper limb rehabilitation in stroke patients. A user participatory design approach will be used for the design and development. Forty-eight stroke patients and 10 therapists working with those stroke patients will be recruited to evaluate the usability of the device. All stroke patients will participate in a 4-week in-home vibration treatment to evaluate the feasibility of the device. Patients will be randomized into four groups receiving vibrations with different frequency (60 Hz or 120 Hz) and amplitude (0.2mm or 2mm). All groups will follow a prescribed dose of vibration based on the therapists' recommendations. Strength and functional outcomes will be measured before and after the 4-week in-home intervention. This pilot study may help to develop a novel sustainable wearable system providing vibration-based muscle activation for upper limb function rehabilitation.

A. Specific Aims

Specific Aim 1: To design, develop and bench test a wearable device that applies vibration to specific muscles, and allows therapist to use an app to adjust the treatment and to receive feedback in real-time.
Design Objective (DO) 1a: To incorporate stroke patients and therapists into the design process to prioritize system capabilities, refine performance criteria, and clarify design requirements of WearUL.
DO 2b: To design a customizable, fully wearable module that is easy to wear and take off, easy to set up without interfering with movement and function, and that provides maximum comfort to patients.
DO 2c: To develop a robust WearUL prototype that meets or exceeds the following design criteria:
1) Individualized shape molding around the whole arm with six vibration motors to deliver vibratory stimuli in six different muscle locations.

2) Each vibration motor will deliver a frequency between 60-300Hz, and amplitude between 0.1-10mm.
3) Controllable activation and deactivation of each vibration motor and adjustable vibration parameters.
4) Easy to use interface for therapists to monitor and adjust usage of the system. *Testing Objective (TO) 2*: To evaluate the reliability, robustness, accuracy and tolerability of the prototype through bench and in-lab testing.
Specific Aim 2: To evaluate the usability of WearUL, to assess the feasibility of WearUL for upper limb rehabilitation via a 4-week in home study, and to establish the effective focal vibration parameters.
Hypothesis 2a: We hypothesize that after 4 weeks' in-home usage of WearUL, more than 90% of patients and clinicians will rate the usability of WearUL high. *Hypothesis 2b*: After 4 weeks of vibration treatment, all subjects will demonstrate improvements of the affected side over baseline values in grip strength measured by a dynamometer, function outcomes measured by Chedoke Arm and Hand Activity Inventory – 7 (CAHAI-7), Fugl-Meyer Assessment of the Upper Extremity (FMA-UE), Action Research Arm Test (ARAT), and Motor Activity Log (MAL).
Hypothesis 2c: The changes in outcomes of subjects treated by different vibration parameters in terms of different combinations of frequency and amplitude will be different.
Hypothesis 2d: All subjects will tolerate the vibration without adverse side effects and report high levels of satisfaction after the 4 weeks of treatment.

B. Background and Significance

Each year, approximately 795,000 people in the United States have strokes. Stroke is the leading cause of serious, long-term disability in the United States[1], and up to 85% of stroke survivors experience some degree of paresis of the upper limb[2]. Moreover, about 50% of stroke survivors experience chronic upper limb and hand function impairment[3]. Upper limb impairments can lead to functional limitations in reach, grasp, and manipulation, critical for completing basic activities of daily living (ADLs) such as self-care, eating/drinking, and meal preparation[4]. While numerous therapies have been developed over the last 10 years to treat acute ischemic stroke, the stark reality remains that 95% of these patients continue intervention in the chronic stage, and go on to live with significant disability for many years[5,6]. Patients have difficulty moving out of the upper extremity flexion synergies that often dominate attempts to function after stroke[7]. Changes in muscle activation is the key underlying factor for these synergies. Despite study results from several interventions on muscle activation and motor coordination, wide-scale adoption remains largely elusive due to the lack of sustainability of those interventions[8]. The main reason for the unsustainability is the under-doses of the interventions. The issue is exacerbated with the low patient compliances and participation because stroke recovery and rehabilitation often require multiple treatment sessions and visits to the study site.

Vibration has over time gained an important role in physical and rehabilitative medicine. Mechanical perturbations of small amplitude and localized on specific muscles or tendons, known as focal vibration, can easily be kept within safe limits for muscle activation. Researchers have established benefits of focal vibration including reduction in spasticity, facilitation of muscle contraction for functional activity, and enhancement of motor learning in patients with stroke. With the current possibility to use various vibration modality and frequency and with the new evidence in the literature, it is possible that focal vibration can be an important tool for upper limb rehabilitation after stroke. At present however, studies on focal vibration are lack of uniform protocols and sustainability. In this project, we will design and development a novel, sustainable

low-cost vibration- based wearable upper limb rehabilitation system (WearUL), and assess the feasibility of using the WearUL for in-home rehabilitation for stroke patients.

C. Preliminary Studies/Progress Report

Our team has substantial experience in rehabilitative technology research using sensors, wearable devices, machine learning, and upper limb function assessment. We have summarized our most relevant previous work here.
An objective and quantitative unsupervised outcome measure is a key for in- home rehabilitation assessment. We have conducted a preliminary study recording upper limb movement via wearable sensors of able-bodied individuals to test feasibility of using multiple different machine learning settings to automate the assessment of quality of the movement using FMA-UE. Our preliminary result shows that by recording five movements within FMA-UE, we can achieve overall accuracy as high as 99.5% with minimum specificity of 99.5% and minimum sensitivity of 98.7%. These accurate estimations of shoulder elbow movement will support our proposed work on automating FMA-UE using machine learning for remote upper limb functional movement assessment.

D. Research Design and Methods

This project will be conducted in two phases (see Timetable). Phase I (0-21 months) aims to design, develop and in-lab bench test a prototyped WearUL. Phase II (22-36 months) aims to investigate the usability and feasibility of real- world usage of the WearUL.

Phase I: Design, Development and Bench Testing of WearUL Prototype

Participants

We will assemble an advisory team, including two occupational therapists (OT), two physical therapists (PT), and a user group comprised of four stroke patients, who will be involved throughout the design and development phase. The OTs and PTs will be aged 18 years or older and have at least three years of clinical experience working with stroke patients. The stroke patients will be in chronic phase of stroke recovery and be in a medically stable condition. The advisory team will be able to come to the research laboratory or participate remotely at least once a month for 12 months to discuss the design and development of the WearUL for up to 2 hours per meeting.

Protocols

We will work with MYOVOLT Limited in this project and use their core kits as a choice for the wearable sleeve of WearUL. We will use a user participatory design (UPD) approach that the original PI, Dr. Hongwu Wang, used for his previous projects throughout the entire design and development. We will meet at least once a month with the advisory team to discuss the design and development of WearUL (DO1a). Sports, exercise, and fitness users' feedback is that the MYOVOLT core kits are comfortable, easy to use, affordable and flexible (DO1b). The WearUL will integrate a modified MYOVOLT sleeve, two single-cell batteries with a capacity of 1800 mAh and voltage of 3.7v, an Arduino MEGA 2560 microcontroller board with 54 digital input/output pins and 15 pulse-width- modulation (PWM) outputs to control the six vibration motors, an HC-06 Bluetooth module, six 12mm eccentric rotating mass vibration DC motors (output frequency 50~300HZ, amplitude 0.01~20mm), two Estimote Bluetooth® low energy Beacons (one

attaches to forearm and one to upper arm, as used in previous work above), and a smart phone carried by the user (DO1c). For the hardware development, we choose low-cost sensors and electronics been used in our previous studies with demonstrated capabilities. The firmware of WearUL will combine information from the vibration motor controller and Beacons to obtain frequency, amplitude, duration and arm movement using a real-time clock, and to transmit the data to the smartphone via low energy Bluetooth (DO1c). The WearUL will send the information to the smartphone when it is in use. The software design and development will be based on the framework and apps we developed previously to meet all the criteria specified above (DO1c). The main functions for WearUL are to deliver targeted focal vibration to desired muscles safely, to log usage information of the vibration, to upload Beacons data for remote arm movement assessment, and to enable real-time connection between patients and therapists. The vibration will be programmed in intensity, duration, and interval of actuation or can be continuous. For the bench testing, we will test the reliability, robustness and accuracy of these functions continuously for more than 12 hours (TO1). Based on the results of the test, appropriate modifications and calibration will be performed to maximize reliability, robustness and accuracy. We will also conduct a tolerability test with the advisory team for a two-hour duration to assess ease of use and comfort provided by WearUL. The WearUL will be worn throughout the testing, and different vibratory stimuli will be administered (differing in intensity, duration, and interval between stimuli) at different muscles. We will collect the testing vibration delivery locations and parameters, Beacons data, and comfort scores during the tolerability test.

Phase II: Usability and Feasibility Study of WearUL

Participants

We aim to recruit 48 participants and 10 therapists (see below Sample Size Calculations). To participate in the study, patient subjects will meet the following criteria: Ischemic or hemorrhagic stroke with Chedoke McMaster's Stroke Assessment (CMSA) level four or above; over 18 years of age; and live within 40 miles from the University of Oklahoma Health Sciences Center (OUHSC). Patients with a history of fractures or dislocations in the shoulder, elbow, or wrist from which the participant has not fully recovered, or severe impairment of verbal communication ability (for example, severe aphasia), or inability to consent (for example, dementia), or simultaneous participation in another treatment study targeting stroke recovery will be excluded. Subjects will be recruited through multiple sources including the College of Allied Health clinics, and the Comprehensive Stroke Centers at the College of Medicine, OUHSC. Therapist participants will be sampled from those who provide rehabilitation services to the 48 participants, and have been using a smartphone more than one year.

Protocols

Participants will be screened at the first visit with the CMSA and other inclusion/exclusion criteria. Eligible and willing patients and therapists will sign an IRB approved informed consent. After signing informed consent, all subjects will complete a basic information questionnaire. For stroke patient, the questionnaire will survey the interventions been received since onsite of stroke, frequency of smartphone usage, basic demographics, work history, history of medical problems, and current medications. Subjects will be randomized using a computer-generated random table in four blocks of four (four different vibration doses) to equalize the group numbers across the study period. For therapists, the questionnaire will survey their experience in stroke rehabilitation, frequency of smartphone usage, basic demographics, and work history. Each subject will come to the research laboratory two times over a 4-week study period (see Figure 4). During these visits, the following activities will take place a) WearUL Training and Instructions (Baseline), b) Usability Questionnaire and Survey (Baseline and Weeks 4), c). Grip Strength and Functional Testing (Baseline and Weeks 4 for patients only). A blind assessor will record all study outcome measures.

Vibration Treatment

For the feasibility study, we will prescribe a fixed frequency (either high (100Hz) or low (50Hz)) and amplitude (either high (2mm) or low (0.2mm)). These frequency and amplitude combinations are safe and effective in clinical and research settings based on previous studies on focal vibration. Two groups of muscles will be involved. The first involves the reaching component of upper limb functional reach, grasp, and manipulation. We propose vibration to three sets of muscles, the triceps, the common extensor tendon origin on the lateral epicondyle, and the tendons of the dorsal wrist. This vibration pattern will allow patients to complete an extension-based reaching synergy. Following that, we will facilitate a grasp component, also including three sets of muscles, the biceps brachii, the common extensor tendon on the lateral epicondyle of the humerus, and the common flexor tendons on the palmer surface of the wrist. This vibration pattern will facilitate wrist extension combined with finger flexion, providing a strong functional grasp66. Facilitating wrist extensors with finger flexors helps to prevent over-shortening of the long finger flexor tendons. The WearUL will deliver the vibration in rotation over the six muscle groups in 30-second duration periods per muscle for a total of 30 minutes per day five days a week for four weeks. *WearUL Training and Instructions*

The research team will give a brief introduction of the WearUL, including purpose of it, how to wear and take it off, how the system delivers vibration, how the system records its usage, and an overview of the WearUL app. After an introduction, participants will be given two tasks: 1) receiving one reminder to wear the system and following the instructions to complete a vibration treatment and 2) receiving one safety warning reminder and following the instructions to stop a treatment. The two tasks simulate the two types of reminders or messages to users. The feedback messages for all of the reminders and warnings will include a short description about the reminder/warning and an animated image indicating the prescribed vibration treatment including muscles to be vibrated, duration, and intensity. The reminders/warnings will not disappear if the users do not follow the instructions or do not follow the instructions correctly. After completing these two tasks, participants will be given sufficient time to use the WearUL and its app and to ask any questions about the WearUL system. The therapists will be asked to complete the same two tasks and will also be asked to review the function of customizing the app, including adjustability of the treatment duration and intensity and the settings for safety warnings and usage reminders. They will be asked to interact with the website portal as well.

Usability Questionnaire and Survey

We will use a paper-based questionnaire to gather the participants' feedback on the WearUL before and after the 4-week study. The questionnaires include 24 questions about general impressions of the WearUL system. Five common usability components will be included in the questionnaires: the visibility of the WearUL app; ease of use of the app; error prevention; usefulness, and satisfaction in terms of hardware and software. Users will rate their preferences for these usability components on a five-point Likert scale. Other questions will ask which features of the WearUL system the participants like most, whether the participants will use or recommend it to their friends to use if the system becomes commercial, and their concerns about the whole system. The interview follow-up on the questions in the questionnaire will be to provide an open forum for discussing concerns or to provide suggestions.

Grip Strength and Functional Testing

The grip strength will be measured by a dynamometer. Functional testing will be measured by those outcomes with demonstrated psychometric properties, CAHAI-7, FMA-UE, ARAT, and MAL.

E. Statistical Methods

Distributions of all data will be examined. Means and standard deviations, or medians and ranges, as appropriate, will be calculated for all variables. Factor analysis using principal component analysis (PCA) will be used for analyzing the constructs of usability questions in our questionnaire to test construct validity (Hypothesis 2a). Descriptive analysis will be performed on each question to compare the differences between the two visits of the stroke patients group (before and after four-week in-home trial) and the therapists. A PC algorithm will be performed to infer causal links with acyclic directed graph among different usability questions in the questionnaire from both groups of participants based on correlation tests. The Spearman's rho will be used to perform the correlation test85. The reason for using the PC algorithm to discover the casual relationship between each usability question is to investigate the factors that might determine whether the participants will use the WearUL system or recommend this to their friends if the system becomes available. Paired t-tests or Wilcoxon signed-rank tests will be used to compare grip strength and functional outcomes before and after the 4-week vibration treatment (Hypothesis 2b). Independent analysis of variance (ANOVA) will be used to compare subject demographics and outcome measures among four groups at baseline and a mixed model ANCOVA to compare differences within and between groups over time (Hypothesis 2c). Clinical-demographic characteristics (age, gender, disease duration, and CMSA scores at baseline) will be added as covariates. Should significant main and interaction effect differences be found ($p < 0.05$), post-hoc analyses with Bonferroni corrections will be used to examine the differences in variables across the groups and time points. A paired t-test or Wilcoxon signed-rank test will be used to assess satisfaction after the treatment (Hypothesis 2d).

Sample Size Calculations

As the major comparisons are the within subjects effects of focal vibration on grip strength and functional outcomes, power analysis will be conducted based on paired t-test. In previous works on focal vibration effect on FAM-UE, the effect sizes were 0.44 and 0.54 separately. In this study, we expect the effect should be greater than 0.4 as we are investigating patients with CMSA level four and above. Given an alpha of 0.05, a change of at least 40% in either FMA-UE or other functional outcomes, we will need 41 participants to obtain 80% power for the study. We acknowledge that we may be underpowered for detecting differences among the four vibration interventions but believe that the pilot data will provide rich information on feasibility of the vibration protocols, perceived usefulness, functional performance gains, and acceptance and tolerance to vibration treatment, which is important to know for the planning of future studies. We seek to enroll 48 subjects (12 per group) and factoring a 20% attrition rate, we expect to have at least 10 subjects per group for the analysis. According to a study that investigated the number of subjects needed for usability testing, 80 percent of usability problems can be detected by the first four or five subjects. We will sample 10 therapist from those who provide rehabilitation services to the patient subjects.

F. Gender/Minority/Pediatric Inclusion for Research

This protocol will include all adult volunteers between 18 and 64 years of age.

G. Human Participants

For Phase I: Participants enrolled (n=8) will provide feedback in a user advisory group on the design, development and evaluation of the prototype. Two occupational therapists (OT), two physical therapists (PT), and a user group comprised of four stroke patients will be recruited. The OTs and PTs will be aged 18 years or older and have at least three years of clinical experience working with stroke patients. The stroke patients will be in chronic phase of stroke recovery and be in a medically stable condition. The advisory team will be able to come to the research laboratory or participate remotely at least once a month for 12 months to discuss the design and development of the system for up to 2 hours per meeting.

For Phase II: Participants enrolled (n=56) will evaluate the usability and feasibility of the developed prototype. Forty-eight stroke patients and 10 therapists will be recruited. To participate in the study, patient subjects will meet the following criteria: ischemic or hemorrhagic stroke with Chedoke McMaster's Stroke Assessment (CMSA) level four or above; over 18 years of age; have been using a smartphone more than one year; and live within 40 miles from the University of Oklahoma Health Sciences Center (OUHSC). Patients with a history of fractures or dislocations in the shoulder, elbow, or wrist from which the participant has not fully recovered, or severe impairment of verbal communication ability (for example, severe aphasia), or inability to consent (for example, dementia), or simultaneous participation in another treatment study targeting stroke recovery will be excluded. Therapists will be recruited from those who provide rehabilitation services to the 48 stroke patients, and have been using a smartphone more than one year.

Sources of potential human subjects: The investigators will be able to recruit subjects from the State of Oklahoma as well as the investigators' clinical practices on the OUHSC campus. An IRB approved study flyer will be posted on the Department of Rehabilitation Sciences website (http://alliedhealth.ouhsc.edu/Departments/RehabilitationSciences.aspx) and Facebook page. In addition, the flyer may be posted in local rehabilitation facilities, outpatient facilities, and disability organizations, e.g., the College of Allied Health clinics, the Comprehensive Stroke Centers at the College of Medicine of OUHSC, INTEGRIS Jim Thorpe Rehabilitation, and the stroke program of Valir Rehabilitation Hospital. Therapists will be recruited from the hospitals or clinics providing rehabilitation services to the stroke patients. We will monitor the inclusion of women and if it appears that too few women are enrolling in the study, we will actively recruit women from our subject registries. No exclusion criteria shall be based on race, ethnicity, gender or HIV status.

Recruitment and consent plans: All recruitment and consent procedures will be formally approved by the OUHSC IRB prior to the initiation of the study. People meeting the inclusion criteria will be recruited through electronic invitation, personal email contact from investigators, and through IRB-approved advertisement. The telephone screening will be used to give the potential subject more information and to allow them to ask questions regarding the research study to help them determine their interest in participating. During the phone

screening we will also ask them basic questions to see if they qualify for the study. These questions will be based on the inclusion/exclusion criteria for the study. We want to make every effort to assist in determining that a participant would potentially qualify for the study prior to their contacting their therapists for permission. Prior to asking the participants these questions, we will make sure the subject understands why we are asking these questions and obtain their permission to do so. We will note the date and time of the permission obtained. The therapist's

screening will assess the potential participant's overall health prior to starting the vibration intervention. We will not see any of the medical records. The therapist's consent form will detail the study as well as list the contraindications of the study.

Risk and protection of subjects to minimize risk: All risks will be fully explained by the investigators using approved IRB protocol. All data collected will include the minimal information necessary to achieve the objectives of the proposed research. All data collected will be generated specifically for the purposes of this research study. Each participant will be in the study for two 3-hour visits. There may be anticipated circumstances under which participation may be terminated by the investigator without regard to consent, for example, if the investigators feel that it is in a participant's medical best interest to stop and/or a participant reports an increase (of 2 points on a 10-point pain scale) in discomfort during testing. Participants can stop participating in this study at any time. However, if they decide to stop participating in the study, the investigators encourage participants to talk to the researcher and their regular doctors first. While on the study, there is a less likely but possible risk: uncomfortable sensation from stimulation. The proposed research activity, which entails the application of focal vibration to the upper extremities, has been studied extensively in healthy individuals and individuals with stroke. Moreover, the effects of vibration on the body have been extensively studied and guidelines have been developed to regulate exposure to such stimuli. The frequency, amplitudes and exposures used in previous vibration studies and the proposed study are considered acceptable and safe. Subjects in the survey can choose to participate or not. Subjects in the focus groups will be informed of the risk of others possibly not liking their comments and thoughts and will be informed they can withdraw from the conversation at any time. Subjects may choose not to participate in the study without recourse or added cost to them. Efforts will be made to keep personal information confidential. Participants will not be identifiable by name or description in any reports or publications about this study. The investigators cannot guarantee absolute confidentiality. Personal information may be disclosed if required by law. The participants will be asked to sign a separate authorization form for use or sharing of their protected health information.

Benefit: Each person will be fully informed that they will not derive any direct benefit from their participation in this study, but they may gain the satisfaction of contributing to research that may assist with future development and improving the capabilities of upper limb rehabilitation in the home and community. Subjects will also be compensated monetarily for their participation.

H. Data and Safety Monitoring Plan

All data are de-identified and secured on a restricted-access, encrypted hard drive in the Technology of Occupational Laboratory lab. Signed consent and

HIPAA forms will be secured and separate from the collected data in a locked drawer in the PI's locked office. A data safety and monitoring plan will be implemented to ensure that there are no changes in the benefit/risk ratio during the study and that confidentiality of research data is maintained. Investigators, and study personnel involved in the study will meet bi-monthly to discuss the study (e.g. study goals, progress, modifications, documentation, recruitment, retention, data analysis, and confidentiality) and address any issues or concerns at this time. These meetings are overseen by the PI. Minutes are kept for these meetings, and will be on file. Any instances of adverse effects will be reported immediately using the standard forms and/or procedures set forth by the Institutional Review Board. In addition, the PI may periodically

review study documentation and/or consent forms to ensure that subject's confidentiality is maintained.

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