Title:

A Longitudinal Retrospective Study of a Wearable Neuromuscular Electrical Stimulation (NMES) System Shows Significant Improvement of Arm Usage in Hemiparetic and Hemiplegic Patients

Submitted to:

Journal of NeuroEngineering and Rehabilitation

Date Submitted: July 31, 2022

This is a preprint; it has not been peer reviewed by a journal.

A Longitudinal Retrospective Study of a Wearable Neuromuscular Electrical Stimulation (NMES) System Shows Significant Improvement of Arm Usage in Hemiparetic and Hemiplegic Patients

Philip Muccio *, BS, CPO [1], Rafik Salama, PhD [2], Nipun Chopra, PhD [3], Josh Schueller, MS, PT [1], David Durrant, DC, PhD [4], Edward Dabrowski, MD [5].

1 Axiobionics, LLC, Ann Arbor, MI 48103

2 Nuffield Department of Medicine, University of Oxford

3 Department of Biology, DePauw University, Greencastle, IN 46135

4 Chicago Neuroscience Institute, Elgin, IL 60123

5 Beaumont Pediatric Physical Medicine and Rehabilitation, Royal Oak, MI 48073

***Corresponding Author**

Abstract:

Background: Hemiparesis and hemiplegia are commonly observed motor consequences of brain injury and infarction. Brain disorders such as traumatic brain injury (TBI), stroke (cerebrovascular accident, or CVA), and cerebral palsy (CP), as well as surgical interventions, can result in aberrant motor function in the contralateral upper and lower limbs, resulting in paralysis, weakness and/or spasticity in the arm and leg. NMES has been previously used to stimulate affected muscle groups and to increase arm mobility in a variety of brain and spinal cord diseases, yet there remains a paucity of longitudinal evidence examining NMES-mediated improvements in arm usage after brain compromise.

Methods: In this retrospective cohort study (n=38), we examined longitudinal (up to 10 years) self-reported arm usage in patients with 1) TBI, 2) stroke, 3) prior hemispherectomy, or 4) cerebral palsy who wore an NMES device, Axiobionics' BioSleeve, and we compared this to arm usage achieved from years of conventional therapy (physical and occupational therapy) prior to use of the wearable NMES device in this study.

Results: We found that the patients saw an average increase in arm usage from 9.9% to 43.5% by the end of the study. This result was well represented across age groups and genders, with varying degrees across different diagnoses. Specifically, the TBI subcohort had a consistent increase in arm usage of 5.5% per year over the term of treatment.
Conclusion: This study supports the literature identifying NMES as a therapeutic intervention and complements the literature suggesting that NMES application can be used as a long-term method to increase arm usage in hemiplegic patients.

Keywords: Rehabilitation, Stroke, Brain Injury, Cerebral Palsy, Hemiparesis, NMES, Hemispherectomy, Wearable Therapy, Arm Disability

Background:

Cortical Diseases Linked to Motor Impairments

Hemiparesis (partial motor loss) and hemiplegia (total motor loss) are the reduction or inability to move the affected limbs on one side of the body and occur for a multitude of reasons. TBI, cerebral palsy, hemispherectomy, and stroke are independent underlying causes of impaired contralateral hemiparesis and hemiplegia, including a reduction in arm usage. Impaired arm positioning negatively affects arm usage and activities of daily living (ADL), such as grooming, eating and reaching for objects (Figure 1). Therefore, increasing arm usage remains a key therapeutic goal to facilitate recovery after these disorders.

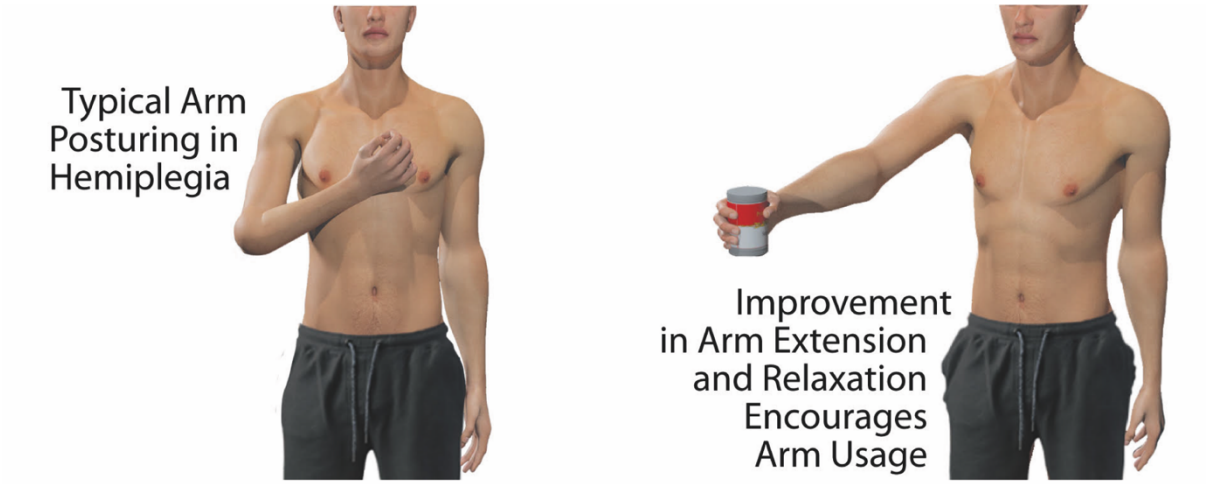


Figure 1: Graphical representation of how hemiplegia can adversely affect arm positioning and usage: Hypertonic flexor muscles cause flexion of the elbow, wrist and fingers and prevent the patient from voluntarily extending the arm (left image). Re-education, relaxation of muscles and joint looseness encourage the patient to extend the arm to reach and grasp objects (right image).

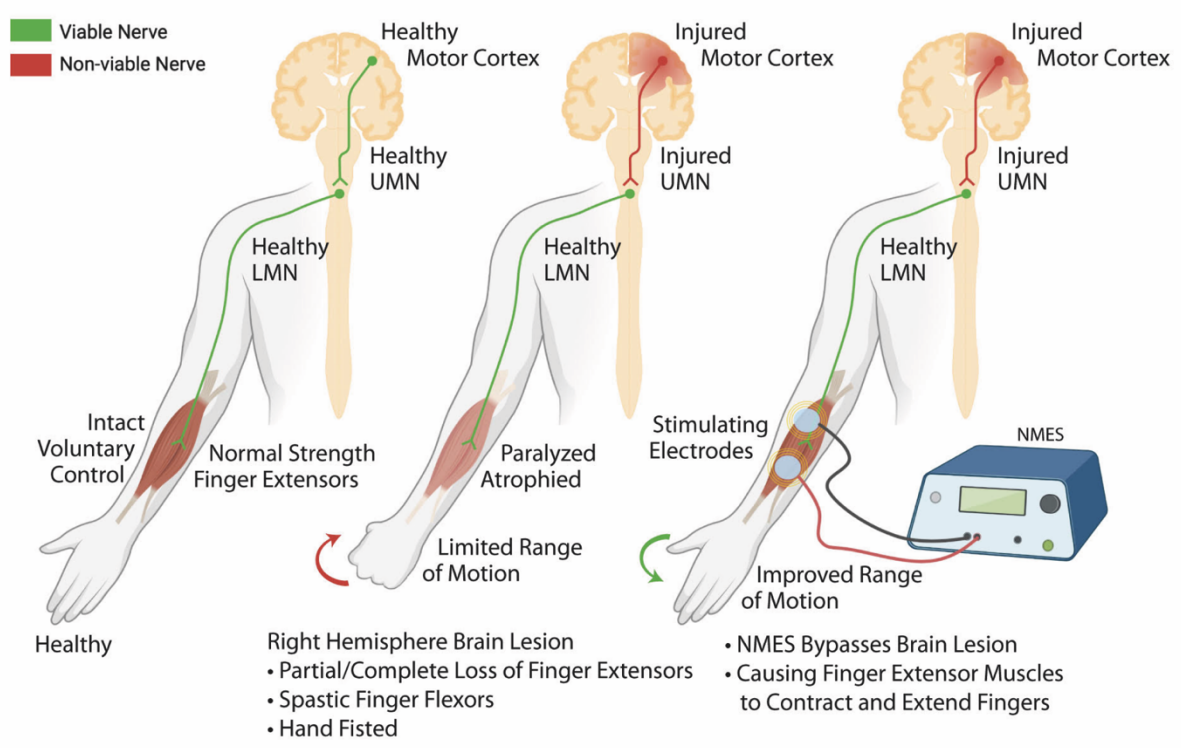


Figure 2: Graphical representation of how NMES treats hemiplegic muscles: Normal individual with intact motor cortex and viable motor neurons (left image), left hemiplegic arm with spastic finger flexors due to lesion of the right cortex and surrounding area (middle image), NMES bypasses the central nervous system lesion by stimulating the intact lower motor neurons, which then activate the finger extensors. Contracting finger extensors extend the fingers, reduce the effect of hypertonicity in the finger flexors, and increase the range of motion of the fingers (right image). Image generated using Biorender.

49

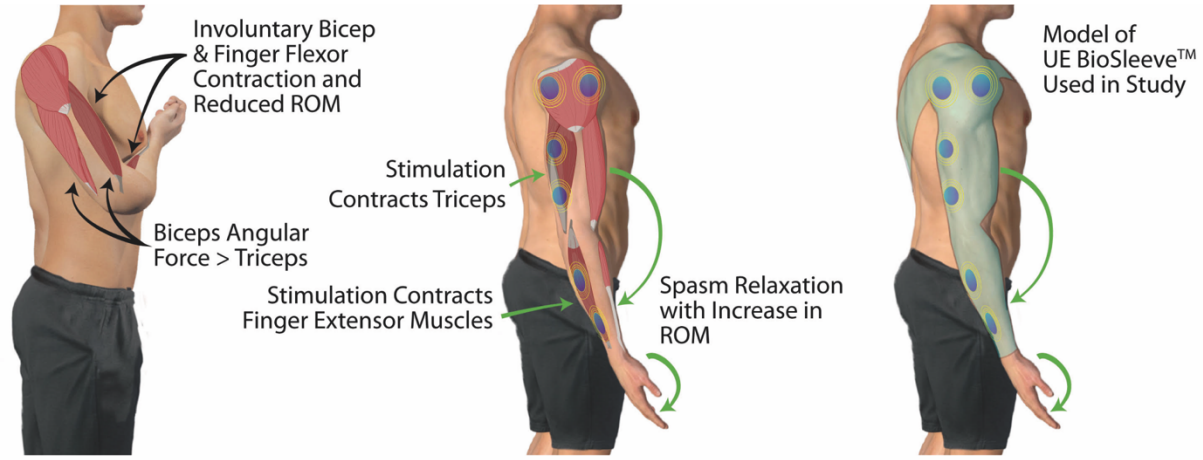


Figure 3: Limited range of joint motion and posturing in the hemiplegic right arm (left image) can be corrected via NMES on the triceps and finger extensors, which improves elbow and finger range of motion (middle image). The approximate position of electrodes (blue) in our study is shown in the graphical BioSleeve (right image).

TBI is a leading cause of long-term disability among children, young adults, and the elderly in the United States. Previous work estimated that 3.3 million Americans are living with TBI-related disability (1). TBI is often a complex disorder acquired from an external mechanical force to the cranium that is of sufficient magnitude to cause temporary or permanent brain

tissue damage related to neuronal or axonal damage. TBIs can be classified as mild, moderate, or severe (2, 3). Broadly, there are four types of traumatic brain injuries: 1) Concussions, 2) Brain Contusions, 3) Penetrating Brain Injuries, and 4) Anoxic Brain Injuries. This study focuses on contusion injuries sustained due to mechanical injury to the left- or right-hemispheric motor cortex because of automotive accidents. One possible outcome, depending on the severity of insult and damage to the motor cortex, is partial or complete paralysis to the contralateral upper limb muscles. Previous attempts to increase arm mobility have included singular approaches or combinations of pharmaceutical interventions, physiotherapy and electrical stimulation (ES). An analysis by Hillier (1997) estimated that long-term upper limb motor dysfunction occurs in 30% of TBI patients (4). Approaches to addressing functional impairment have focused on pharmaceutical interventions such as baclofen or therapeutic modalities such as exercise. Current work examining the usage of NMES on TBI motor recovery has produced inconsistent results (5).

Along with TBI, stroke is a leading cause of mortality and disability worldwide. Strokes can affect a variety of brain regions due to thrombotic, embolic or hemorrhagic infarcts, wherein affected regions experience lowered glucose and oxygen supplies resulting in inflammation, excitotoxicity, reactive oxygen species (ROS) release, necrosis and neuronal death. The middle cerebral artery (MCA) provides nutrients and oxygen to the motor cortex; subsequently, MCA infarcts are often associated with contralateral motor impairments, paresis, facial droop, and other abnormalities (6, 7). One study showed that motor function in the arm is aberrantly affected in 65% of stroke patients (8).

Pediatric conditions such as cerebral palsy and epilepsy-related hemispherectomy also result in contralateral motor impairments (9, 10). Cerebral palsy occurs in approximately 0.2% of births (9) and is associated with abnormal prenatal brain development (11). Affected infants commonly exhibit spasticity and motor abnormalities along with cognitive impairments. One approach to controlling intractable epilepsy includes neurosurgical interventions to excise or

disconnect seizure origin (12). The use of hemispherectomy (removal of one hemisphere of the brain) and hemispherotomy (localized disconnection and targeted removal of brain tissue) can reduce the occurrence of seizures but is also associated with contralateral motor deficits. Due to the small body size and brain size of infants and toddlers, both procedures can be complicated and risky (13).

In all aforementioned brain conditions, motor cortical activity is impaired or ablated. The motor cortex is the area of the brain responsible for the initiation, planning and control of movement. When the motor cortex is damaged, partial or complete paralysis ensues, muscle tone is altered, muscle activity diminishes, spasticity occurs, and atrophy and weakness set in (14). Impairment of the motor cortex due to cerebral palsy, TBI, stroke or hemispherectomy leads to hemiparesis or hemiplegia where the opposite side of the body is partially or completely paralyzed (7, 15-23). The motor network in the brain consists of the primary motor cortex, lateral premotor cortex, supplementary motor area, and subcortical areas such as the basal ganglia, thalamus, cerebellum, and brainstem nuclei. Injury to these regions or changes in the white matter fiber tracts that connect these regions can damage the synergistic control of the motor network and thus affect muscle function of a patient's limbs.

Motor Control Pathways

Controlled upper extremity movement is a synchronized neurocognitive and sensory process that begins in the planning stages in the premotor cortex and is executed by the primary motor cortex (M1). Injuries to the motor cortical areas are associated with impaired motor control and movement. Affected skeletal muscles atrophy (24, 25) or weaken even when remnant neurological control exists. Movement can diminish or vanish entirely because the atrophied muscles (Figure 4) no longer generate sufficient force to move the limb or to overcome its weight (26).

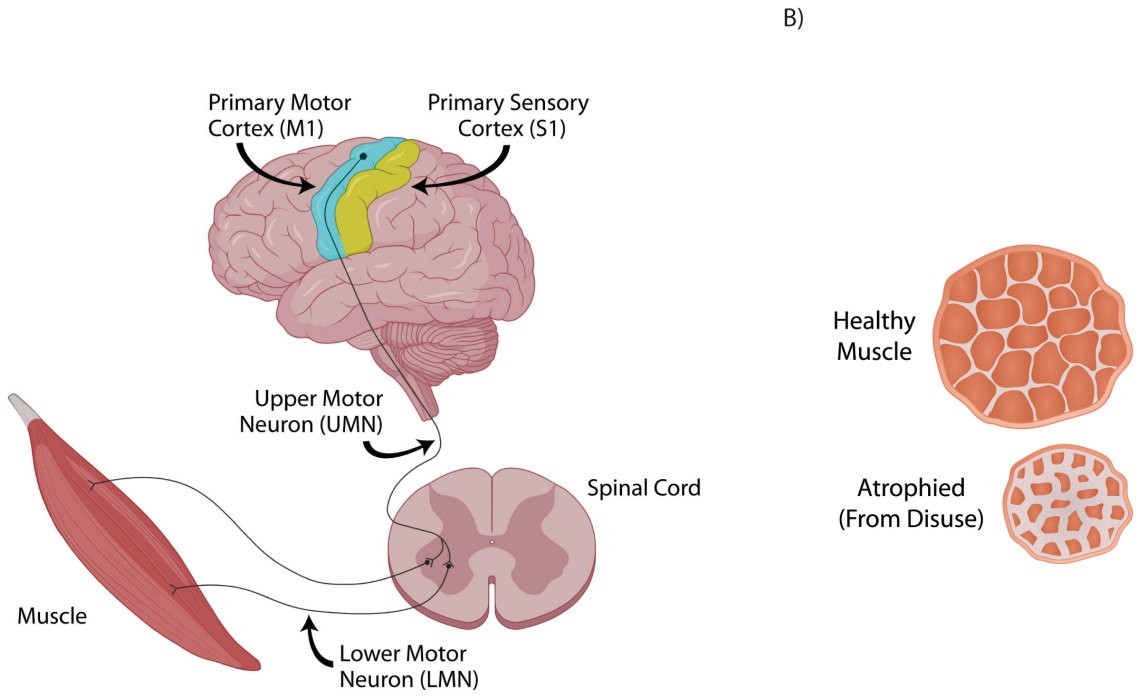


Figure 4: A) Upper motor neurons (UMNs) transmit motor cortex-initiated voluntary impulses via the corticospinal tract to the lower motor neurons (LMNs). The LMN emerges from the anterior horn in the spinal cord to innervate myofibrils. Brain infarction, disease or injury results in impaired activation of the UMN, resulting in an inability to activate the LMN. B) This loss of neuronal transmission results in reduced myofibril activation and muscle atrophy. Image generated using Biorender.

A second orthopedic problem associated with paralysis is joint stiffness and reduced range of motion (27, 28) arising from limbs staying in one position over an extended period. This condition is exacerbated by the presence of hypertonicity (29) in certain muscle groups, causing them to remain in a state of spasm (or sustained contraction), further limiting joint motion. Reduced range of motion in the upper limb diminishes arm function, and considerable effort in rehabilitation is needed to reverse the loss of mobility with limited success (30-34).

As a result of brain injury or insult, the UMN projections are unable to normally activate the LMN (35), which results in a loss of bilateral upper- and lower-limb movements (quadriplegia), loss of bilateral lower limb movements (paraplegia) or a reduction in unilateral upper- and lower-limb movement (hemiplegia) or weakness (hemiparesis). These abnormalities result in

a diminished ability to volitionally activate motor units (36) or changes in the motor units themselves, such as changes in mean twitch contraction time (37) (Figure 3). In the upper limb, the combination of paresis, loss of fractionated movements, flexor hypertonia, and somatosensory abnormalities often manifests as difficulty extending the elbow and opening the hand in a functional manner, which severely limits the ability to perform necessary functions (38-41). Therefore, any therapeutic intervention that improves upper limb movement is valuable in the field of neurorehabilitation of brain infarct patients. One such therapy for reducing hemiplegia is electrical stimulation (ES).

Neuromuscular Electrical Stimulation (NMES) and Hemiplegia

Neuromuscular electrical stimulation (NMES) can be used to activate muscle groups with the goal of addressing the weakness or paralysis associated with CNS injury (42, 43). The stimulus used during NMES is not sufficient to directly cause muscle contraction. Instead, during surface NMES, two or more gel-attached electrodes are placed on the skin and are used to send electrical impulses to the descending lower motor neuron pathways to activate targeted muscles, causing contraction (Figure 2). While a few studies have attempted to test NMES in clinical settings, these studies have produced inconsistent results related to a variety of factors, including lack of control groups, inconsistent experimental parameters and experimental bias (44). Therapeutic stimulation variables included frequency, dosage, waveform, amplitude, ramp time, duty cycles and electrode placement. NMES has been used as an intervention for the treatment of motor abnormalities related to various brain dysfunction syndromes, including stroke, TBI and cerebral palsy. However, to our knowledge, little work has been done to track patients longitudinally past early treatments (44).

A systematic analysis by Freitas et al. (2018) identified five studies that met acceptable standards of clinical work to appropriately test the applicability of NMES as a therapeutic modality in the treatment of upper- and lower-limb muscle weakness in CNS disorders,

161 although this work focused on spinal cord injury (30, 45-48). Of these five, the two higher
162 quality studies show conflicting results. Harvey EA (2010) enrolled SCI patients into two arms
163 – a control (no intervention) and an experimental arm (NMES). They found that the
164 experimental group showed increased voluntary strength in the quadricep muscle after a 24-
165 to 96-month intervention wherein participants were exposed to a 50 Hz frequency, 300 μs
166 pulse width, 100 mA intensity and a 12:12 s ratio for 3 days/week, performing 12 series and
167 10 repetitions/day (49). On the other hand, work by Glinsky EA (2009) showed no difference
168 in wrist muscle strength under similar parameters, with two key differences: a shorter total
169 intervention time (~5 months vs. 24-96 months) and a lower intensity of stimulation (70 mA
170 with a 6:6 ratio versus 100 mA with a 12:12 ratio) (45). Another key difference in the two
171 studies was the population sampled: Glinsky's study population enrolled tetraplegics, whereas
172 Harvey's study enrolled both hemiplegic and tetraplegic patients. Altogether, these two high-
173 quality studies have not yet settled the question about the applicability of NMES to muscle
174 recovery after brain and/or SCI insult.
175
176 Although the question of whether the long-term usage of NMES reverses the loss of
177 mobility associated with hemiparesis remains unanswered, NMES has been shown to
178 produce inconsistent short-term improvements in arm usage in acute and subacute
179 hemiplegic patients (50-53). Rosewilliam et al. (2012) showed that the extent of recovery was
180 dependent on continual NMES intervention (52). In an interventional study (Tashiro et al.,
181 2019), 23 stroke patients with severe upper limb hemiplegia underwent 3 weeks of daily NMES
182 therapy supplanted with electrophysiological intervention (54). The daily NMES intervention
183 produced improvements in motor function and proprioceptive feedback but not
184 somatosensation. Fujiwara et al. (2015) performed a similar interventional study to
185 demonstrate that NMES combinatorial therapy improved upper extremity motor function in
186 patients with hemiparesis (55). While other studies demonstrate the potential suitability of
187 combinatorial approaches (56, 57), the studies are heterogenous in their methods and

interpretation (58). An additional consideration is the financial, logistical, and temporal burdens placed upon the patient when additional outpatient and invasive interventions are used. Therefore, there remains a need for an at-home intervention to improve motor impairment associated with brain infarcts. Previous work has shown a beneficial effect of the home-based motor training program on motor function in patients with stroke, which was accompanied by enhanced interhemispheric functional connectivity of the M1 areas (59).

The question, then, is as follows: can function be regained in patients with hemiplegia after initial recovery? In a study of TBI patients assessing neuromotor function longitudinally, Walker and Pickett concluded that patients make their largest gains in function in the acute phase but over time that leveled off by the 12^{th} month and about a third had persistent impairment at 2 years (60).

Wearable NMES devices can, prima facie, be used to facilitate the at-home improvement of brain-insult-related motor impairments by re-educating muscles lacking proper cortical control. Axiobionics' wearable BioSleeve muscle stimulation is such a device. The objective of this paper is to analyze the outcome data obtained from using the upper extremity BioSleeve muscle stimulation system in hemiplegic patients to gain insight into the muscle re-education process. This paper does not present data on the mechanism of action of how muscles are re-educated; it asks two critical questions. 1) Does use of the upper extremity BioSleeve muscle stimulation system help to increase arm usage beyond what was achieved in standard therapy; 2) To what extent can function improve?

Methods:

BioSleeve Device and Patient Protocol

Patients with hemiparesis and hemiplegia were fitted with an Axiobionics custom upper extremity BioSleeve (Figure 5). The BioSleeve comprised six electrodes, with 2 BioGel Velcro electrodes over the deltoid, 2 over the triceps, and 2 over the finger extensors on the affected limb (Figures 3 and 5). The sleeve was designed to overlay the three muscle groups from the shoulder to the wrist. Each hemiparetic and hemiplegic patient was outfitted with a BioSleeve on the affected extremity with embedded wires and electrodes fastened to the interior of the garment with a hook and loop fastener. Electrode position was determined by the clinician at the time of the device initial fitting and was placed over the motor point of the targeted muscles. Electrode position was adjusted over time if needed to improve contraction force, to reduce discomfort, or to reduce unwanted joint deviation. Deltoid electrodes were placed over the anterior and posterior deltoid so that stimulation would contract all three heads of the deltoid (anterior, middle, posterior). The triceps electrodes were placed over the midline of the triceps with one placed proximally and one placed distally (Figure 5). The finger extensor electrodes were positioned with one electrode proximally and one distal to the proximal electrode. Every effort was made to produce finger and thumb abduction with as little wrist extension as possible and with minimal to no radial or ulnar wrist deviation. If wrist extension was more pronounced than finger extension, a static wrist-hand orthosis was applied to maintain wrist neutrality in the sagittal plane. The intensity of stimulation delivered to each muscle minimally varied between patients.

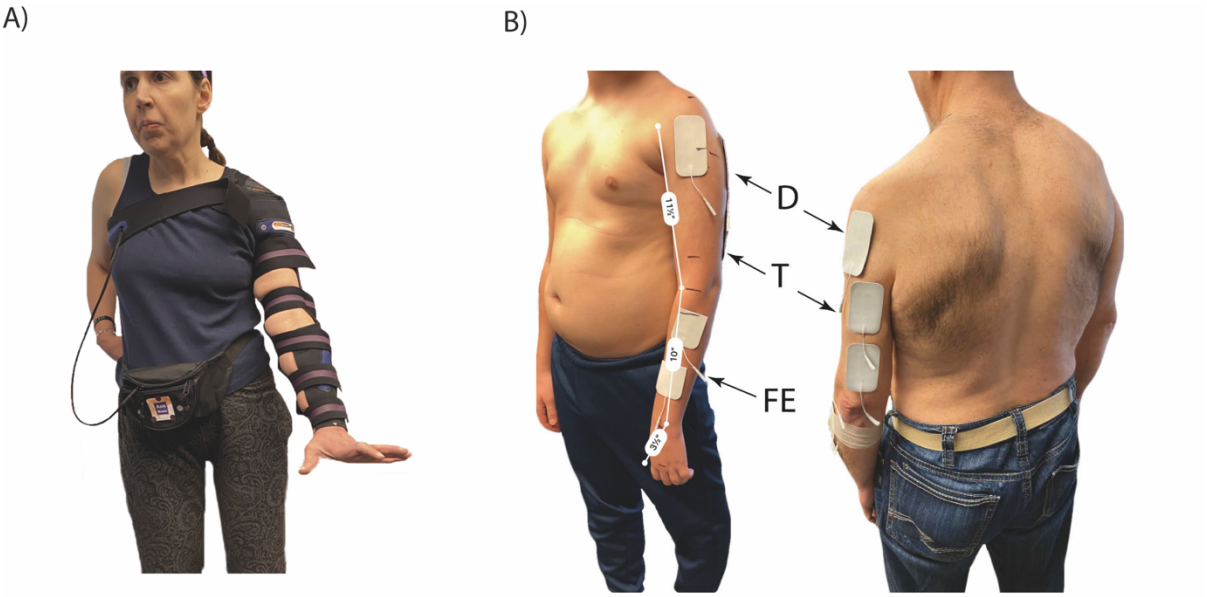


Figure 5: A) BioSleeve (front view) shows the assembly of the BioSleeve. B) The position of electrodes over the deltoid (D), triceps (T) and finger extensors (FE) is shown.

Stimulation levels were not designed to produce maximum contraction force. Rather, the level of stimulation was limited to an intensity that delivered the maximum range of motion at a particular joint without overextending the joint. For the deltoid, intensity was chosen when the humerus abducted 5-10 degrees, or if the humerus was subluxated, the intensity was determined by the amount of stimulus needed to fully approximate the glenoid fossa. This was confirmed by palpation of the space between the acromion and the head of the humerus before and during stimulation. Stimulation was applied to the triceps until the elbow extended to its endpoint. Not all elbows were able to achieve full extension when a flexion contracture was present. If spasticity was present in the biceps, the intensity was set to overcome the

flexion force of the biceps without aggressively forcing the elbow into extension. The level of intensity for the finger extensors was determined when the fingers fully extended or reached their endpoint if restricted by joint stiffness or contracture. The finger extension force was kept low to moderate. Care was taken not to forcefully extend the fingers. If the stimulus intensity reached a level that triggered spasticity in the finger flexors, the intensity was adjusted to induce extension but not spasticity. The levels of stimulation required were labeled on the front face of the stimulator for patient reference. The patient was instructed to input the number for each channel every time the system was applied. Some variation in stimulus output was allowed to minimize/eliminate discomfort or to produce a slightly stronger muscle force to achieve the desired joint range of motion and limb movement. Stimulus parameters other than current intensity were kept consistent across all patients as follows: 1) Stimulus ON Time: 10 sec, 2) Stimulus OFF Time: 10 sec, 3) Frequency: 50 Hz, 4) Pulse Width: 300 μsec, 5) Ramp Up: 3 sec, 6) Ramp Down: 2 sec. These parameters are consistent with other studies utilizing NMES for recovery (51, 61, 62).

Patients were provided a protocol to follow, including an acclimation protocol to slowly build the stimulation time from 30 minutes up to 12 hours. Patients were asked to wear the Bio Sleeve on day one for 30 minutes during the first half of the day and then another 30 minutes during the second half. They were instructed to increase the 30-minute sessions by 10 minutes every day thereafter up to 12 hours per day, if tolerated. Wear times of 12 hours were not mandated. Patients were encouraged to wear the BioSleeve 5-7 days per week or as much as tolerated but never past a point that would cause discomfort or pain.

Retrospective Cohort

The retrospective study included 38 patients (24 males, 63%, and 14 females, 37%) who were referred by a physiatrist, physical therapist, or occupational therapist or who came by self-referral to the Axiobionics clinic for a BioSleeve. All patients were treated by and reported

results to the same clinician. During the evaluation visit (before the BioSleeve was fitted), the clinician verbally asked the following question to establish baseline arm usage: "*What percentage of time are you using the affected arm in your own environment?"* Additional clarification was given that arm activity included any activity, whether the affected arm was used by itself or as an assist to the unaffected arm. This question was not intended to discover and report function; rather, it was seeking the amount of time spent in each activity in which the affected arm was used. No distinction was made to distinguish between arm usage in and out of the BioSleeve. The same question was asked during each subsequent follow-up visit after the BioSleeve was fitted. The clinician provided additional verbal guidance by explaining that 0% meant the arm wasn't used at all and 100% meant the arm was used in a normal fashion as it would before hemiplegia took place. The clinician also recorded whether the patient was using the BioSleeve device and, if, so, recorded the patient-reported number of hours the BioSleeve device was used per day. Parents or guardians of patients under the age of 18 years old or those who could not comprehend the question due to cognitive deficits were asked to report for the patient. The data were recorded in the patient chart at the time of the patient visits and extracted for the purpose of this retrospective study.

Inclusion Criteria: Hemiparesis and hemiplegia patients seen by the examiner from 2012 to 2021 for traumatic brain injury, stroke, cerebral palsy and hemispherectomy (> 3 months postinjury) who were treated with the Upper Extremity BioSleeve Muscle Stimulation System stimulating the deltoid, triceps and finger extensors and who were able to understand and answer the home arm usage question at initial evaluation and subsequently on follow-up were reviewed for inclusion in this retrospective analysis if they were seen for at least one follow-up visit no less than 2.0 months after the initial fitting. Age was not a determining factor in the inclusion criteria. Children whose parents were able to understand and answer this same question were included in this analysis.

Exclusion Criteria: Patients were not included in this retrospective analysis if they or their parents or guardians were not able to report arm usage. Patients who received a BioSleeve that stimulated muscle other than the deltoid, triceps, and finger extensors were excluded from the study. Additionally, patients were excluded from treatment if they had a cardiac condition that necessitated the implantation of a demand cardiac pacemaker or defibrillator. Pregnant women (safety of muscle stimulation during pregnancy is not known), patients with dementia, patients with severe receptive or global aphasia that confounded testing and training (operationally defined as a likely inability to understand the protocols and procedures, as judged from an inability to follow commands) and patients with active cancer were excluded from treatment. Patients who had sustained cerebral injury in the past 3 months were also excluded.

Statistical Analysis

The statistical evaluations were carried out with the statistical program R (Version 3.1, R Foundation for Statistical Computing, Vienna, Austria). Continuous measures are represented by the means and standard deviations, and discrete features are represented by absolute frequencies. For the statistical analysis, normality was determined using the Shapiro–Wilk test. To model changes, for example, in success rates or complication rates, generalized logistic regression with a logit link function was used. The parameter significance of the generalized linear models was calculated using the Wald test (63), with the null hypothesis that the parameter was 0. A parameter was considered significant if the p value of the test was less than $\alpha=0.05$. Given the number of possible variables that could explain the outcome, the best model that explained the outcome was selected, relying mainly on stepwise regression to identify the model.

Stepwise regression was assessed using the Bayesian information criterion (BIC) of the model, where a higher BIC indicated that the factor combination of the model was a better model. To evaluate the best combination of factors, we iterated through the model, starting from the full model (i.e., including all independent variables that we intended to study).

Variables were then randomly dropped to evaluate the BIC. If the BIC of the new model was higher than that of the current model, then we utilized this combination of variables for the next comparison. Randomly every n step, we added a random variable back of the set of variables that was dropped to find better forward models. We continued to iterate until we were unable to make improvements to the BIC of the model. For the final model, we selected the model that best fit the data we had. A power calculation for the study was performed by simulating sampling from a statistical distribution representing the effect measured with the same sample size while measuring the probability of having a significant outcome (<0.05). The resulting power was then defined as the percentage of time we obtained the significant result under the same sample size and the uncertainty in the statistical distributions.

	Total	CP group	CVA group	Hemispherectomy group	TBI group		Power
Count	N= 38	N = 7	N = 4	N = 4	N = 23		
Average and Range of Age of Disease Onset (in years) (M±SE)	13.8 ± 2.8 (0-72)	0 ± 0 (0–0)	43.8 ± 4.9 (0–72)	1.85 ± 0.22 (0–3)	14.9 ± 1.8 (0–34)	2.84e-05*	0.75
Gender (n) (Male/Female)	24/14	4/3	1/3	3/1	16/7	0.392	1.0
Average and Range of Number of Years in Conventional Therapy (M±SE)	12.4 ± 1.8 (0–38)	20.8 ± 1.73 (9–38)	7.25 ± 1.6 (1–22)	2.37 ± 0.22 (1.1–4)	12.46 ± 1.8 (0–37)	0.0413*	1.0
Average and Range of Age of Patients Started Using the BioSleeve (M±SE)	26.18 ± 2.68 (1.8–73)	20.8 ± 1.7 (9–38)	51.0 ± 3.4 (22–73)	4.2 ± 0.43 (1.8–7)	27.3 ± 2.02 (7.0–53)	0.000107*	0.83
Average and Range of Number of	2.59 ± 0.36 (0.2 – 9)	2.28 ± 0.22 (1.0-5.0)	3.5 ± 0.38 (1.0-6.0)	0.57 ± 0.1 (0.2-1.5)	2.88 ± 0.4 (0.4-9.0)	0.233	1.0

Years BioSleeve was Worn (M±SE)							

Table 1: The current cohort of patients was tested for differences between diagnosis, disease onset age, gender, and number of therapy years - either conventional or BioSleeve. This was to identify if there were statistically significant differences between the groups along with the statistical power of the tests. There were significant differences in age of disease onset, BioSleeve age, and conventional therapy years across diagnoses. The cohort does not show significant differences in gender or BioSleeve years. See Supplementary Figures 1-5.

Table 1: The current cohort of patients was tested for differences between diagnosis, disease onset age, gender, and number of therapy years - either conventional or BioSleeve. This was to identify if there were statistically significant differences between the groups along with the statistical power of the tests. There were significant differences in age of disease onset, BioSleeve age, and conventional therapy years across diagnoses. The cohort does not show significant differences in gender or BioSleeve years. See Supplementary Figures 1-5.

Results:

BioSleeve is Associated with a Significant Increase in Arm Usage

We found that the BioSleeve intervention significantly increased arm usage compared to baseline within our cohort (Figure 6), and we observed differences between various diagnoses (Figure 7). An initial generalized linear model was used to model arm usage against patient age, gender, period of treatment, method of treatment, and diagnosis. The method of treatment was assumed to be either conventional or BioSleeve, assuming that any prior treatments to the BioSleeve were conventional treatments. The conventional treatment period was the period from disease onset to fitting of the BioSleeve. BioSleeve, on the other hand, was associated with multiple follow-up periods, and each one was recorded against the age of the patient at the time of follow-up and the total period length. The model accounts for the impact of age, length of treatment period, gender, diagnosis and arm usage. The final model,

identified by stepwise regression, included only the method of treatment as the best-fitting model to explain arm usage. The model showed a highly significant correlation (p value < 0.0001) for the method of treatment irrespective of the other factors modeled. Accordingly, the period of treatment, patient age, gender, and diagnosis were secondary to the method of treatment to explain arm usage.

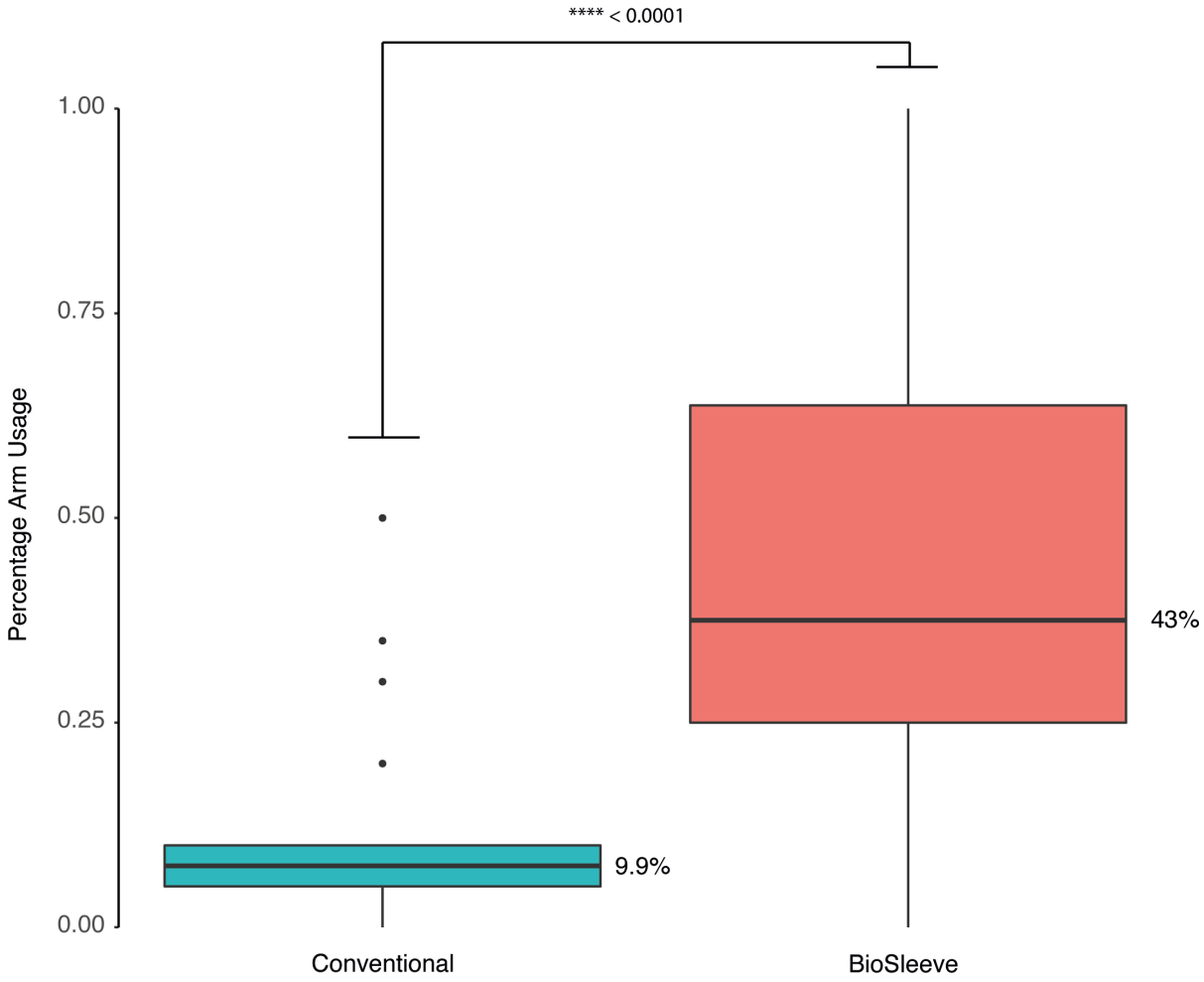


Figure 6: BioSleeve intervention significantly (p<0.0001) increased arm usage in our cohort of disease compared to previously administered conventional therapy.

A second stepwise generalized linear model of arm usage considering the period of BioSleeve use against patient age, gender, period of treatment, usage hours per day, and diagnosis identified the period of treatment and hours of usage per day as the main factors in the final model. Interestingly, the usage hours per day was not a significant factor; however, the cohort of patients did not show a wide variation in the time used per day. This indicates that the period of treatment is the main significant factor in determining the final arm usage of the patients using the BioSleeve.

	Total	**CP group**	**CVA group**	**Hemispherectomy Group**	**TBI group**	**P Value**	**Power**
Count	N= 38	N = 7	N = 4	N = 4	N = 23	N/A	N/A
Average and Range of Arm Usage Before Bio Sleeve (%) (M±SE)	9.9 ± 1.7 (0–50)	10 ± 1.75 (0.0–30.0)	7.5 ± 0.44 (5.0–10)	1.7 ± 0.38 (0.0–5.0)	11.7 ± 1.9 (0.0–50.0)	0.374	1.0
Average and Range of Arm Usage After Wearing the BioSleeve (%) (M±SE)	42 ± 4.2 (0-100)	33.0 ± 3.4 (0.0–60.0)	25.0 ± 2.7 (15.0–50.0)	36.2 ± 4.3 (5.0–70.0)	48.8 ± 4.49 (0.0–100.0)	0.241	1.0
Average and range of change in arm usage after BioSleeve – before BioSleeve (%) (M±SE)	32.1 ± 3.9 (0–90)	23 ± 3.2 (0–55)	17.5 ± 2.9 (5–45)	34.5 ± 4.4 (3–70)	37.0 ± 4.1 (0–90)	0.345	1.0
Average Time the BioSleeve was worn in one day in Hours (M±SE)	8.08 ± 0.63	7.42 ± 0.82	5.5 ± 0.38	8.75 ± 0.48	8.61 ± 0.62	0.495	1.0
Number of Improved patients	35	6	4	4	21	N/A	N/A

Table 2: Overall, 35/38 patients reported improvement in arm usage in response to BioSleeve intervention. The magnitude of arm improvements varied across the four cohorts. The largest improvement in arm usage was reported in the TBI group

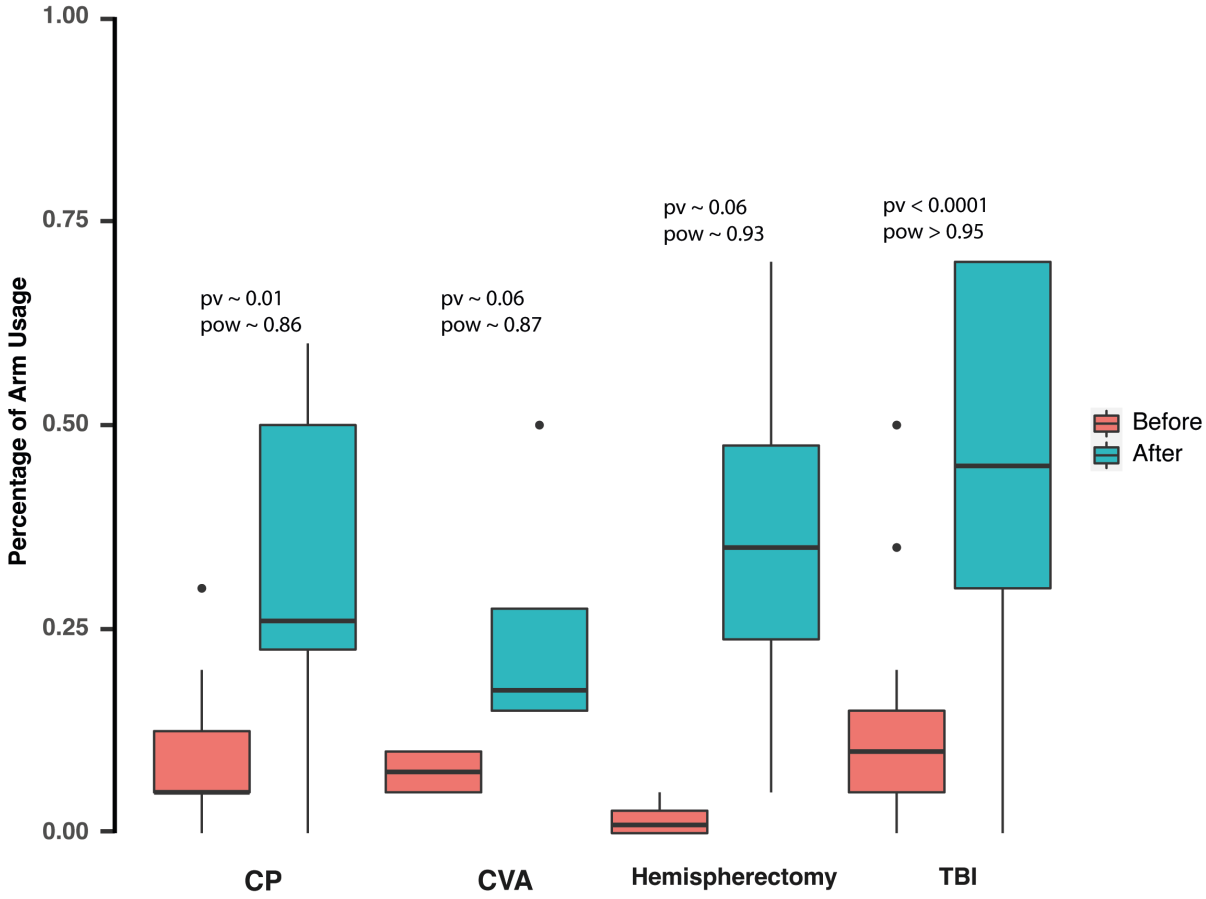


Figure 7: BioSleeve intervention significantly increased arm usage across all 4 diseases with power more than 80% using paired Wilcoxon test. CP, CVA and Hemispherectomy shows marginally significant p-values.

393
394
395
396
397
398

399 **Arm Usage Significantly Increases Progressively with BioSleeve Intervention**

400 Patients were tracked for up to a period of 10 years post-BioSleeve intervention. A third
401 generalized linear mixed-effects regression was used to model the progressive change in
402 percentage of arm usage across follow-ups against the fixed effect of disease onset age, age

403 of patient at the start of BioSleeve usage, arm usage before the BioSleeve, and patient
404 diagnosis. In addition, the number of years of BioSleeve usage was modeled as a random
405 effect for every patient. The random effect accounts for variations in patient response
406 themselves and variations between patients. Stepwise regression was used to select the best
407 model. The final model showed a significant positive correlation with the number of years that
408 the patient wore the BioSleeve, with an average increase of 5.31% in arm usage every year
409 ($p<0.0001$). The model showed, however, that TBI patients are the cohort of patients showing
410 the most remarkable changes. TBI patients showed a high average prior arm usage of 23.6%,
411 which progressively increased over the years, and a posttreatment arm usage of 88.3% at the
412 last follow-up. The linear mixed-effects model of the TBI patients showed a significant
413 relationship between years since fitting and arm usage ($p<0.001$), with an average effect of
414 5.67% per year (Figure 8).

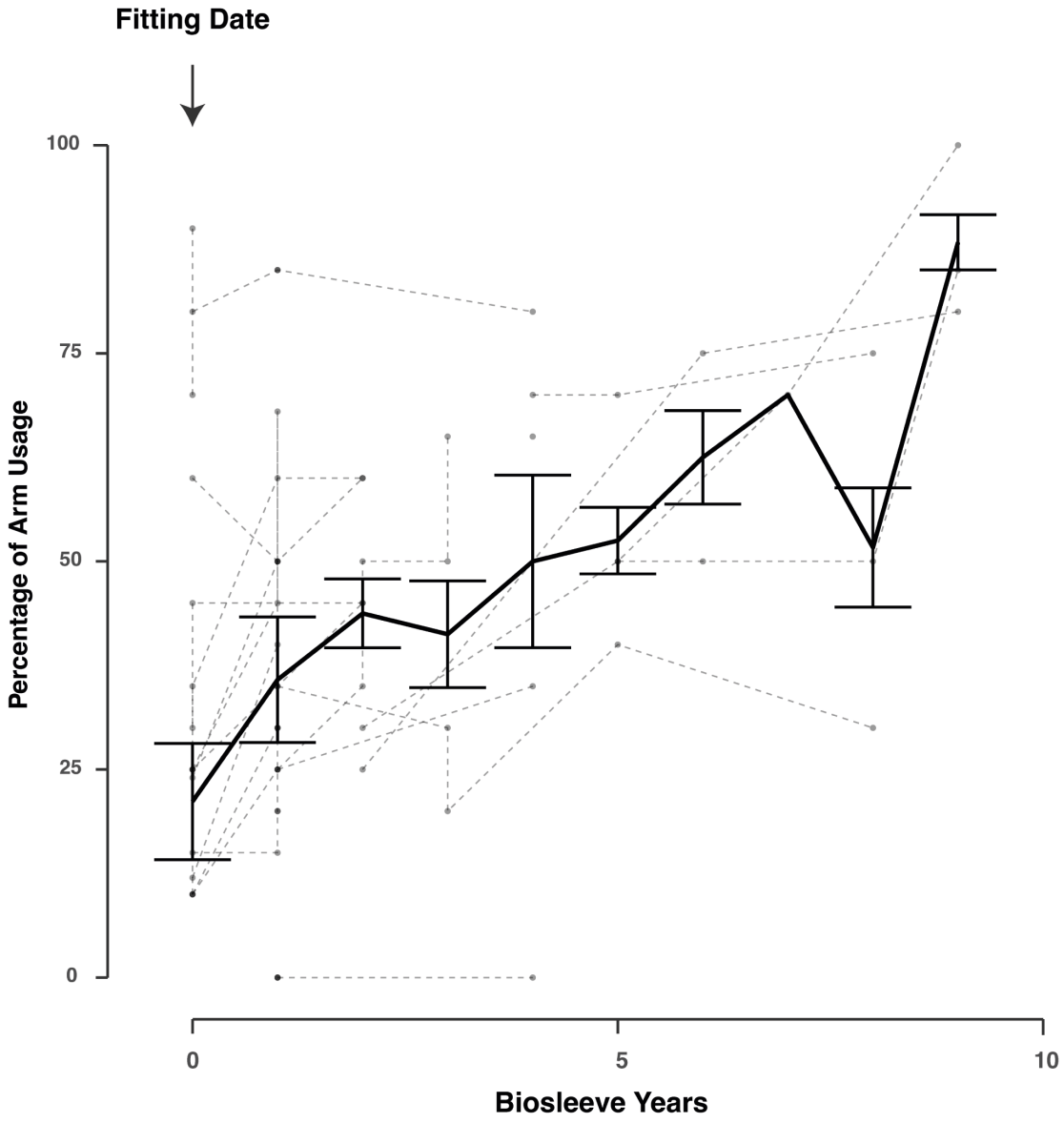


Figure 8: Longitudinal arm usage for all TBI patients, restricting arm usage to 10 years prior to the fitting of the BioSleeve. All patients were baselined to the fitting date at 0 years with patient follow-up continuing for up to 10 years, with some patients lost to follow-up. The plot shows the average arm usage per year across all patients who wore the BioSleeve in the follow-up phase. The percentage of the group that reported arm usage every year is represented by an average ± 1.96 * SE. The plot also includes dotted connected lines per patient who show per patient performance. Arm usage at 0 years should be taken as the baseline after conventional therapy.

415

416

417

418

While a similar trend was observed in the CVA patients (Supplementary Figure 7), the cerebral palsy (Supplementary Figure 8) and hemispherectomy cohorts (Supplementary Figure 9) did not show similar effects, although those groups comprised smaller sample sizes. Interestingly, some patients in the non-TBI cohorts showed a decline in arm usage function (Supplementary Figure 6). As shown in Figure 6, a decrease in the percentage of arm usage is primarily due to the contribution of a few patients who either stabilized or reported less arm usage in the year 9 follow-up. The year 10 follow-up showed improvement, perhaps biased by improvements associated with both patients who adhered to follow-ups. The mixed-effects model considered both the cohort and patient effects.

Study Limitations:

Retrospective cohort studies such as ours have known limitations. First, the study may be subject to recall and recency bias (wherein patients are likely to overrepresent recent observations over longer trends); however, the reported arm usage improvement is more significant than a random variation in arm usage over time, as shown in the longitudinal statistical models. Second, the data were not systematically randomly sampled, but we relied on random patient walking into the clinic. Additionally, the TBI group is overrepresented, as they were able to benefit from medical insurance to obtain the device. Hence, we tested the TBI group independently from the other groups. Third, the potential for biased reporting exists, i.e., patients may feel compelled to report improved outcomes. To control for this experimenter bias, patients were not given an incentive to report improvements – they were not paid to participate in the study, no additional therapy was provided, and no increase in medical benefits resulted from participation in the study. Fourth, our study did not have a control group to compare; however, in the analysis, we relied on case crossover methodology, wherein patient response was compared pre- and postintervention. Fifth, our study is semiquantitative, as individual perceptions may interpret arm usage differently; for example, a 60% arm usage for one patient may not mean the same for another patient. This would have affected the

stability of the reported arm usage; however, we found less variability than the significant variability of the improvements. Sixth, follow-up visits were not consistent between patients, and some complied better than others; therefore, some patients were followed over a longer period than others. However, we treated all patients as one cohort with expected dropout percentages, all baselined to the same start. Seventh, although reporting clinical outcomes is a first critical step in the discovery of medical knowledge and is sometimes the impetus for future research, this retrospective study was the culmination of work done by Axiobionics, which has commercialized the BioSleeve device. To overcome inherent bias, the data collected were reviewed by an independent expert in medical statistics who performed all mathematical computations. Future studies will be conducted in conjunction with one or more independent institutions, randomized and controlled.

Discussion:

Impaired primary motor cortex (M1) cortical function results in a reduction or absence of contralateral limb mobility. The rehabilitation of arm mobility after brain insults and infarcts remains a necessary therapeutic goal (64). Current therapeutic interventions include neurorehabilitation via in- and outpatient therapy (64, 65), noninvasive cortical activation (such as transcranial magnetic stimulation (66, 67), and subcutaneous and transcutaneous electrical stimulation (67-69). However, there remains vast inconsistency in the literature with respect to technological intervention, individual experimental parameters, sampling and, consequently, results (70). NMES is one type of ES wherein affected limbs can be activated by stimulation with an array of cutaneous electrodes. Previous work has shown promise for the usage of NMES in rehabilitation settings such as urinary retention (71), dysphagia (72) and ataxia (73). However, there remains a scarcity of evidence tracking long-term interventional NMES effects on arm usage. Herein, we tested the use of the Axiobionics

BioSleeve NMES device in a retrospective study consisting of patients with hemiplegia or hemiparesis.

In our study, hemiparetic and hemiplegic patients (n=38) were fitted with an NMES device (BioSleeve). The current retrospective study followed patients up to 10 years, recording their reported arm usage during the follow-up visits. To our knowledge, this makes our study the longest retrospective analysis examining the effects of electrical stimulation of muscle as a rehabilitation therapy. Initially, we compared the patient's conventional therapy with the NMES therapy, as each patient received some therapy since disease onset. The conventional therapy outcome was determined to be baseline reported arm usage prior to the BioSleeve fitting. The current cohort studied had a majority of TBI (n=23) patients, followed by CP (n=7), CVA (n=4), and hemispherectomy (n=4). This disparity in sample size was due to a logistical limitation. Currently, NMES devices are not easily approved for insurance coverage, except in cases of insurance payouts from automobile accidents resulting in TBIs. On the other hand, cerebral palsy (CP), stroke, or hemispherectomy patients paid out of pocket and were therefore less likely to purchase the NMES device. Hence, we see the highest power in our TBI patients; however, we did not exclude the results of other diagnoses, as it offered the ability to test the generality of the method of treatment across all four diagnoses.

We used a mixed-effects model to test the general impact across all diagnoses. The model assumed a case crossover, where the same case undergoes conventional therapy and subsequently participates in NMES therapy. The model showed that NMES therapy provided significant improvement over conventional therapy when accounting for diagnosis, the age of the patient, length of treatment, and gender. The model showed that the method of treatment (conventional vs. NMES) was the main distinguishing factor of improvement in arm usage. We utilized a stepwise regression method as an iterative mechanism for our model. Stepwise regression is the recommended statistical approach to identify the optimal combination of variables that best fit the data, given the assumption that the variables are independent.

We observed an improvement in arm usage irrespective of diagnosis; however, we observed the largest improvement in TBI, with an average increase of 48.8% ± 27.7%. Our other cohorts showed smaller improvements in arm usage, CVA followed by CP, and hemispherectomy (see Figure 6). A total of 21/23 of our TBI patients exhibited an increase in self-reported arm usage, demonstrating evidence for the suitability of the BioSleeve for facilitating arm recovery in this type of patient. Our results support existing work that has established cutaneous or transcutaneous electrical stimulation to reverse the loss of arm movement (70, 74-76). Our study shows that there is potential for long-term improvements in arm usage across hemiparetic patients. Unlike other studies, the usage of the BioSleeve facilitates the ability to stimulate the affected arm without discomfort and in the home environment.

The disproportionate increase in motor recovery in TBI patients compared to other diseases is potentially biased by a significant disparity in sample sizes in our cohort. Interestingly, a recent study examining potential improvements in arm usage after cutaneous electrical intervention also observed a greater improvement in their TBI groups (n=8) over their stroke group (n=8), although their result was not statistically significant (74). If there is indeed a robust difference in rehabilitation related to disease states, this may be due to the neurobiology and neuropathology of the disease states themselves. Recovery has been reported to include the activation of the premotor cortex (77) and other motor pathways (78-80). Yeo and Jang (2012) reported that arm recovery can occur via activation of the ipsilesional motor cortex after an MCA infarct (80). The interrelationship between infarct severity and penumbra recovery results in significant heterogeneity in the presentation of stroke-related motor deficits. This is in line with established knowledge that the risk for stroke onset increases significantly with age (81). Consistent with the results of that study, our stroke cohort was older than our other cohorts. Another source of heterogeneity is the severity of the initial motor deficit, as it has been previously reported that individuals experiencing mild to moderate poststroke arm paresis show larger improvement outcomes than individuals with severe paresis (82-85). Our study

tracked a small population of stroke patients with a range of arm mobilities at the time of intervention.

We postulate that the combination of the relatively young age of the cohort and the potential for focal TBI may enable an increased chance of recovery in comparison to other groups. Our TBI group was younger than the stroke group. It is posited that the potential for angiogenesis (86, 87), neuroplasticity (88, 89), and rewiring of brain regions decreases as a function of increasing age, potentially due to an age-dependent loss of neural progenitor cells (86). Conversely, other studies have shown that muscle re-education and recovery do occur, even in elderly patients in response to activity (90-92). Therefore, it is possible that the disproportionately large improvement in our TBI cohort, relative to our stroke cohort, may be a result of an underpowered stroke cohort and/or the relatively young age of the TBI cohort. Concomitantly, hemiparesis associated with TBI can be due to a heterogeneity of affected brain regions but likely includes the motor cortex. Without knowledge of the severity of TBI – data unavailable to us – we were unable to factor TBI severity as an additional variable to consider in terms of motor recovery. It is plausible, however, that there was a self-selection bias among the TBI group – only those individuals who experienced moderate TBI and maintained some arm mobility were likely to use the BioSleeve. Individuals suffering from mild TBI (e.g., sports-related concussions) often do not experience motor abnormalities and are less likely to participate in such a study. Concomitantly, individuals who experienced a severe TBI – potentially resulting in severe sequelae – may not consider arm usage recovery to be a therapeutic priority. Future work with the BioSleeve should examine whether improvements in motor function are inversely correlated with disease severity.

A key finding from our study was that incremental improvements were not related to the age of the patient, gender, hours of device usage per day, or disease onset age. The main factor affecting the progress of arm usage rehabilitation was the total number of years that this device was used. Conversely, some patients in each group showed either no improvements or a

558 decline in arm usage. The potential reasons for limited responses are multifactorial but include
559 heterogeneity in disease severity, inconsistent or incorrect usage of the device, differences in
560 usage time or settings, differences in age and errors in patient reporting. Additionally, early
561 BioSleeve intervention may be more beneficial than late intervention due to better
562 management of muscle weakness and atrophy.
563
564 We observed significant heterogeneity within disease groups. Specifically, 3 out of 4 patients
565 in the stroke group showed marginal (10%) improvements, while the final patient (#25) showed
566 a 55% improvement in arm usage. While patient 25 (Supplementary Figure 6) had the highest
567 time of intervention out of the group, this is likely not the only reason for this disparity in
568 improvement, as patient 27 had a similar intervention length but showed a marginal
569 improvement. In the TBI group, we observed the best response to the BioSleeve intervention,
570 although there were two individuals in our TBI cohort who did not show any improvements.
571 These individuals (Patients 19 and 23) had a self-reported score of 0 arm usage both before
572 and after the BioSleeve intervention. On the other hand, other patients in the TBI group (#3,
573 #31 and #36) reported increased arm usage despite starting at a score of 0. Therefore, even
574 within our TBI cohort, there remains some heterogeneity in response. Future work should
575 explore this disparity in response and may elucidate new avenues for personalized medicine.
576
577 The wearable BioSleeve device increased arm usage compared to conventional therapy
578 alone, as shown in the first model that showed the method of treatment as the main significant
579 effector for patients across the 10 years of follow-up before and after the BioSleeve device
580 was fitted. The second result also showed that the device showed a significant linear
581 improvement in patients with time.
582
583 While our retrospective longitudinal design does not allow for an understanding of causation
584 for improvements in upper arm mobility related to NMES, other work has posited a variety of
585 potential mechanisms. These mechanisms range from a direct, short-term effect, such as

impaired motor protein or ion channel expression (93, 94), to a long-term indirect effect, such as a potential long-term potentiation (LTP)-like mechanism involving rewiring and strengthening of synaptic connectivity (14, 95-97). Veldman et al. (2014) have speculated that this LTP-like pathway begins via activation of the sensory neurons emerging from the NMES-activated muscle, projecting axons to the dorsal root ganglion in the spinal cord. Subsequently, activation of the sensory dorsal medial lemniscus pathway is followed by the decussation of spinocortical projections and the activation of contralateral S1 sensory cortices via intermediate thalamic projections (14). Consequently, projections between S1 and M1 are hypothesized to potentiate the M1 motor cortex (14, 98, 99). This innervation and potentiation of the affected and unaffected M1 cortices is an exciting potential focus for future work but remains speculative for now. More research is needed to determine the mechanism underpinning the BioSleeve-mediated increase in arm usage.

Conclusion:

To our knowledge, this is the first research study showing improvement in arm function in hemispherectomy patients. Intractable seizures that do not respond to pharmaceutical management (100) can respond to surgical intervention by eliminating epileptogenic tissue (101), particularly in pediatric patients (10). The temporal cortex is a region associated with a comparatively high risk of seizure origin (102). Due to its proximity to the parietal lobe and the difficulty of performing these surgeries on developing brains, excision of tissue from the temporal lobe can result in hemiparesis, potentially due to loss of motor cortex gray matter and/or associated white matter tracts (103-105). This results in the loss of upper motor neuron function due to the loss of somatosensory neural tissue. For reasons not entirely understood, postsurgical motor sequelae of hemispherectomy negatively affect upper limb function more than lower limb function (106). The usage of the BioSleeve significantly increased arm movement in a subset of our patients, although the variance in response was high, with 1 out of 4 patients not showing any improvement in arm usage. Similarly, we observed a statistically nonsignificant increase in arm usage in our CP patients. The inconsistency of outcomes in these two cohorts may be related to a low sample size, the inconsistency of hemispherectomy

surgeries, and the difficulty of ascertaining improvement in a pediatric population due to an additional layer of observer bias introduced by parental reporting.

In summary, we report a novel wearable and commercially available device, the BioSleeve, that increases arm mobility after cortical insult, infarction, or excision. The study revealed the most robust results in a sample of TBI patients. The device was well tolerated for usage across a wide age range (1.8-73 years) and has the potential for long-term, at-home usage. Future studies should compare the usage of the device in affected individuals utilizing a prospective cohort design.

Future Considerations:

In this study, we present the potential benefits associated with the application of a wearable neuromuscular rehabilitation system suitable for long-term (ambulatory) use. It is critical that further efforts be made to develop cost-efficient, comfortable, and effective wearable rehabilitative systems that provide intervention outside the walls of a traditional health care system.

Wearable NMES solutions offer a cost-effective and practical method for individuals to help re-educate motor function, improve limb mobility, reduce muscle atrophy, improve joint range of motion, and enhance local blood flow to maximize patient potential.

Individuals who suffer from hemiplegia require access to better long-term assistive and rehabilitative approaches. Emerging research and converging technologies support the future use of neuromodulation techniques and neuroprosthetics, including wearable systems. Future solutions will be adaptive, guided by central nervous system interfaces and external sensors coupled with predictive artificial intelligence.

Abbreviations:

ADL: Activities of Daily Living

BIC: Bayesian Information Criterion

CNS: Central Nervous System

CP: Cerebral Palsy

CVA: Cerebrovascular Accident

ES: Electrical Stimulation

FDA: Food and Drug Administration

IRB: Institutional Review Board

M1: Primary Motor Cortex

MCA: Middle Cerebral Artery

LMN: Lower Motor Neuron

LTP: Long-Term Potentiation

NMES: Neuromuscular Electrical Stimulation

ROS: Reactive Oxygen Species

S1: Primary Sensory Cortex

TBI: Traumatic Brain Injury

UMN: Upper Motor Neuron

Declarations:

Ethics Approval: The progress of patient arm usage was the main outcome of this study. IRB Protocol #21-AXIO-102. Human Subjects Research: This study was determined by the Institutional Review Board to be Exempt according to FDA 21 CFR 56.104 and 45CFR46.104(b)(4): (4) Secondary Research Uses of Data or Specimens on 10/01/2021. IRB review was provided by Gretchen Parker, PhD, RAC, CIP IRB Chair, Pearl IRB 29 East McCarty Street, Suite 100 Indianapolis, IN 46225.

Consent for Publication: Consent was provided by the participant shown in Figure 5.

Availability of Data and Materials: All data will be published and available as supplementary information.

Competing Interests: PM is the founder and CEO of Axiobionics, LLC. JS is an employed clinician at Axiobionics, LLC.

Funding: All work was funded by Axiobionics, LLC.

Authors' Contributions: PM served as the primary clinician in the study and collected all data. RS performed the statistical and qualitative data analysis. DD, ED and NC provided guidance on adherence to clinical standards. JS was involved in data collection efforts. All authors were involved in the writing and editing of the manuscript.

Acknowledgements: None.

1. Zaloshnja E, Miller T, Langlois JA, Selassie AW. Prevalence of long-term disability from traumatic brain injury in the civilian population of the United States, 2005. J Head Trauma Rehabil. 2008;23(6):394-400.

2. McKee AC, Daneshvar DH. The neuropathology of traumatic brain injury. Handb Clin Neurol. 2015;127:45-66.

3. Fesharaki-Zadeh A. Chronic Traumatic Encephalopathy: A Brief Overview. Front Neurol. 2019;10:713.

4. Hillier SL, Sharpe MH, Metzer J. Outcomes 5 years post-traumatic brain injury (with further reference to neurophysical impairment and disability). Brain Inj. 1997;11(9):661-75.

5. Synnot A, Chau M, Pitt V, O'Connor D, Gruen RL, Wasiak J, et al. Interventions for managing skeletal muscle spasticity following traumatic brain injury. Cochrane Database Syst Rev. 2017;11:CD008929.

6. Jenkinson PM, Preston C, Ellis SJ. Unawareness after stroke: a review and practical guide to understanding, assessing, and managing anosognosia for hemiplegia. J Clin Exp Neuropsychol. 2011;33(10):1079-93.

7. Byrd EM, Jablonski RJ, Vance DE. Understanding Anosognosia for Hemiplegia After Stroke. Rehabil Nurs. 2020;45(1):3-15.

8. Cauraugh JH, Kim SB. Chronic stroke motor recovery: duration of active neuromuscular stimulation. J Neurol Sci. 2003;215(1-2):13-9.

9. Vitrikas K, Dalton H, Breish D. Cerebral Palsy: An Overview. Am Fam Physician. 2020;101(4):213-20.

10. Dallas J, Englot DJ, Naftel RP. Neurosurgical approaches to pediatric epilepsy: Indications, techniques, and outcomes of common surgical procedures. Seizure. 2020;77:76-85.

11. Wittenberg GF. Motor mapping in cerebral palsy. Dev Med Child Neurol. 2009;51 Suppl 4:134-9.

12. Shinnar S, Pellock JM. Update on the epidemiology and prognosis of pediatric epilepsy. J Child Neurol. 2002;17 Suppl 1:S4-17.

13. Benifla M, Otsubo H, Ochi A, Weiss SK, Donner EJ, Shroff M, et al. Temporal lobe surgery for intractable epilepsy in children: an analysis of outcomes in 126 children. Neurosurgery. 2006;59(6):1203-13; discussion 13-4.

14. Veldman MP, Maffiuletti NA, Hallett M, Zijdewind I, Hortobagyi T. Direct and crossed effects of somatosensory stimulation on neuronal excitability and motor performance in humans. Neurosci Biobehav Rev. 2014;47:22-35.

15. Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: a clinical overview. Transl Pediatr. 2020;9(Suppl 1):S125-S35.

16. Odding E, Roebroeck ME, Stam HJ. The epidemiology of cerebral palsy: incidence, impairments and risk factors. Disabil Rehabil. 2006;28(4):183-91.

17. McGuire C, Kristman VL, Martin L, Bedard M. Characteristics and Incidence of Traumatic Brain Injury in Older Adults Using Home Care in Ontario from 2003-2013. Can Geriatr J. 2017;20(1):2-9.

18. Park CH, Kim SH, Jung HY. Diffusion-Tensor-Tractography-Based Diagnosis for Injury of Corticospinal Tract in a Patient with Hemiplegia Following Traumatic Brain Injury. Diagnostics (Basel). 2020;10(3).

19. Marque P, Gasq D, Castel-Lacanal E, De Boissezon X, Loubinoux I. Post-stroke hemiplegia rehabilitation: evolution of the concepts. Ann Phys Rehabil Med. 2014;57(8):520-9.

20. Buntragulpoontawee M, Euawongyarti P, Wongpakaran T, Ashford S, Rattanamanee S, Khunachiva J. Preliminary evaluation of the reliability, validity and feasibility of the arm

726 activity measure - Thai version (ArmA-TH) in cerebrovascular patients with upper limb
727 hemiplegia. Health Qual Life Outcomes. 2018;16(1):141.
728 21. Kumar P. Hemiplegic shoulder pain in people with stroke: present and the future. Pain
729 Manag. 2019;9(2):107-10.
730 22. Rasmussen T, Villemure JG. Cerebral hemispherectomy for seizures with hemiplegia.
731 Cleve Clin J Med. 1989;56 Suppl Pt 1:S62-8; discussion S79-83.
732 23. Peacock WJ, Wehby-Grant MC, Shields WD, Shewmon DA, Chugani HT, Sankar R,
733 et al. Hemispherectomy for intractable seizures in children: a report of 58 cases. Childs Nerv
734 Syst. 1996;12(7):376-84.
735 24. Hafer-Macko CE, Ryan AS, Ivey FM, Macko RF. Skeletal muscle changes after
736 hemiparetic stroke and potential beneficial effects of exercise intervention strategies. J Rehabil
737 Res Dev. 2008;45(2):261-72.
738 25. von Walden F, Jakobsson F, Edstrom L, Nader GA. Altered autophagy gene expression
739 and persistent atrophy suggest impaired remodeling in chronic hemiplegic human skeletal
740 muscle. Muscle Nerve. 2012;46(5):785-92.
741 26. Hu XL, Tong KY, Li L. The mechanomyography of persons after stroke during
742 isometric voluntary contractions. J Electromyogr Kinesiol. 2007;17(4):473-83.
743 27. Rath S. Hand kinematics: Application in clinical practice. Indian J Plast Surg.
744 2011;44(2):178-85.
745 28. Brown JK, Rodda J, Walsh EG, Wright GW. Neurophysiology of lower-limb function
746 in hemiplegic children. Dev Med Child Neurol. 1991;33(12):1037-47.
747 29. Waters PM, Van Heest A. Spastic hemiplegia of the upper extremity in children. Hand
748 Clin. 1998;14(1):119-34.

30. Harvey LA, Katalinic OM, Herbert RD, Moseley AM, Lannin NA, Schurr K. Stretch for the treatment and prevention of contracture: an abridged republication of a Cochrane Systematic Review. J Physiother. 2017;63(2):67-75.

31. Skalsky AJ, McDonald CM. Prevention and management of limb contractures in neuromuscular diseases. Phys Med Rehabil Clin N Am. 2012;23(3):675-87.

32. Wood KS, Daluiski A. Management of Joint Contractures in the Spastic Upper Extremity. Hand Clin. 2018;34(4):517-28.

33. Matozinho CVO, Teixeira-Salmela LF, Samora GAR, Sant'Anna R, Faria C, Scianni A. Incidence and potential predictors of early onset of upper-limb contractures after stroke. Disabil Rehabil. 2021;43(5):678-84.

34. De D, Wynn E. Preventing muscular contractures through routine stroke patient care. Br J Nurs. 2014;23(14):781-6.

35. Hara Y, Akaboshi K, Masakado Y, Chino N. Physiologic decrease of single thenar motor units in the F-response in stroke patients. Arch Phys Med Rehabil. 2000;81(4):418-23.

36. Gemperline JJ, Allen S, Walk D, Rymer WZ. Characteristics of motor unit discharge in subjects with hemiparesis. Muscle Nerve. 1995;18(10):1101-14.

37. Young JL, Mayer RF. Physiological alterations of motor units in hemiplegia. J Neurol Sci. 1982;54(3):401-12.

38. Legg LA, Lewis SR, Schofield-Robinson OJ, Drummond A, Langhorne P. Occupational therapy for adults with problems in activities of daily living after stroke. Cochrane Database Syst Rev. 2017;7:CD003585.

39. Zahuranec DB, Skolarus LE, Feng C, Freedman VA, Burke JF. Activity limitations and subjective well-being after stroke. Neurology. 2017;89(9):944-50.

772 40. Fujitani J, Ishikawa T, Akai M, Kakurai S. Influence of daily activity on changes in
773 physical fitness for people with post-stroke hemiplegia. Am J Phys Med Rehabil.
774 1999;78(6):540-4.
775 41. Van Zelst BR, Miller MD, Russo R, Murchland S, Crotty M. Activities of daily living
776 in children with hemiplegic cerebral palsy: a cross-sectional evaluation using the Assessment
777 of Motor and Process Skills. Dev Med Child Neurol. 2006;48(9):723-7.
778 42. Knutson JS, Fu MJ, Sheffler LR, Chae J. Neuromuscular Electrical Stimulation for
779 Motor Restoration in Hemiplegia. Phys Med Rehabil Clin N Am. 2015;26(4):729-45.
780 43. Chae J, Sheffler L, Knutson J. Neuromuscular electrical stimulation for motor
781 restoration in hemiplegia. Top Stroke Rehabil. 2008;15(5):412-26.
782 44. de Freitas GR, Szpoganicz C, Ilha J. Does Neuromuscular Electrical Stimulation
783 Therapy Increase Voluntary Muscle Strength After Spinal Cord Injury? A Systematic Review.
784 Top Spinal Cord Inj Rehabil. 2018;24(1):6-17.
785 45. Glinsky J, Harvey L, van Es P, Chee S, Gandevia SC. The addition of electrical
786 stimulation to progressive resistance training does not enhance the wrist strength of people with
787 tetraplegia: a randomized controlled trial. Clin Rehabil. 2009;23(8):696-704.
788 46. Klose KJ, Schmidt DL, Needham BM, Brucker BS, Green BA, Ayyar DR.
789 Rehabilitation therapy for patients with long-term spinal cord injuries. Arch Phys Med Rehabil.
790 1990;71(9):659-62.
791 47. Needham-Shropshire BM, Broton JG, Cameron TL, Klose KJ. Improved motor
792 function in tetraplegics following neuromuscular stimulation-assisted arm ergometry. J Spinal
793 Cord Med. 1997;20(1):49-55.
794 48. Kohlmeyer KM, Hill JP, Yarkony GM, Jaeger RJ. Electrical stimulation and
795 biofeedback effect on recovery of tenodesis grasp: a controlled study. Arch Phys Med Rehabil.
796 1996;77(7):702-6.

797 49. Harvey LA, Fornusek C, Bowden JL, Pontifex N, Glinsky J, Middleton JW, et al.
798 Electrical stimulation plus progressive resistance training for leg strength in spinal cord injury:
799 a randomized controlled trial. Spinal Cord. 2010;48(7):570-5.
800 50. Powell J, Pandyan AD, Granat M, Cameron M, Stott DJ. Electrical stimulation of wrist
801 extensors in poststroke hemiplegia. Stroke. 1999;30(7):1384-9.
802 51. Malhotra S, Rosewilliam S, Hermens H, Roffe C, Jones P, Pandyan AD. A randomized
803 controlled trial of surface neuromuscular electrical stimulation applied early after acute stroke:
804 effects on wrist pain, spasticity and contractures. Clin Rehabil. 2013;27(7):579-90.
805 52. Rosewilliam S, Malhotra S, Roffe C, Jones P, Pandyan AD. Can surface neuromuscular
806 electrical stimulation of the wrist and hand combined with routine therapy facilitate recovery
807 of arm function in patients with stroke? Arch Phys Med Rehabil. 2012;93(10):1715-21 e1.
808 53. Lin Z, Yan T. Long-term effectiveness of neuromuscular electrical stimulation for
809 promoting motor recovery of the upper extremity after stroke. J Rehabil Med. 2011;43(6):506-
810 10.
811 54. Tashiro S, Mizuno K, Kawakami M, Takahashi O, Nakamura T, Suda M, et al.
812 Neuromuscular electrical stimulation-enhanced rehabilitation is associated with not only motor
813 but also somatosensory cortical plasticity in chronic stroke patients: an interventional study.
814 Ther Adv Chronic Dis. 2019;10:2040622319889259.
815 55. Fujiwara T, Honaga K, Kawakami M, Nishimoto A, Abe K, Mizuno K, et al.
816 Modulation of cortical and spinal inhibition with functional recovery of upper extremity motor
817 function among patients with chronic stroke. Restor Neurol Neurosci. 2015;33(6):883-94.
818 56. Farmer SE, Durairaj V, Swain I, Pandyan AD. Assistive technologies: can they
819 contribute to rehabilitation of the upper limb after stroke? Arch Phys Med Rehabil.
820 2014;95(5):968-85.

821 57. Nascimento LR, Michaelsen SM, Ada L, Polese JC, Teixeira-Salmela LF. Cyclical
822 electrical stimulation increases strength and improves activity after stroke: a systematic review.
823 J Physiother. 2014;60(1):22-30.
824 58. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, et al.
825 Interventions for improving upper limb function after stroke. Cochrane Database Syst Rev.
826 2014(11):CD010820.
827 59. Chen P, Liu TW, Kwong PWH, Lai CKY, Chung RCK, Tsoh J, et al. Bilateral
828 Transcutaneous Electrical Nerve Stimulation Improves Upper Limb Motor Recovery in Stroke:
829 A Randomized Controlled Trial. Stroke. 2022;53(4):1134-40.
830 60. Walker WC, Pickett TC. Motor impairment after severe traumatic brain injury: A
831 longitudinal multicenter study. J Rehabil Res Dev. 2007;44(7):975-82.
832 61. Mesci N, Ozdemir F, Kabayel DD, Tokuc B. The effects of neuromuscular electrical
833 stimulation on clinical improvement in hemiplegic lower extremity rehabilitation in chronic
834 stroke: a single-blind, randomised, controlled trial. Disabil Rehabil. 2009;31(24):2047-54.
835 62. Mangold S, Schuster C, Keller T, Zimmermann-Schlatter A, Ettlin T. Motor training of
836 upper extremity with functional electrical stimulation in early stroke rehabilitation.
837 Neurorehabil Neural Repair. 2009;23(2):184-90.
838 63. Wald A. Tests of Statistical Hypotheses Concerning Several Parameters When the
839 Number of Observations is Large. Transactions of the American Mathematical Society.
840 1943;54:57.
841 64. Oujamaa L, Relave I, Froger J, Mottet D, Pelissier JY. Rehabilitation of arm function
842 after stroke. Literature review. Ann Phys Rehabil Med. 2009;52(3):269-93.
843 65. Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and
844 arm training after primary middle-cerebral-artery stroke: a randomised trial. Lancet.
845 1999;354(9174):191-6.

66. Dodd KC, Nair VA, Prabhakaran V. Role of the Contralesional vs. Ipsilesional Hemisphere in Stroke Recovery. Front Hum Neurosci. 2017;11:469.

67. Etoh S, Noma T, Takiyoshi Y, Arima M, Ohama R, Yokoyama K, et al. Effects of repetitive facilitative exercise with neuromuscular electrical stimulation, vibratory stimulation and repetitive transcranial magnetic stimulation of the hemiplegic hand in chronic stroke patients. Int J Neurosci. 2016;126(11):1007-12.

68. Chuang LL, Chen YL, Chen CC, Li YC, Wong AM, Hsu AL, et al. Effect of EMG-triggered neuromuscular electrical stimulation with bilateral arm training on hemiplegic shoulder pain and arm function after stroke: a randomized controlled trial. J Neuroeng Rehabil. 2017;14(1):122.

69. Smith LE. Restoration of volitional limb movement of hemiplegics following patterned functional electrical stimulation. Percept Mot Skills. 1990;71(3 Pt 1):851-61.

70. Stein C, Fritsch CG, Robinson C, Sbruzzi G, Plentz RD. Effects of Electrical Stimulation in Spastic Muscles After Stroke: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Stroke. 2015;46(8):2197-205.

71. Zhang YB, Cheng YN. A randomized controlled trial of neuromuscular electrical stimulation for chronic urinary retention following traumatic brain injury. Medicine (Baltimore). 2019;98(2):e14106.

72. Bath PM, Woodhouse LJ, Suntrup-Krueger S, Likar R, Koestenberger M, Warusevitane A, et al. Pharyngeal electrical stimulation for neurogenic dysphagia following stroke, traumatic brain injury or other causes: Main results from the PHADER cohort study. EClinicalMedicine. 2020;28:100608.

73. Nguyen JP, Feve A, Keravel Y. Is electrostimulation preferable to surgery for upper limb ataxia? Curr Opin Neurol. 1996;9(6):445-50.

74. Pundik S, McCabe J, Skelly M, Salameh A, Naft J, Chen Z, et al. Myoelectric Arm Orthosis in Motor Learning-Based Therapy for Chronic Deficits After Stroke and Traumatic Brain Injury. Front Neurol. 2022;13:791144.

75. Rohm M, Schneiders M, Muller C, Kreilinger A, Kaiser V, Muller-Putz GR, et al. Hybrid brain-computer interfaces and hybrid neuroprostheses for restoration of upper limb functions in individuals with high-level spinal cord injury. Artif Intell Med. 2013;59(2):133-42.

76. de Kroon JR, MJ IJ, Lankhorst GJ, Zilvold G. Electrical stimulation of the upper limb in stroke: stimulation of the extensors of the hand vs. alternate stimulation of flexors and extensors. Am J Phys Med Rehabil. 2004;83(8):592-600.

77. Seitz RJ, Hoflich P, Binkofski F, Tellmann L, Herzog H, Freund HJ. Role of the premotor cortex in recovery from middle cerebral artery infarction. Arch Neurol. 1998;55(8):1081-8.

78. Lindenberg R, Renga V, Zhu LL, Betzler F, Alsop D, Schlaug G. Structural integrity of corticospinal motor fibers predicts motor impairment in chronic stroke. Neurology. 2010;74(4):280-7.

79. Kato H, Izumiyama M, Shiga Y, Saito N, Koizumi H, Takahashi A, et al. [Hand motor cortical area reorganization following cerebral infarction evaluated with functional MRI, near infrared spectroscopic imaging, and transcranial magnetic stimulation]. No To Shinkei. 2001;53(9):869-74.

80. Yeo SS, Jang SH. Ipsilateral motor pathway without contralateral motor pathway in a stroke patient. NeuroRehabilitation. 2012;30(4):303-6.

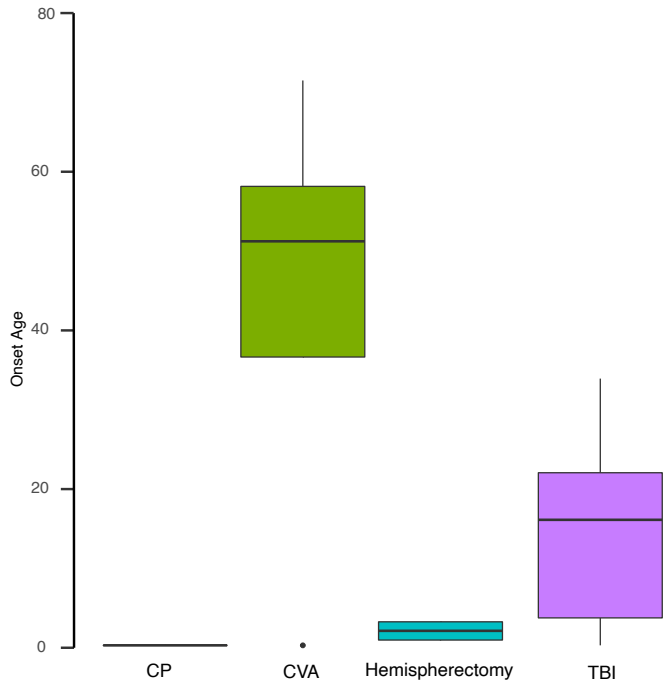
81. Roy-O'Reilly M, McCullough LD. Age and Sex Are Critical Factors in Ischemic Stroke Pathology. Endocrinology. 2018;159(8):3120-31.

894 82. Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional
895 potential in chronic stroke patients depends on corticospinal tract integrity. Brain. 2007;130(Pt
896 1):170-80.
897 83. Stinear CM, Byblow WD. Predicting and accelerating motor recovery after stroke. Curr
898 Opin Neurol. 2014;27(6):624-30.
899 84. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity
900 in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke.
901 Stroke. 2003;34(9):2181-6.
902 85. Coupar F, Pollock A, Rowe P, Weir C, Langhorne P. Predictors of upper limb recovery
903 after stroke: a systematic review and meta-analysis. Clin Rehabil. 2012;26(4):291-313.
904 86. Boldrini M, Fulmore CA, Tartt AN, Simeon LR, Pavlova I, Poposka V, et al. Human
905 Hippocampal Neurogenesis Persists throughout Aging. Cell Stem Cell. 2018;22(4):589-99 e5.
906 87. Zhao Y, Wang LH, Peng A, Liu XY, Wang Y, Huang SH, et al. The neuroprotective
907 and neurorestorative effects of growth differentiation factor 11 in cerebral ischemic injury.
908 Brain Res. 2020;1737:146802.
909 88. Bergado JA, Almaguer W. Aging and synaptic plasticity: a review. Neural Plast.
910 2002;9(4):217-32.
911 89. Dabrowski J, Czajka A, Zielinska-Turek J, Jaroszynski J, Furtak-Niczyporuk M, Mela
912 A, et al. Brain Functional Reserve in the Context of Neuroplasticity after Stroke. Neural Plast.
913 2019;2019:9708905.
914 90. Chunyong L, Yingkai L, Fuda L, Jiang C, Liu Y. Longitudinal changes of motor cortex
915 function during motor recovery after stroke. Top Stroke Rehabil. 2022:1-13.
916 91. Piai V, Meyer L, Dronkers NF, Knight RT. Neuroplasticity of language in left-
917 hemisphere stroke: Evidence linking subsecond electrophysiology and structural connections.
918 Hum Brain Mapp. 2017;38(6):3151-62.

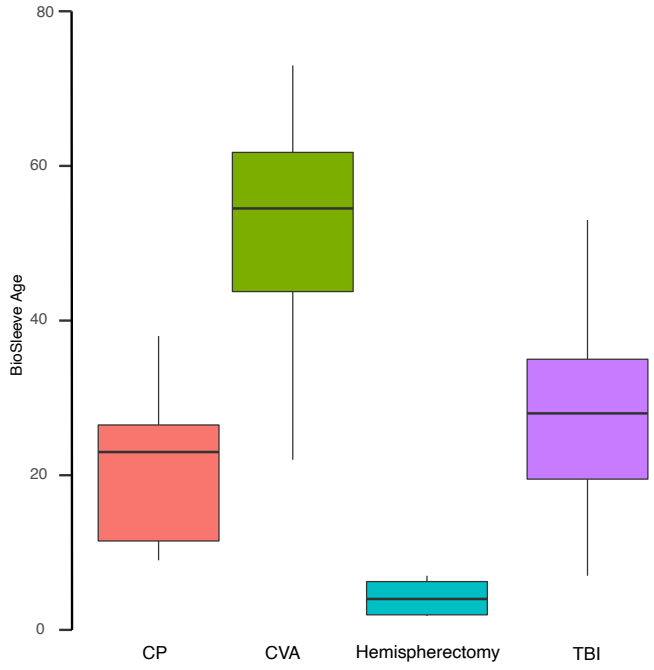
919 92. Murdoch K, Buckley JD, McDonnell MN. The Effect of Aerobic Exercise on
920 Neuroplasticity within the Motor Cortex following Stroke. PLoS One. 2016;11(3):e0152377.
921 93. Bozzo C, Spolaore B, Toniolo L, Stevens L, Bastide B, Cieniewski-Bernard C, et al.
922 Nerve influence on myosin light chain phosphorylation in slow and fast skeletal muscles. FEBS
923 J. 2005;272(22):5771-85.
924 94. Kubis HP, Hanke N, Scheibe RJ, Meissner JD, Gros G. Ca2+ transients activate
925 calcineurin/NFATc1 and initiate fast-to-slow transformation in a primary skeletal muscle
926 culture. Am J Physiol Cell Physiol. 2003;285(1):C56-63.
927 95. Asanuma H, Keller A. Neuronal mechanisms of motor learning in mammals.
928 Neuroreport. 1991;2(5):217-24.
929 96. Kleim JA, Barbay S, Nudo RJ. Functional reorganization of the rat motor cortex
930 following motor skill learning. J Neurophysiol. 1998;80(6):3321-5.
931 97. Plautz EJ, Milliken GW, Nudo RJ. Effects of repetitive motor training on movement
932 representations in adult squirrel monkeys: role of use versus learning. Neurobiol Learn Mem.
933 2000;74(1):27-55.
934 98. Buonomano DV, Merzenich MM. Cortical plasticity: from synapses to maps. Annu
935 Rev Neurosci. 1998;21:149-86.
936 99. Terao Y, Ugawa Y, Hanajima R, Furubayashi T, Machii K, Enomoto H, et al. Air-puff-
937 induced facilitation of motor cortical excitability studied in patients with discrete brain lesions.
938 Brain. 1999;122 (Pt 12):2259-77.
939 100. Greenfield LJ, Jr. Molecular mechanisms of antiseizure drug activity at GABAA
940 receptors. Seizure. 2013;22(8):589-600.
941 101. Kim JS, Park EK, Shim KW, Kim DS. Hemispherotomy and Functional
942 Hemispherectomy: Indications and Outcomes. J Epilepsy Res. 2018;8(1):1-5.

943 102. Maizuliana H, Usui N, Terada K, Kondo A, Inoue Y. Clinical, semiological,
944 electroencephalographic, and neuropsychological features of "pure" neocortical temporal lobe
945 epilepsy. Epileptic Disord. 2020;22(1):55-65.
946 103. Wyllie E, Comair YG, Kotagal P, Bulacio J, Bingaman W, Ruggieri P. Seizure outcome
947 after epilepsy surgery in children and adolescents. Ann Neurol. 1998;44(5):740-8.
948 104. Kral T, Kuczaty S, Blumcke I, Urbach H, Clusmann H, Wiestler OD, et al. Postsurgical
949 outcome of children and adolescents with medically refractory frontal lobe epilepsies. Childs
950 Nerv Syst. 2001;17(10):595-601.
951 105. Sinclair DB, Aronyk K, Snyder T, McKean JD, Wheatley M, Gross D, et al.
952 Extratemporal resection for childhood epilepsy. Pediatr Neurol. 2004;30(3):177-85.
953 106. Delalande O, Bulteau C, Dellatolas G, Fohlen M, Jalin C, Buret V, et al. Vertical
954 parasagittal hemispherotomy: surgical procedures and clinical long-term outcomes in a
955 population of 83 children. Neurosurgery. 2007;60(2 Suppl 1):ONS19-32; discussion ONS.
956

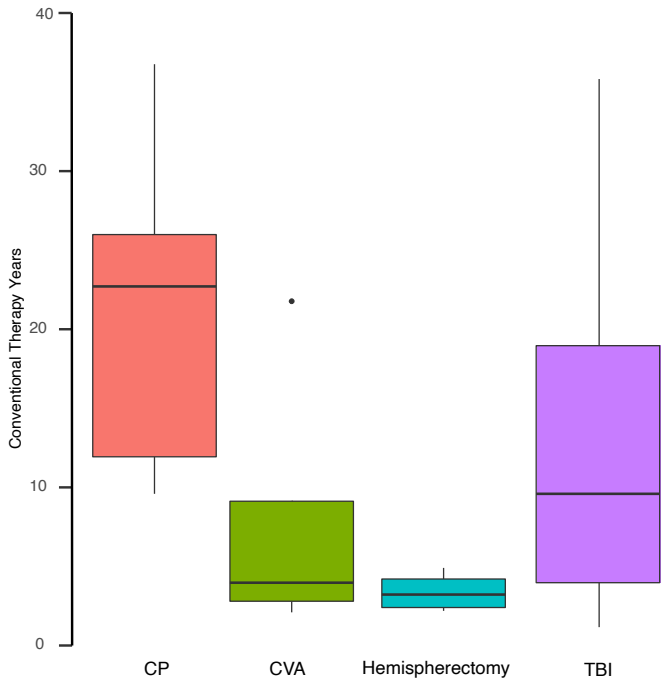
957 **Supplementary Document**
958
959
960



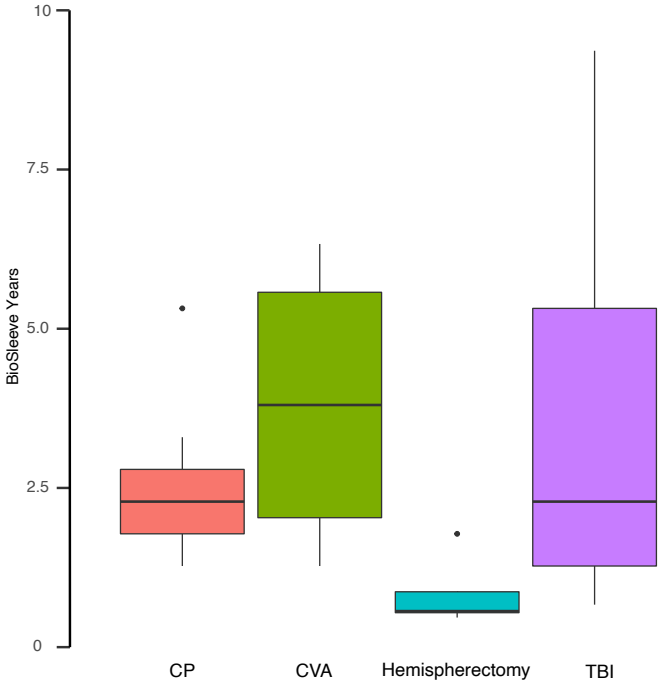
961
962
963 *Supplementary Figure 1: Age of disease onset, showing CP and Hemispherectomy as the youngest patients,*
964 *followed by TBI and CVA as the oldest.*
965



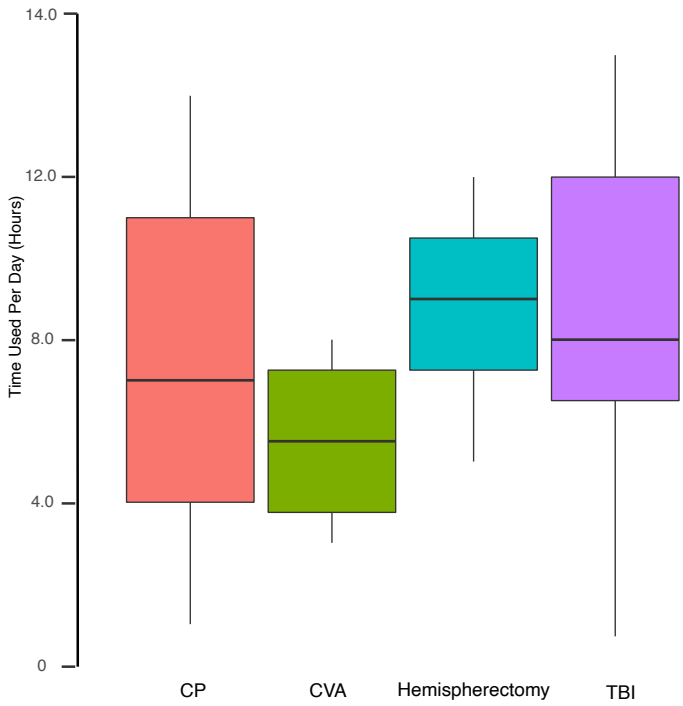
966
967
968
969 *Supplementary Figure 2: Age the BioSleeve was initiated. Hemispherectomy was the youngest age group to*
970 *receive the BioSleeve, followed by CP, TBI, and CVA as the oldest, respectively.*
971
972



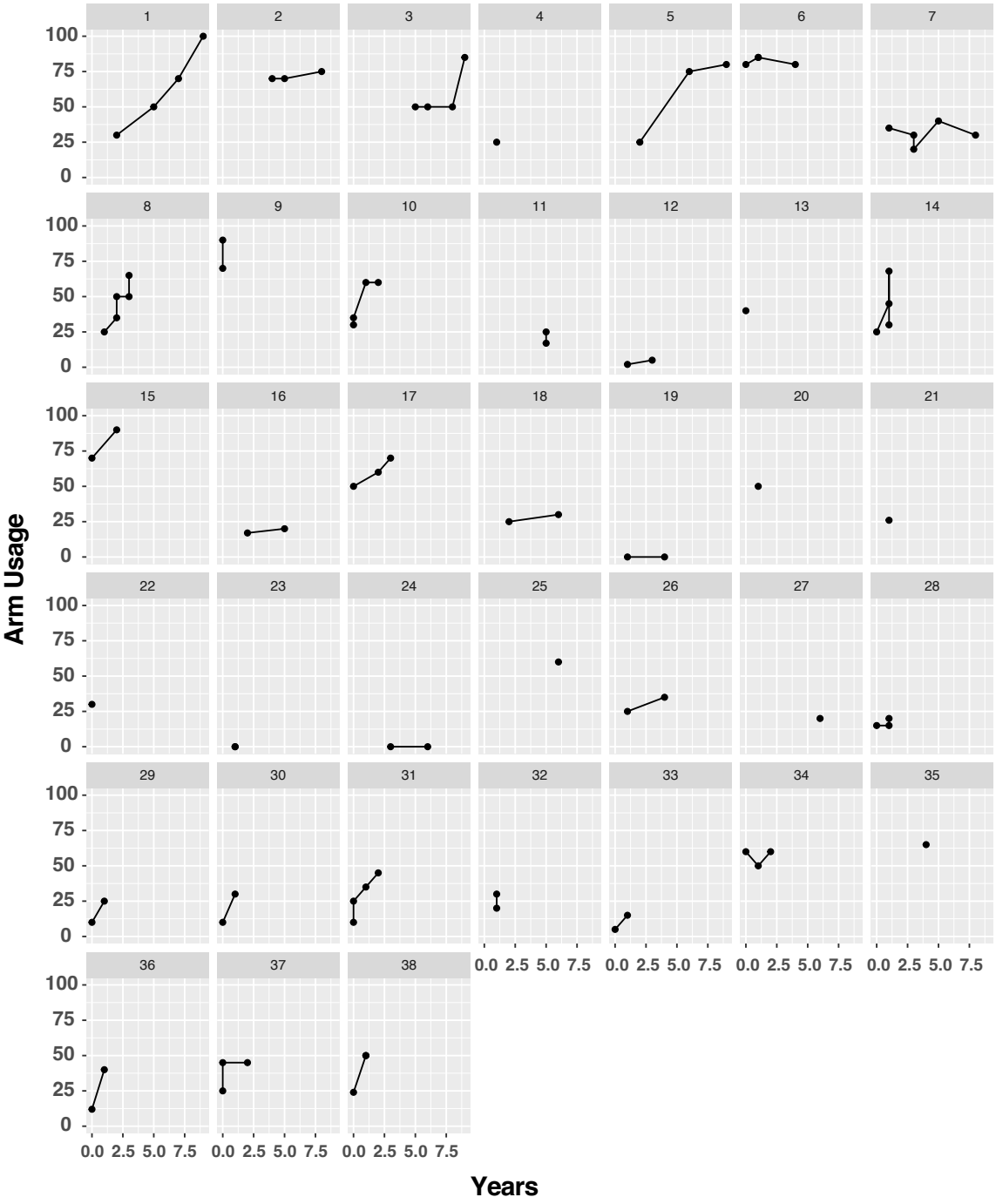
Supplementary Figure 3: The number of years patients underwent conventional therapy prior to BioSleeve intervention. Hemispherectomy underwent the the lowest number of conventional therapy years, followed by CVA, TBI and CP, respectively.



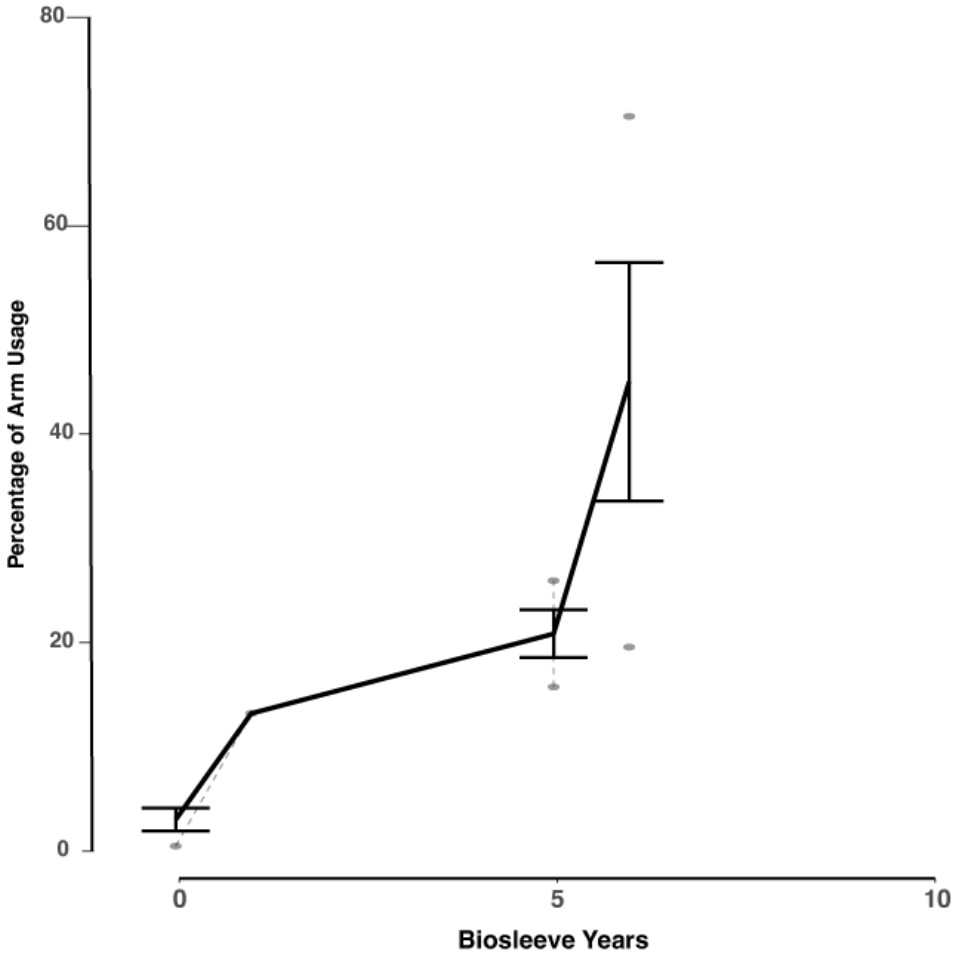
Supplementary Figure 4: The number of years patients used the BioSleeve intervention. Hemispherectomy was used the lowest number of years, followed by CP, TBI and CVA, respectively.



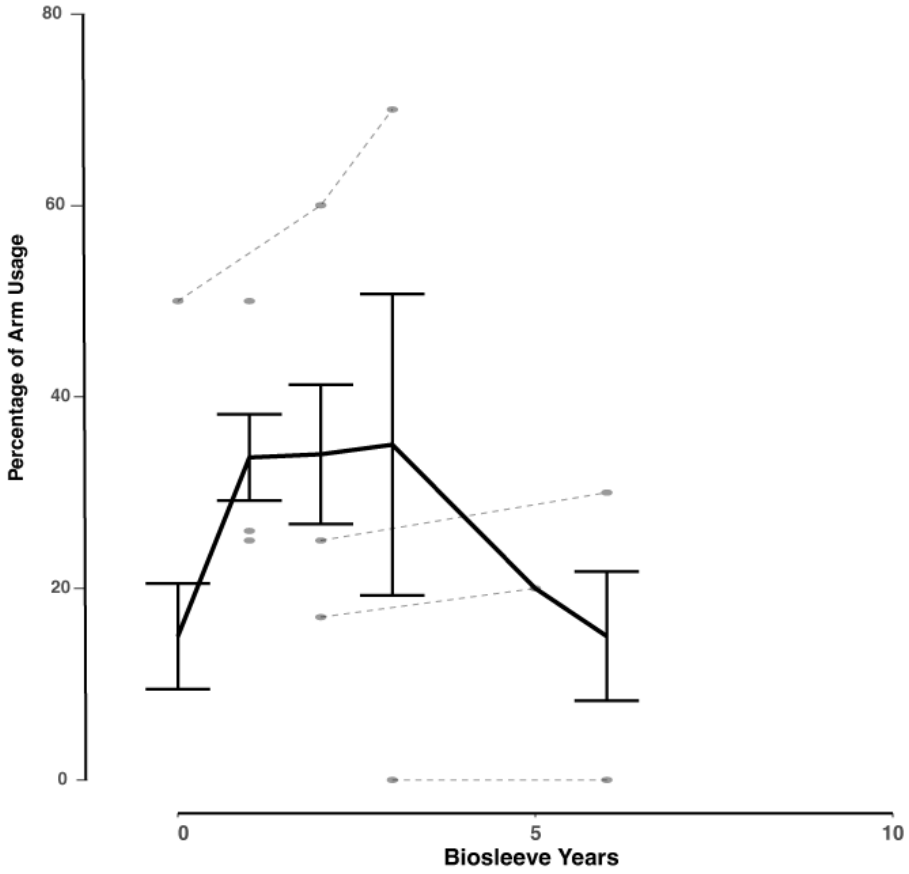
Supplementary Figure 5: Time that the BioSleeve device was used by each subcohort. Hemispherectomy used the BioSleeve the greatest number of hours per day, followed by TBI, CP and CVA, respectively. Collectively, the average amount of time the BioSleeve was used was 8 hours per day.



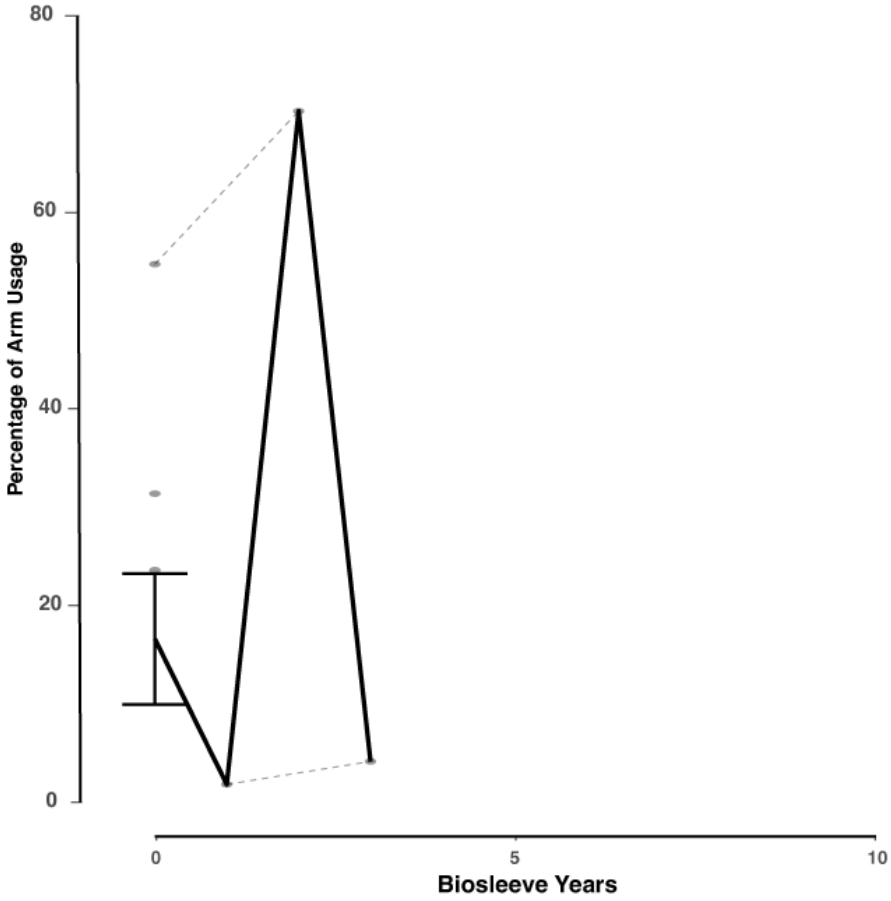
Supplementary Figure 6: Arm usage per patient with the BioSleeve across the follow up years, by patient ID, followed up to 10 years. The plot shows all patients follow up timeline. The plot showed heterogeneity in patient response to the BioSleeve.



*Supplementary Figure 7: Longitudinal arm usage for all CVA patients. All patients were baselined to the fitting date at 0 years with patient follow-up continuing for up to 10 years, with some patients lost to follow-up. The plot shows the average arm usage per year across all patients who wore the BioSleeve in the follow-up phase. The percentage of the group that reported arm usage every year is represented by an average ± 1.96 * standard error. The plot also includes dotted connected lines per patient who show per patient performance. Arm usage at 0 years should be taken as the baseline after conventional therapy.*



*Supplementary Figure 8. Longitudinal arm usage for all CP patients. All patients were baselined to the fitting date at 0 years with patient follow-up continuing for up to 10 years, with some patients lost to follow-up. The plot shows the average arm usage per year across all patients who wore the BioSleeve in the follow-up phase. The percentage of the group that reported arm usage every year is represented by an average ± 1.96 * standard error. The plot also includes dotted connected lines per patient who show per patient performance. Arm usage at 0 years should be taken as the baseline after conventional therapy.*



*Supplementary Figure 9: Longitudinal arm usage for all Hemispherectomy patients. All patients were baselined to the fitting date at 0 years with patient follow-up continuing for up to 10 years, with some patients lost to follow-up. The plot shows the average arm usage per year across all patients who wore the BioSleeve in the follow-up phase. The percentage of the group that reported arm usage every year is represented by an average ± 1.96 * standard error. The plot also includes dotted connected lines per patient who show per patient performance. Arm usage at 0 years should be taken as the baseline after conventional therapy.*