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# Longitudinal Retrospective Study of a Wearable NMES System to Determine the Effects on Arm Usage in Hemiparetic and Hemiplegic **Patients**

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The development of a Wearable Therapy™ muscle stimulation product has the potential to improve thousands of lives of individuals with TBI, stroke, and other hemiplegic conditions to resume an active participation in life and community.



#### Longitudinal Retrospective Study of a Wearable NMES System to Determine the

### Effects on Arm Usage in Hemiparetic and Hemiplegic Patients

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Corresponding author: Philip MUCCIO philipmuccio@axiobionics.com. Abstract:

**Background:** Brain disorders such as traumatic brain injury (TBI), stroke, cerebral palsy (CP), and surgical interventions can result in aberrant motor function in the contralateral limbs, resulting in paralysis, weakness, and/or spasticity. It is known that in the short term, neuromuscular electrical stimulation (NMES), the application of low-level electrical currents to motor nerves to induce muscle contractions in paralyzed muscles, can stimulate affected muscle groups and increase arm mobility. However, there remains a paucity of longitudinal evidence examining NMES-mediated improvements of arm usage.

**Objective:** To determine the effectiveness of a long-term BioSleeve intervention on the recovery of arm mobility in hemiparetic patients.

Study Design: Retrospective cohort study.

**Methods:** We examined self-reported arm usage in patients with 1) TBI, 2) stroke, 3) hemispherectomy, or 4) CP who wore Axiobionics' BioSleeve NMES device and compared this to arm usage achieved from years of conventional therapy.

**Results:** The device was well-tolerated. Patients reported an average increase in arm usage from 9.9% to 43.5%, with the TBI subcohort reporting a consistent increase in arm usage of 5.7% per year over the treatment period.

**Conclusion:** This study supports the literature suggesting that longitudinal NMES can be used to increase arm usage in hemiplegic patients.

**Clinical Relevance Statement:** This study supports the use of wearable NMES intervention in the treatment of arm hemiparesis.

Word count: 3,270 words, excluding references.

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

# Introduction

# **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, can occur for a multitude of reasons. Traumatic brain injury (TBI), cerebral palsy (CP), hemispherectomy, and stroke are independent underlying causes of impaired contralateral hemiparesis and hemiplegia, including reduced arm usage. Impaired arm positioning negatively affects arm usage and activities of daily living (ADL), such as grooming, eating, and reaching objects (Figure 1). Therefore, increasing arm usage remains a key therapeutic goal for facilitating recovery from 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). Reeducation, relaxation of muscles and joint looseness encourage the patient to extend the arm to reach and grasp objects (right image).

An estimated 30% of patients with TBI experience upper limb motor dysfunction <sup>1</sup>. Along with TBI, stroke is a leading cause of mortality and disability worldwide <sup>2,3</sup> with a reported reduction in arm motor function in 65% of stroke patients <sup>4</sup>. Pediatric conditions, such as CP and epilepsy-related hemispherectomy, performed with the goal of reducing seizure origin <sup>5,6</sup>, also result in motor impairments <sup>7,8</sup>. When the motor cortex is damaged, partial or complete

paralysis ensues, muscle tone is altered, muscle activity diminishes, spasticity occurs, and is followed by atrophy and weakness in patients (Figure 2) <sup>9</sup>, resulting in hemiparesis or hemiplegia <sup>3,10-18</sup>.



**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.

# **Motor Control Pathways**

Due to motor cortical impairment, the affected skeletal muscles can atrophy <sup>19,20</sup>. Movement can diminish or vanish entirely because the atrophied muscles no longer generate sufficient force to move the limb or overcome its weight <sup>21</sup> (Figure 3 and Figure 4). Additionally, 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 <sup>22-32</sup>. These abnormalities result in diminished ability to volitionally activate motor units <sup>33</sup> or changes in motor units themselves <sup>34</sup> (Figure 3 and 4). Therefore, any therapeutic intervention that improves upper-limb movements is valuable for neurorehabilitation. Neuromuscular electrical stimulation (NMES) is one such therapy used to reverse the effects of hemiplegia.

NMES applies a low-level electrical current to motor nerves which induces muscle

contractions in paralyzed muscles.



**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).



**Figure 4**: 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 (left). This loss of neuronal transmission results in reduced myofibril activation and muscle atrophy (right)y. Image generated using Biorender.

#### **NMES and Hemiplegia**

NMES can be used to activate muscle groups <sup>35,36</sup> although the stimulus used during NMES is insufficient to directly cause muscle contraction. Instead, gel-attached electrodes are placed on the skin and used to send electrical impulses that stimulate descending lower motor neuron pathways, which then activate the targeted muscles, causing muscle contraction (Figure 2). Although the question of whether long-term use of NMES reverses the loss of mobility associated with hemiparesis remains unanswered<sup>28,37-41</sup>, NMES can produce short-term improvements in arm usage in hemiplegic patients <sup>42-48</sup>.

The objective of this study was to determine whether the BioSleeve NMES device could increase arm mobility in the long term. This study does not present data on the mechanism of action of muscle re-education; it asks two critical questions. 1) Does the 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 upperextremity BioSleeve (Figure 5). The BioSleeve is a fabric-based device with embedded wiring to distribute current from the Axiobionics 4 channel neuromuscular stimulator to the three sets of muscles (deltoid, triceps, finger extensors). Deltoid electrodes were placed over the anterior and posterior deltoid so that stimulation would contract all three heads of the deltoid (anterior, middle, and posterior). The triceps electrodes were placed over the midline of the triceps, with one placed proximally and the other distally (Figure 5). The finger

extensor electrodes were positioned proximally, with one electrode and one distal to the proximal electrode. 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 BioSleeve was comprised of six BioGel Velcro electrodes over the deltoid, over the triceps, and over the finger extensors on the affected limb (Figures 3 and 5). The sleeve was designed to overlay three muscle groups from the shoulder to the wrist. Embedded wires and electrodes were fastened to the interior of the garment using a hook-and-loop fastener (Figures 5A and 5B). The electrodes are detachable from the sleeve and positioned so that they can be placed over their respective muscle motor points (Figures 5A and 5B). The sleeve make electrical connection via a magnetic coupling system that also ensures that the electrodes go back into position each time the sleeve is used.



**Figure 5: Assembly of the BioSleeve and electrode placement.** BioSleeve (front view, top) shows the assembly of the BioSleeve. The position of electrodes over the deltoid (D), triceps (T) and finger extensors (FE) (below) is shown.

The BioSleeve was fitted to each patient by first measuring the affected arm then creating a blueprint from the measurements to create individually designed sleeves to ensure an intimate

fit took place. Tailoring of the sleeve took place during the initial visit if there were problems noted with the fit. Once the fit was determined to be satisfactory, the electrodes were gelled (Figure 5B) and shifted into proper placement on the sleeve (Figure 5A). The sleeve was donned on the patient and the intensity of stimulation was increased in each of the three channels to produce muscle contractions. If the contractions were not desirable or if the patient felt discomfort, the electrodes were shifted until the best contraction was achieved that was tolerated by the patient. The electrode position was adjusted over time if needed to improve the contraction force, reduce discomfort, or reduce unwanted joint deviation. The intensity of stimulation delivered to each muscle varied minimally between patients.

The 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 without overextending the joint. For the deltoid (Figure 5B), the intensity was chosen when the humerus abducted 5-10 degrees, or if the humerus was subluxed, 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 head of the humerus before and during stimulation. Stimulation was applied to the triceps (Figure 5B) until the elbow extended to its endpoint. Not all elbows achieved full extension when flexion contractures were 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 to extend. The level of intensity for the finger extensors (Figure 5B) was determined when the fingers were fully extended or reached their endpoint if restricted by joint stiffness or contracture. If the stimulus intensity reached a level that triggered spasticity. The required levels of stimulation were labeled on the front face of the stimulator for reference. Some variation in

stimulus output was allowed to minimize discomfort or produce a slightly stronger muscle force to achieve the desired 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 s, 2) Stimulus OFF Time:10 s, 3) frequency: 50 Hz, 4) Pulse Width: 300  $\mu$ s, 5) Ramp Up: 3 s, 6) Ramp Down: 2 s. These parameters are consistent with those of other studies that utilized NMES for recovery <sup>43,49,50</sup>.

Patients were provided a protocol to follow and were asked to wear the BioSleeve on day one for 30 min during the first half of the day and another 30 min during the second half. They were instructed to increase the 30-minute sessions by 10 min every day thereafter for up to 12 hours per day for 5-7 days/week, as tolerated.

#### **Retrospective Cohort**

The retrospective study included 38 patients (24 males, 63%; 14 females, 37%) who were referred by a physiatrist, physical therapist, occupational therapist, or who were self-referred to the Axiobionics clinic for a BioSleeve (Table 1). All the patients were treated and reported by the same clinician. During the evaluation visit, 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. The same question was asked during each follow-up visit after the BioSleeve was fitted. The clinician explained that 0% meant that the arm was not used and 100% meant that the arm was used in a normal fashion, as it would before the onset of hemiplegia. The clinician also recorded the patient-reported number of hours the device was used daily.

*Inclusion Criteria:* Hemiparesis and hemiplegia patients seen by the examiner from 2012 to 2021 for TBI, stroke, CP and hemispherectomy (> 3 months post-surgery) who were treated with BioSleeve stimulating the deltoid, triceps, and finger extensors and who were able to understand and answer the home arm usage question at initial evaluation and follow-up.

*Exclusion Criteria:* Patients were excluded from this retrospective analysis if they or their parents or guardians were unable to report arm use. Additionally, patients were excluded from treatment if they had a cardiac pacemaker or a defibrillator. Pregnant women, patients with dementia, severe receptive or global aphasia, cancer, and patients who had sustained cerebral injury in the previous three months were also excluded.

#### **Statistical Analysis**

Statistical evaluations were carried out with the statistical program R. Continuous measures are represented by the means and standard deviations, and discrete features are represented by absolute frequencies. For statistical analysis, normality was determined using the Shapiro-Wilk test. Generalized logistic regression with a logit link function was used to model the changes in success or complication rates. The parameter significance of the generalized linear models was calculated using the Wald test <sup>51</sup>, with the null hypothesis that the parameter was 0. P-values were examined at  $\alpha$ =0.05.

Stepwise regression was assessed using the Bayesian information criterion (BIC), in which a higher BIC resulted in the selection of the factor combination for iteration. To evaluate the best combination of factors, we iterated through the model, starting from the full model (i.e., including all independent variables). The variables were then randomly dropped to evaluate

the BIC. If the BIC of the new model was higher than that of the previous model, we used a new combination of variables for the next comparison. Every 'n' step, we added a random dropped variable back to find better forward models. For the final model, we selected the one that best fit the data. 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 defined as the percentage of time we obtained a significant result for the same sample size and uncertainty in the statistical distributions.

#### **Results**:

#### BioSleeve is Associated with a Significant Increase in Arm Usage

The BioSleeve intervention correlated with a significantly increased arm usage compared to baseline and differences in responses between various diagnoses were observed (Figure 6). An initial generalized linear model was used to model arm usage according to patient age, sex, period of treatment, method of treatment, and diagnosis. The conventional treatment period was the period from disease onset to the fitting of the BioSleeve. On the other hand, BioSleeve was associated with multiple follow-up periods and each was recorded against the age of the patient at the time of follow-up and the total period. The model accounts for the impact of age, length of treatment period, sex, diagnosis, and arm usage. The final model, identified by stepwise regression, included only the treatment method as the best-fitting model to explain arm usage. The model showed a significant correlation (p < 0.0001) for the treatment method, irrespective of the other factors modeled.

A second stepwise generalized linear model of arm usage, considering the period of BioSleeve use against patient age, sex, period of treatment, usage hours per day, and diagnosis, identified the period of treatment and hours of usage per day as the main correlative factor in the final model. Interestingly, usage hours per day were not statistically significant factors.



**Figure 6: BioSleeve intervention significantly increased arm usage across all 4 diseases.** Power was more than 80% using paired Wilcoxon test. CP, CVA and Hemispherectomy shows marginally significant p-values.

#### Significant Progressive Increases in Arm Usage Correlated with BioSleeve Intervention

Patients were tracked for up to 10 years after BioSleeve intervention. A third generalized linear mixed-effects regression was used to model the progressive change in the percentage of arm usage across follow-ups against the fixed effect of disease onset age, age at the start of BioSleeve usage, arm usage before BioSleeve, and patient diagnosis. In addition, the number of years of BioSleeve use was modeled as a random effect for every patient. Random effects account for variations in patient responses and variations between patients. A stepwise



Figure 7: 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 solid line 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  $\pm 1.96$  \* standard error. The dotted lines indicate per patient performance. Arm usage at 0 years was used as the baseline after conventional therapy.

regression was used to select the best model. The final model showed a significant positive correlation with the number of years that the patient wore the BioSleeve, with an average increase of 5.31% in arm usage per year (p<0.0001) (Figure 7). TBI patients showed a high average prior arm usage of 23.6%, which progressively increased over the years, and post-treatment arm usage of 88.3% at the last follow-up (Figure 6 and 7). The linear mixed-effects model of patients with TBI showed a significant relationship between years since fitting and arm usage (p<0.001), with an average effect of 5.67% per year (Figure 7). A similar trend was observed in the CVA (Supplementary Figure 7), CP (Supplementary Figure 8), and hemispherectomy cohorts (Supplementary Figure 9), which did not show

statistically significant results. Interestingly, some patients in the non-TBI cohort showed a decline in arm usage function (Supplementary Figure 6).

#### **Discussion:**

Impaired primary motor cortex (M1) 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 <sup>52</sup>. Current therapeutic interventions include neurorehabilitation via in- and out- patient therapy <sup>52,53</sup>, non-invasive cortical activation (such as transcranial magnetic stimulation) <sup>54,55</sup>, and subcutaneous and transcutaneous ES <sup>55-57</sup> but show great variation in outcomes <sup>58</sup>. Orthotic devices, such as the Myomo MyoPro that uses volitionally generated electromyographic (EMG) signals to assist arm movement have shown positive results over 18 weeks <sup>59</sup>. In addition, previous work has shown promise for NMES in rehabilitation settings, such as urinary retention <sup>60</sup>, dysphagia <sup>61</sup> and ataxia <sup>62</sup>. Short term studies of NMES using The Mollii® suit over 6 weeks showed positive effects in study patients <sup>63</sup>. However, there is a scarcity of evidence for tracking long-term NMES interventions and arm usage. Herein, we tested the use of the Axiobionics BioSleeve NMES device in a retrospective study of patients with hemiplegia or hemiparesis.

In our study, hemiparetic and hemiplegic patients (n=38) were fitted with a BioSleeve and tracked for up to 10 years, recording their reported arm usage during the follow-up visits. To our knowledge, this is the longest retrospective analysis examining the effects of ES of muscles as a rehabilitation therapy. Initially, we compared improvements in patient mobility after using the BioSleeve, compared to the baseline of the patient's past conventional therapy up to the BioSleeve fitting, as each patient underwent various therapeutic modalities since

disease onset. The conventional therapy outcome was determined to be the baseline reported arm usage prior to BioSleeve fitting. The current cohort studied had the majority of patients with TBI (n=23), followed by CP (n=7), CVA (n=4), and hemispherectomy (n=4). NMES devices are not easily approved for insurance coverage, except in cases of insurance payouts from automobile accidents that result in TBIs. In contrast, CP, stroke, or hemispherectomy patients were paid out of pocket and were therefore less likely to purchase the NMES device. However, we did not exclude the results of other diagnoses, as it offered the ability to test the generality of the treatment method across all four diagnoses.

We observed an improvement in arm usage over 10 years of BioSleeve use irrespective of the diagnosis; however, we observed the largest improvement in TBI, with an average increase of  $48.8\% \pm 27.7\%$ . The other cohorts showed smaller improvements in arm usage, CVA followed by CP, and hemispherectomy (Figure 6). A total of 21/23 TBI patients exhibited an increase in self-reported arm usage, demonstrating the suitability of BioSleeve for facilitating arm recovery in this type of patient. Our results support the existing work that established cutaneous or transcutaneous electrical stimulation to reverse the loss of arm movement 58,59,64,65

A key finding of our study was that incremental improvements were not related to the age of the patient, sex, 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 of Biosleeve use. Conversely, some patients in each group showed either no improvement or decline in arm usage. The potential reasons for the limited responses are multifactorial, and may include heterogeneity in disease severity, inconsistent or incorrect usage of the device, differences in usage time or settings, differences in age and errors in patient reporting, and potential differences in time between injury/infarct and BioSleeve intervention.

Significant heterogeneity was observed among the disease groups. Specifically, three out of four patients in the stroke group showed marginal (10%) improvements, while the final patient (#25) showed a 55% improvement in arm usage. While Patient 25 (Supplementary Figure 6) had the highest time of intervention out of the group, this is likely not the only reason for this disparity in improvement, as Patient 27 had a similar intervention length but showed a marginal improvement. Two patients in our TBI cohort did not show any improvement. These individuals (Patients 19 and 23) had a self-reported score for 0 arm usage both before and after the BioSleeve intervention. In contrast, other patients in the TBI group (#3, #31, and #36) reported increased arm usage despite starting at a score of 0. Therefore, even within our TBI cohort, there was some heterogeneity in the response.

While our retrospective longitudinal design does not allow for an understanding of the causation for improvements in upper arm mobility related to NMES, other studies have posited a variety of potential mechanisms. These mechanisms range from a direct, short-term effect, such as impaired motor protein or ion channel expression <sup>66,67</sup>, to a long-term indirect effect, such as a potential long-term potentiation (LTP)-like mechanism involving rewiring and strengthening of synaptic connectivity <sup>9,68-70</sup>.

#### **Study Limitations:**

Retrospective cohort studies such as ours have limitations. First, the study may have been subject to recall and recency biases. Second, the data were not systematically randomly

sampled, but we relied on random patient self-enrollment. Additionally, the TBI group was overrepresented as they were able to benefit from medical insurance to obtain the device. Third, the potential for biased reporting exists; that is, patients may feel compelled to report improved outcomes. Fourth, our study did not have a control group for comparison; however, in the analysis, we relied on a case crossover methodology, wherein patient responses were compared pre- and post-intervention. Fifth, our study is semiquantitative, as individual perceptions may interpret arm usage differently; for example, 60% arm usage for one patient may not be the same for another patient. Sixth, follow-up visits were not consistent between patients, and some complied better than others; therefore, some patients were followed up over a longer period than others. Seventh, this retrospective study was the culmination of the work done by Axiobionics, which commercialized the BioSleeve device. To overcome inherent bias, the collected data were reviewed by an independent expert in medical statistics.

#### **Conclusion**:

In summary, we report a novel wearable and commercially available device, BioSleeve, in which use over 10 years correlates with increases in arm mobility in a cohort of patients with TBI. The device was well tolerated across a wide age range and has the potential for long-term at-home usage.

#### **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

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