

Tactical Application of Sensorimotor Prosthetic Technology

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Abstract-Clinical application of neural prosthetic technology raises a multitude of questions about neuromuscular anatomy and physiology. Such knowledge can be used to identify efficient and effective sites at which to apply stimulation and to identify stimulation parameters that are likely to produce the desired therapeutic effects. The scientific literature is often surprisingly patchy when it comes to making such decisions, but recently developed methodologies provide many useful tools. These have led us to a number of novel approaches that are now being tested in preclinical and clinical trials.

Keywords - FES, muscle, neural prosthetics

I. INTRODUCTION

When the voluntary ability to activate muscles is lost, a wide range of functional disabilities and secondary medical complications ensue. To avoid some of these problems, it is now possible to apply patterned electrical stimulation in order to restore muscle contractions using a growing armamentarium of technology (stimulators, electrodes, control systems, etc.). One such technology is the BION™, a new class of modular stimulators that can be injected into or near various muscles and nerves. These leadless devices receive power and command signals by inductive coupling from an external RF coil [1]. In order to decide how to deploy such a generic technology, it is necessary to combine clinical understanding of pathophysiology plus basic scientific knowledge of neuromuscular anatomy and physiology. We here provide some examples of how such a systematic approach can be used to develop novel clinical treatments for a wide range of disabilities.

II. LEVEL OF ORGANIZATION

A. Neuromuscular Compartmentalization

Muscles vary greatly in the complexity of their structure and function. Some have simple architectures in which constituent muscle fibers are organized into broadly distributed motor units. Contraction of a single motor unit contributes an increment of force to the single mechanical action of the whole muscle. More typically, muscles are composed of more than one muscle fiber type, and these may be organized into motor units that are distributed unevenly along the breadth and even the length of the muscle [2]. The muscle may be able to produce different force vectors as a result of a distributed origin or insertion and the motor units contributing to these force vectors may be segregated physically into neuromuscular compartments and/or functionally into task groups [3]. Nonspecific electrical

stimulation applied to the more complex muscles may result in net force vectors that are undesirable functionally or even potentially damaging to the muscle [4].

One particularly complex muscle is the genioglossus muscle of the tongue. Tongue movement is produced by compression, stiffening and bending of a hydraulic system composed of contractile but incompressible muscle fibers oriented in various directions throughout the body of the tongue. A single cranial nerve (hypoglossal - XII) supplies all of its motoneurons, each of which appears to innervate muscle fibers that are specifically oriented and confined to a small region of the tongue. The anatomical distribution of the muscle nerve branches, individual motor axons and endplates onto muscle fibers can be seen clearly using Sihler's stain [5].

The genioglossus muscle is of particular interest clinically because prolapse of the tongue into the airway appears to be the mechanical problem in a majority of patients suffering from obstructive sleep apnea [6]. Electrical stimulation of the hypoglossal nerve [7] or within the tongue [8] has been proposed to alleviate this obstruction, but may not do so if the "wrong" motor units are recruited. Examination of the neuromuscular organization of the tongue suggested that the desired symmetrical protrusion movements of the tongue could be achieved efficiently by stimulating in the vicinity of the endplates of the posterior radial muscle fibers. These endplates (and the terminal branches of their motor units) approach the midline from both sides, where they lie in a well-organized band near the middle of the muscle fascicles. This is 1-2cm deep to the mucosal surface of the tongue, where stimulation of cutaneous afferents might disturb a sleeping patient.

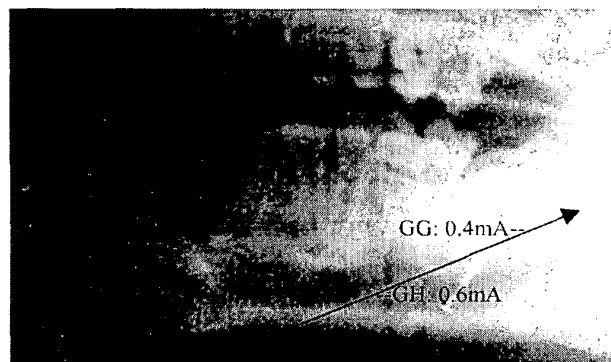


Figure 1: Implantation of BION in pig tongue, measuring thresholds for contraction of geniohyoid (GH) and genioglossus (GG) as insertion tool was advanced on indicated line (final orientation of device appears rotated because of palpation of tongue during implantation).

In order to align the elongated BION implants with the radial muscle fascicles, the desired injection approach appears to be in the sagittal plane through the base of the jaw, starting just inside the anterior angle of the mandible and heading obliquely toward the posterior portion of the tongue (Figure 1). The insertion tool traverses first the endplate zone of the geniohyoid and then the endplate zone of the genioglossus. During insertion of the BION implants along that line into the tongue of a pig, we used electrical stimulation to determine the threshold for eliciting palpable muscle contractions in various portions of the tongue complex. As predicted, the first region of low threshold activation produced contractions of the geniohyoid. When the insertion tool was advanced further, threshold increased until a second low threshold region was found that produced midline contractions of the posterior tongue (0.4mA x 0.2ms). With further advancement of the insertion tool, threshold increased even though the tip of the needle was palpated to be still well beneath the mucosal surface of the tongue. The BION implant was then placed at the low threshold point for the genioglossus. Following surgery, the pig recovered uneventfully with no impairment of swallowing or appetite. The animal was sacrificed after two weeks and the adjacent tissues are being evaluated histologically.

The cathodic stimulation electrode of the BION implant was coated with a layer of Procion Yellow fluorescent stain in a molten sugar solution prior to implantation. This stain dissolves immediately and binds covalently to the adjacent endomysial collagen, providing a convenient marker to compare the original position of the implant with that determined post mortem [9].

B. Trophic Effects of Electrically Induced Muscle Exercise

Electrical stimulation of weak or paralyzed muscles can be used to prevent or reverse disuse atrophy by inducing trophic effects in the activated muscle fibers. The mechanism for this may be mediated by low levels of sarcoplasmic calcium [10] rather than by the high levels of force output normally associated with body-building exercises. This would be fortunate because sustained high force contractions tend to be fatiguing and perhaps even damaging to atrophic muscles, tendons and bones. However, it is obvious that such a trophic mechanism can only be effective in muscle fibers that have actually been recruited. Thus, electrical stimulation needs to recruit all or at least most of the motor units in a given muscle.

We tested various combinations of stimulus pulse frequency and exercise period duration in order to identify effective and efficient programs of exercise to prevent disuse atrophy in a rat model of paralysis without denervation. The model uses a chronically implanted osmotic minipump to deliver tetrodotoxin, a sodium channel blocker, to a nerve cuff wrapped around the sciatic nerve [11]. BION implants were used to produce various exercise patterns in the

functionally paralyzed muscles. The results confirmed that low frequency stimulation (2pps) for even a small percentage of the day (2h) was at least as effective as higher rates and longer periods [12].

C. Peripheral Nerve Branching

When using electrical stimulation to treat disuse atrophy (see above) or to prevent contractures of spastic antagonist muscles (see below), it is often desirable to activate a number of substantially synergistic muscles without requiring selective control of them individually. In order to reduce the costs and simplify the procedure, it is desirable to identify single loci that can effectively recruit all of the desired muscles without producing undesirable side effects. Often these synergistic muscles are innervated by branches of a common muscle-nerve trunk that may run separately from proximally branching cutaneous nerves. These innervation patterns can usually be inferred from anatomical dissection of cadavers and from textbooks of peripheral neurology, although they may need to be supplemented by acute animal or intraoperative human studies in which electrical stimulation can be applied to individual nerve branches and muscle activation can be assessed visually or electromyographically.

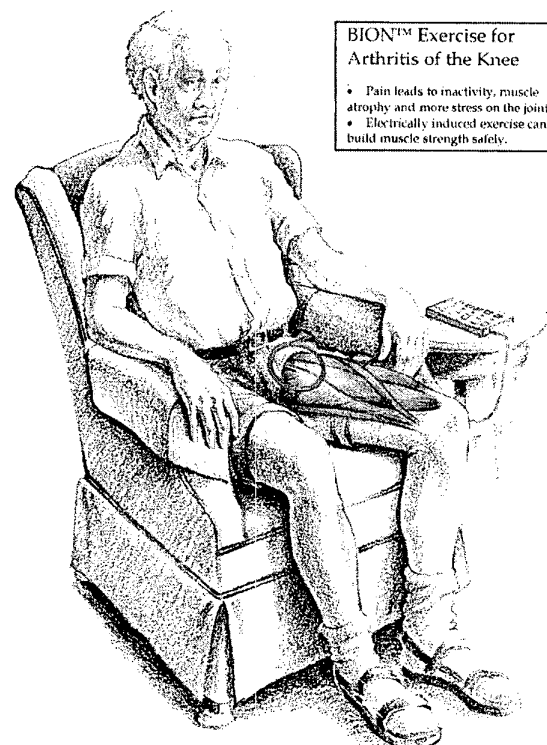


Figure 2: Implantation site of a single BION in groin to activate all quadriceps femoris muscle heads.

We have been using BIONs to exercise the quadriceps femoris muscles in patients suffering from chronic osteoarthritis of the knee (Fig. 2) [13]. Because of chronic knee pain, these patients find it difficult or impossible to perform the high-force voluntary contractions required to recruit their fast, fatigable motor units. The resulting muscle atrophy places more strain on the knee during normal use, accelerating the degeneration of the cartilage. "Quadriceps" means four anatomically distinct heads, some of which appear to be further subdivided into separately innervated neuromuscular compartments. Perhaps 6-8 electrode sites would be required in order to recruit this muscle group fully via intramuscular electrical stimulation. However, all of these muscle nerves originate from the femoral nerve in the groin. We have successfully implanted BIONs adjacent to the femoral nerve in five patients. Low thresholds of stimulation were able to activate the entire muscle complex. The cutaneous saphenous nerve also branches from the femoral nerve in this region, but the low frequencies of electrical stimulation required to treat disuse atrophy (see above) produce relatively little sensation. In the first three patients, we also implanted one BION in the vastus medialis, which produced focal contractions of this muscle head, but this proved to be unnecessary given the results from the femoral nerve site. All of these patients successfully used an in-home stimulation program to reduce the symptomatology of their arthritis. Two of the patients, however, noticed vaguely uncomfortable pressure sensations when sitting with the hip flexed, apparently as a result of skin folds pressing the BION against its encapsulating connective tissue and perhaps towards the femoral nerve itself.

We are also beginning a clinical trial of BION implants to activate the finger and wrist extensor muscles in stroke patients who are at risk of developing flexion contractures of the hand. Passive exercises to maintain range of motion are difficult for patients and their caregivers to administer over the long term and they do nothing to strengthen the atrophic muscles. Effective stretching of all of the spastic flexors requires simultaneous activation of two wrist extensors and three or more finger extensor muscles. Rather than implanting each of these muscles with BIONs, we are examining the feasibility of placing a single BION adjacent to the radial nerve at the elbow just distal to the branching of its cutaneous division.

D. Triggering Events

Functional use of electrical stimulation generally requires some means to integrate the evoked muscle contractions with the ongoing behavioral activity of the patient. Complex functions such as reaching for and grasping an object require sophisticated sources of command signals that may be fine-tuned by the patient during the execution of the task [Loeb et al., companion paper]. For simpler functional applications, however, a careful analysis of the biomechanics of the

behavior may suggest control schemes that require much simpler and less obtrusive interactions with the patient.

Stroke patients often recover most functional use of a hemiparetic leg but many continue to be unable to dorsiflex the ankle. The resulting "footdrop" slows their gait and puts them at risk of stumbling. The WalkAide™ restores dorsiflexion by stimulating the peroneal nerve and dorsiflexion muscles via transcutaneous electrodes [14]. Previous devices have required a separate heel switch in the patient's shoe [15], and this has made the system more cumbersome to use. The WalkAide provides both triggering and stimulation from a single device that is strapped to the shin and detects its angle of tilt. From the mechanics of the leg, it is apparent that the beginning of the swing phase in which stimulation is required coincides with a forward tilt of the shank. We are now working to incorporate two BION implants in place of the single transcutaneous stimulation channel both to eliminate activation of skin nerves and to improve the control of inversion/eversion of the ankle during dorsiflexion.

Obstructive sleep apnea (OSA) poses another interesting control problem. In previous attempts to use electrical stimulation of the hypoglossal nerve, stimulus trains were triggered synchronously with inspiration by means of an implanted substernal pressure sensor [7]. The design and surgical implantation of the mechanical transducer substantially complicated the system and its deployment in patients. The BION implant site in the tongue described above lends itself well to remote powering and control via an RF transmission coil in the patient's pillow. However, much of the advantage of such an untethered system would be lost if the patient were required to have an implanted or even external sensor to detect inspiration or obstruction. Is it possible that we are overcomplicating the problem? When we examine the respiratory pattern of an OSA patient, it is apparent that the patient prolongs the inspiratory phase for many seconds when obstruction occurs. The patient typically attempts unsuccessfully to overcome obstruction by more forceful effort until finally awakened by the hypercapnia and/or hypoxia. We hypothesized that it may not be necessary to provide *any* feedback signal to synchronize the stimulation. If the airway were kept open (by any means) on about the same schedule as the mean inspiratory phase of the patient's sleeping respiratory rate, we speculated that the patient would tend to become synchronized to the treatment. This might obviate the need to synchronize the treatment to the patient. We tested the hypothesis by gating the application of conventional CPAP therapy (continuous positive airway pressure) in a sleeping OSA patient who was CPAP dependent. Our preliminary results indicated that the patient occasionally happened to begin an inspiratory phase during a period when the airway was occluded, but then simply sustained the inspiratory effort for the few seconds until the CPAP was gated on. At this point, the patient could again breathe in. The patient tended to remain synchronized to the CPAP gate for most of

the sleeping periods. An extension of this study is underway in additional patients and normal healthy controls to see if they will synchronize to periodic opening of an obstructing valve, without the confounding effects of positive pressure.

III. CONCLUSION

In theory, neuromuscular electrical stimulation can be used to treat a wide range of disorders and disabilities associated with paralyzed, weakened, and/or atrophic muscles. The growing armamentarium of interface and control technologies is rapidly expanding the set of clinical applications that could be addressed safely, effectively and efficiently. In practice, each of these potential applications requires a host of decisions about design and deployment strategies that must be informed by a thorough understanding of the underlying anatomy, physiology and biomechanics. Fortunately, there is also a growing armamentarium of methodologies to perform the necessary experiments. More effort needs to be devoted to ensuring interactions amongst teams of clinicians, engineers and basic scientists, if we are to identify the most promising approaches to a given application *before* spending time and resources on suboptimal designs.

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REFERENCES

- [1] Cameron, T., Loeb, G.E., Peck, R.A., Schulman, J.H., Strojnik, P. and Troyk, P.R. Micromodular implants to provide electrical stimulation of paralyzed muscles and limbs. *IEEE Trans. Biomed. Engng.*, 44:781-790, 1997.
- [2] Loeb, G.E. and Richmond, F.J.R. Architectural Features of Multiarticular Muscles. *Human Movement Science* 13:545-556 (1994).
- [3] Loeb, G.E. The functional organization of muscles, motor units, and tasks. In: *The Segmental Motor System* (Eds.) M.D. Binder and L.M. Mendell, Oxford Univ. Press, New York, 1990, pp. 23-35.
- [4] Cameron, T., Liinamaa, T.L., Loeb, G.E. and Richmond, F.J.R. Long-term biocompatibility of a miniature stimulator implanted in feline hind limb muscles. *IEEE Trans. Biomed. Engng.*, 45:1024-1035, 1998.
- [5] Mu, L. and Sanders, I. Neuromuscular Specializations of the Pharyngeal Dilator Muscles: II. Compartmentalization of the Canine Genioglossus Muscle. *Anat. Rec.* 260:308-325, 2000.
- [6] Remmers, J.E., Degroot, W.J., Sauerland, E.K. and Anch, A.M. Pathogenesis of Upper Airway Occlusion during Sleep. *J Appl Physiol* 44:931-938, 1978.
- [7] Schwartz, A.R., Bennett, M.L., Smith, P.L., Backer, W.D., Hedner, J., et al. Therapeutic Electrical Stimulation of the Hypoglossal Nerve in Obstructive Sleep Apnea. *Arch Otolaryngol Head Neck Surg.* 127:1216-1223, 2001.
- [8] Mann, E.A., Burnett, T., Cornell, S. and Ludlow, C.L. The Effect of Neuromuscular Stimulation of the Genioglossus on the Hypopharyngeal Airway. *Laryngoscope.* 112(2):351-356, 2002.
- [9] Fitzpatrick, T.L., Liinamaa, T.L., Brown, I.E., Cameron, T. and Richmond, F.J.R. A novel method to identify migration of small implantable devices, *Journal of Long-Term Effects of Medical Implants* 6:157-168, 1996.
- [10] Naya F.J., Mercer B., Shelton J., et al: Stimulation of slow skeletal muscle fiber gene expression by calcineurin in vivo, *J Biol Chem*, 275 (7): 4545-4548, 2000.
- [11] St-Pierre, D. and Gardiner, P. Effect of "disuse" on mammalian fast-twitch muscle: joint fixation compared to neurally applied tetrodotoxin. *Exp Neurol* 90:635-651, 1985.
- [12] Dupont, A.C., Loeb, G.E. and Richmond, F.J.R. Effects of Chronic Stimulation Patterns in an Animal Model of Disuse Atrophy. *Proc 5th Annual Conference of the International Functional Electrical Stimulation Society*, Aalborg University, Denmark, 17-23 June 2000, pp. 192-195
- [13] Dupont, A.C., Bagg, S.D., Creasy, J.L., Romano, C. Romano, D., Richmond, F.J.R. and Loeb, G.E. First patients with BION™ implants for therapeutic electrical stimulation, *Neuromodulation* (in press) 2003.
- [14] Wieler, M., Stein, R.B., Ladouceur, M., Whittaker, M., Smith, A.W., Nauman, S., Barbeau, H., Bugaresti, J., and Aimone, E. Multicenter evaluation of electrical stimulation systems for walking. *Arch Phys Med Rehabil* 80 (5):495-500, 1999.
- [15] Taylor, P.N., Burridge, J.H., Dunkerley, A.L., Wood, D.E., Norton, J.A., Singleton, C., and Swain, I.D. Clinical use of the Oddstock Dropped Foot Stimulator: its effect on the speed and effort of walking. *Arch.Phys.Med.Rehab.* 80:1577-1583, 1999.