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Toward an implantable functional electrical stimulation device to correct strabismus

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Abstract

PURPOSE—To investigate the feasibility of electrically stimulating the lateral rectus muscle to recover its physiologic abduction ability in cases of complete sixth cranial (abducens) nerve palsy.

METHODS—In the feline lateral rectus muscle model, the effects of a charge-balanced, biphasic, current-controlled stimulus on the movement of the eye were investigated while stimulation frequency, amplitude, and pulse duration was varied. Eye deflection was measured with a force transducer. Denervated conditions were simulated by injection of botulinum toxin A.

RESULTS—Three chemically denervated and 4 control lateral rectus muscles were analyzed. In control lateral rectus muscles, the minimum fusion frequency was approximately 170 Hz, and the maximum evoked abduction was 27°. The minimum fusion frequency was unchanged after 4 weeks of chemical denervation. Stimulation of chemically denervated lateral rectus muscle resulted in 17° of abduction. For both innervated and chemically denervated lateral rectus muscle, frequencies greater than 175 Hz yielded very little increase in abduction. Modulating amplitude produced noticeable movement throughout the tested range (0.2 to 9 mA).

CONCLUSIONS—Results from the feline lateral rectus muscle showed that electrical stimulation is a feasible approach to evoke a contraction from a denervated lateral rectus muscle. The degree of denervation of the feline lateral rectus muscle was indeterminate. Varying the stimulation amplitude allowed greater eye movement. It is very likely that both frequency and amplitude must be modulated for finer control of static eye position.

Congenital or acquired anomalous innervation and palsy of the extraocular muscles may result in severe amblyopia, loss of stereopsis, marked deficits in binocular visual fields, and diplopia.[1] The goal of strabismus treatment is to restore fusion and stereopsis and to enlarge

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the binocular visual field. Existing treatment for anomalous-innervation strabismus is limited to surgical procedures that are only partially successful in achieving these goals.

A complete extraocular muscle palsy results in permanent denervation and muscle atrophy, which limits the outcome from surgical intervention on the affected muscle. Surgical correction is challenging and outcomes are limited, with many patients requiring several surgical procedures to reach alignment in the primary position.

Several techniques have been described to remobilize a denervated striate muscle, including nerve-to-nerve anastomosis, neuromuscular pedicle transfer, and functional electrical stimulation (FES).[2–11] The use of FES has long been proposed as a potential treatment for restoring motor function of denervated motor systems.[2,4–11] Recent success has been noted in the ability of FES to allow paraplegics to gain the ability to stand.[5,6,9] FES may protect muscles from atrophy, promote muscle reinnervation from appropriate native motoneurons, and reconnect a muscle to the original endplate and its nerve fiber without interrupting the natural course of reinnervation and the potential for spontaneous recovery.[12–18] The validity of this approach has been demonstrated in humans.

Zealear and colleagues[19,20] and Tobey and Sutton[21] first proposed that axial muscles such as those in the larynx or the extraocular muscles could be stimulated by using a normally innervated agonist muscle as a “master” to control a paralyzed “slave” muscle. The effectiveness of coordinating pairs of muscles with FES was proven feasible for clinical research.[22,23] Zealear and colleagues[22–24] and Billante and colleagues[25] applied FES to a laryngeal muscle (posterior cricoarytenoid) by using input respiratory signals to help patients breathe. In their work, they timed the stimulated laryngeal muscle to contract during the inspiratory phase of respiration.

The extraocular muscle system is an optimal candidate for Zealear and colleagues’ approach in using paired muscles as master and slave. By coordinating the electrical stimulus between a paralyzed muscle and its antagonist muscle, it may be possible to excite a paralyzed extraocular muscle to improve ocular alignment and binocular motor function. To simplify our study, we chose the lateral rectus muscle because of its exclusive innervation by the sixth cranial nerve. Several authors have conducted motoneuron or nerve stimulations of innervated and chemically denervated lateral rectus muscles in cats and monkeys.[26–32]

Our ultimate goal is to develop a miniature implantable electronic system that can perform closed-loop electrical stimulation of extraocular muscles to substantially restore ocular motility. A conceptual system sketch is shown in Figure 1. In this study, we present the feasibility of evoking adequate contractions of chemically denervated feline lateral rectus muscles by using electrical stimulation applied directly to the muscle.

Methods

We designed a study to deliver FES to the lateral rectus muscle. The overall study consists of several feasibility substudies, including correlation between eye position and extraocular muscle force output, determination of stimulation parameters, and muscle electrical stimulation followed by the design of an implantable device based on proven algorithm and electronics.

The present feasibility experiment is a prospective study in which we used an intermediate animal model to evaluate electrical stimulation of the lateral rectus muscle. The study was divided into 3 steps: (1) determine lateral rectus dimension and properties, (2) evaluate electrode design and muscle properties and correlated muscle response, and (3) eye

movement and stimulation parameters. This project fulfilled animal-research-protection regulations of the University of California Los Angeles.

Seven adult cats (mean age, 2 years) were involved in the study. One cat was used to determine the anatomical and physiological characteristics of the lateral rectus muscle, and produced the following results. The muscle was inserted on the sclera at 6.5 mm from the limbus. The width of the muscle near the insertion was 5.5 mm and the resting length was about 35 mm. The areas within the lateral rectus muscle with the strongest response to stimulation were determined with the use of TECA needles and a randomized stimulation protocol, which combined different ranges of amplitude (2 to 8 mA), pulse duration (0.5 to 2.0 ms), and frequency (50 to 250 Hz). Stronger muscle contraction was observed when the electrical stimulus was delivered closer to the neuromuscular junction. Fusion frequency for fused tetanus was found to be between 100 and 200 Hz. The combination of 200 Hz and 1 ms was able to produce a constant contraction (no fatigue) for 1 second. Modulating the amplitude appeared to adequately control lateral rectus muscle contractions. The minimum stimulation duration to first observe eye rotation was 90 ms.

Three cats underwent acute stimulation procedures on the lateral rectus. To determine the ability of the implanted electrodes to stimulate chronically denervated lateral rectus muscle, 5 units (5 units/0.1 mL) of botulinum toxin A (Botox Allergan Inc., Irvine, CA) were injected into one lateral rectus muscle of the remaining 3 cats 4 weeks before the stimulation procedures. The contralateral lateral rectus muscle was used as a control.

Detail descriptions of the experimental procedures, equipment, and protocol are available online as e-Supplement 1 (available at jaapos.org). Surgeries were performed with the cats under general anesthesia. A limbal-conjunctival incision was fashioned temporally. An opening was created between the Tenon's capsule and the sclera. An extraocular muscle hook was positioned under the lateral rectus muscle. The muscle was cleaned from surrounding connective tissue. A lateral orbitotomy was performed to expose approximately 25 mm of the lateral rectus muscle. The globe and muscle were coated with mineral oil to maintain moisture.

Botulinum toxin type A injection procedures were standardized. The lateral rectus muscle was isolated on a muscle hook. Five units of botulinum toxin were injected into the lateral rectus muscle under direct visualization at approximately 20 mm posterior to the scleral insertion.

For the stimulation experiments, a sleeve-type bipolar electrode (Figure 2) was implanted on the lateral rectus muscle. A diagram of the experimental setup is shown in Figure 3. A force-displacement transducer (Model FT03, Grass Telefactor W., Warwick, RI) was used in series with a spring (0.3 g/cm; Grass Telefactor W.) to measure the eye deflection generated by the stimulated lateral rectus muscle. A computer equipped with a data-acquisition card (PCI-6025E, National Instruments Corp., Austin, TX) was used to automatically conduct both recording (10 kHz sampling rate) and stimulation operations.

A biphasic rectangular pulse was used to minimize fatigue and possible metal diffusion into tissue. The computer automatically delivered the stimulation protocol using software developed in LabVIEW 7.0 (National Instruments Corp.). The stimulation amplitude, stimulation frequency, and cathodic and anodic pulse durations were varied within prespecified ranges and delivered in a random sequence. The LabVIEW program recorded data from the FT and converted the raw voltage readings to arc-length displacement through Hooke's Law (ie, $F = k\,x$ with measured force F, spring constant k [0.3 g/cm], and displacement x. The program continued to convert the displacement values to eye-deflection

angles by simple geometry using an average cat-eye radius of 20.92 mm on the horizontal plane.[33]

A video-tracking system consisting of a digital video camera (JVC Everio GZ-MG21U, Yokohama, Japan) was used to record and measure eye movement. The eye movement measured by the force-displacement transducer was compared against the physical displacement seen on the image produced by the video tracking system. Data were analyzed in Matlab 7.0 (The Math Works, Natick, MA). Fusion frequency was verified visually and quantified by the presence of a spike at the stimulated frequency on the Fourier spectrum.

Results

From 4 innervated lateral rectus muscles of 3 cats (Cats 2, 3, and 7), the average eye deflection was 21.8° ± 4.5° (range, 9.6° to 28.4°). Fusion frequency was approximately 170 Hz. Although stimulation frequencies as low as 50 Hz produced visible eye deflections, frequencies <170 Hz did not produce a fused tetanus.

After 4 weeks of chemical denervation, 3 denervated lateral rectus muscles from 3 cats (Cat 4, 5, and 6) produced deflections averaging 17° ± 1.5° (range, 13.1° to 20°). The fusion frequency was similar to the innervated case at approximately 175 Hz.

Both stimulation amplitude and frequency elicited a proportional response on ocular rotation. In innervated lateral rectus (Figure 4), frequencies between 100 and 250 Hz responded mostly to changes in amplitude from 1 mA to 3 mA. Amplitude larger than 4 mA had a less but still noticeable effect on ocular rotation. Amplitudes between 2 and 8 mA responded mostly to frequencies of 100 Hz to 175 Hz. There was almost no change in ocular rotation when the frequency was increased above 200 Hz. At 200 Hz, changes in pulse duration from 0.5 ms to 2 ms at amplitudes ranging from 2 mA to 8 mA had no effect on the magnitude of ocular rotations. In the paralyzed muscle, most of the muscle contraction occurred when using amplitudes between 4 mA and 8 mA and frequencies between 100 Hz and 200 Hz (Figure 5). Varying the asymmetry of the biphasic pulse showed no change in ocular rotations for both innervated and denervated lateral rectus.

Discussion

In this study, we demonstrated the feasibility of electrical stimulation to evoke an abduction of the eye from feline innervated lateral rectus muscles and artificially denervated lateral rectus muscles by botulinum toxin type A injection. Stimulation frequency and amplitude were the only parameters that modulated eye deflection. Frequencies less than approximately 170 Hz did not produce a fused tetanus in normal feline lateral rectus muscles. Varying stimulation amplitude was the most effective parameter in eye position using electrical stimulation.

In 1977, Zealear and colleagues[17,18] proposed that a signal from a normally innervated muscle could be used to control a stimulation signal that modulates the activity of a contralateral denervated muscle. Preliminary studies were performed in paralyzed dog laryngeal muscles stimulated by an open-loop device. Significantly greater tracking accuracies were observed when closed-loop systems were used.

Microscopic examination of chronically denervated muscles showed atrophy of myofibrils, increased adipocytes, as well as collagen degeneration of the muscle. FES increases muscle–fiber diameter, decreases adipocytes and connective tissue content, and reorganizes myofibril regeneration by promoting selective reinnervation and preventing synkinesis.[2,12–16,34]

Extraocular muscles differ from other skeletal muscles in the body in many ways, some of which include the presence of multiple innervated muscle-fibers, high mitochondrial content and, in some species, absence of traditional muscle spindles.[26,35–37] There is continuous remodeling of the muscle by the addition of myofibers from rapidly activated satellite cells. Compared with other skeletal muscles, extraocular muscles incorporate new myofibrils at a much greater rate. Normal muscle innervation is important in satellite cell number and proliferation. Denervation results in muscle fiber transformation into type-2 white, fast, and anaerobic fibers, which are less resistant to fatigue. Regenerated myofibers express adult fast myosin, which rapidly becomes atrophic and degenerates. FES recovers afferent sensory inputs and improves muscle contraction and resistance by inducing regeneration and transformation of muscle fibers to type 1 red, slow, and aerobic fibers.[2,12–16,31,32,34]

Slow steady low-force units located primarily in the orbital layer of the extraocular muscle provide primary position. Denervation results in a greater deterioration of the global layer.[35] Demer and colleagues[38] studied the paralyzed superior oblique muscle. Denervation reduced the whole cross section of the muscle. Although the orbital-layer fiber cross sections were identical in denervated and control muscles, the denervated global-layer fibers had a cross-sectional area 80% lower than the control.

Implantable nerve (epineural), neuromuscular junction (epimysial), or muscle (intramuscular) stimulation systems are ideal for chronic implantation when compared with surface stimulation because of their greater specificity, control, and recruitment. Neural stimulation has the additional advantage of requiring lower current and energy levels. However, the complexity of accessing oculomotor nerves limits its applicability, especially when considering chronic implantation.[2] Our study differs from most previous studies of extraocular muscle stimulation because we attempted to directly stimulate the muscle fibers. Our first feline experiment allowed us to design a muscle electrode for acute implantation that effectively transmitted current without damaging the lateral rectus muscle or spreading the stimulation signal to neighboring muscles, such as the orbicularis. Although intramuscular stimulation is ideal for small and deep muscles, it is more difficult to achieve compared with epineural and epimysial stimulation. Greater levels of energy are required to stimulate muscle fibers directly, which may result in the activation of peripheral sensory and pain fibers.

Our study had several limitations. The number of muscles tested was small. Although all experimental procedures were standardized, some variability in the surgical technique and individual response to the botulinum toxin injection could modify the response of the muscle to the stimulation. The effectiveness of denervation was determined by the limitation of abduction and esotropia. No electromyography was used. Previous studies demonstrated an immediate decrease in amplitude and frequency after direct injection of botulinum toxin type A into the feline lateral rectus muscle.[32,39] Moreno-Lopez and colleagues[38] found that low doses (0.3 ng/kg) of botulinum toxin directly injected to the lateral rectus muscle completely paralyzed the muscle for 15 days, and high doses (3 ng/kg) caused a complete paralysis for 3 months. We limited our study to 4 weeks of chemical denervation using a high-dose (5 units) of botulinum toxin type A to avoid the possibility of muscle recovery. We did not address the degree of paralysis or changes that may result from chronic denervation of extraocular muscles, such as muscle atrophy, which could limit the ability of electrical stimulation to evoke an adequate eye deflection. Our experiments were limited to chemical denervation. It is necessary to create a model in which the lateral rectus muscle is surgically denervated.

Our ultimate goal is a closed-loop system to control the extraocular muscles. Normal muscle activity depends on synchronized muscle contraction and sophisticated sensory feedback.

FES must be forceful, controllable, repeatable, and painless. In a closed-loop system, continuous information about contraction, motion, and force should be transmitted to a control unit that modifies the contraction.[19–23,40–44] There are many challenges to overcome to achieve such a system, including the difficulty of controlling fast-acting extraocular muscles, the effect of fatigue in constant long-duration stimulation, the power requirements for constant stimulation, and finally addressing the need for integration between motor and sensory systems.

In conclusion, artificial stimulation of the lateral rectus muscle is feasible. Eye position can be modified and controlled by modulating stimulation parameters. Implementation of the protocol-generating algorithm used in this study can greatly reduce surgery and experimentation time. Characterizing the response of the lateral rectus muscle to electrical stimulation was an important first step in our ultimate goal of developing a closed-loop system to improve ocular alignment and enable horizontal pursuit movements using antagonist muscle activity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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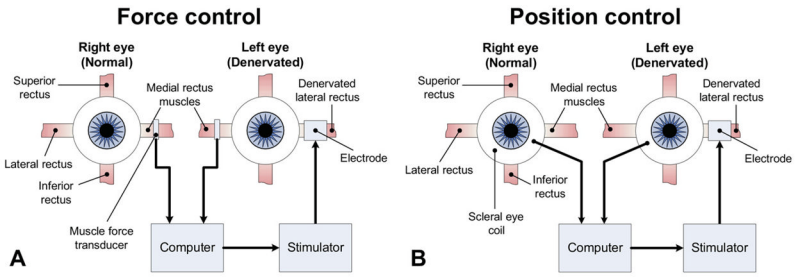

FIG 1.

System sketch of lateral rectus stimulation apparatus to align eye positions. Two types of feedback inputs are under consideration: A, ipsilateral medial-rectus muscle force, and B, contralateral eye position. In both systems, the input is processed by a computer that delivers the stimulus that drives a desired muscle response. The stimulus is adjusted based on the feedback of the input to fine-tune the stimulus.

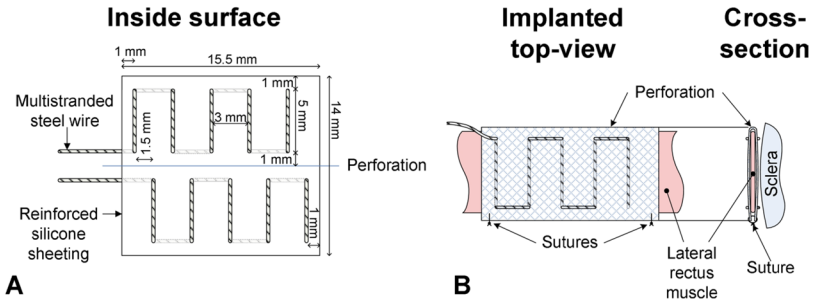

FIG 2.

A, A sleeve-type electrode was constructed from multistranded stainless-steel wire stitched into silicone mesh material. The bipolar electrode positioned one set of stimulating leads on the global surface of the lateral rectus and another set on the orbital surface of the lateral rectus. B, The electrode wraps around the lateral rectus longitudinally and applies stimulus across the width of the muscle. The side facing away from the muscle is insulated from the stimulation in an attempt to localize the stimulating current.

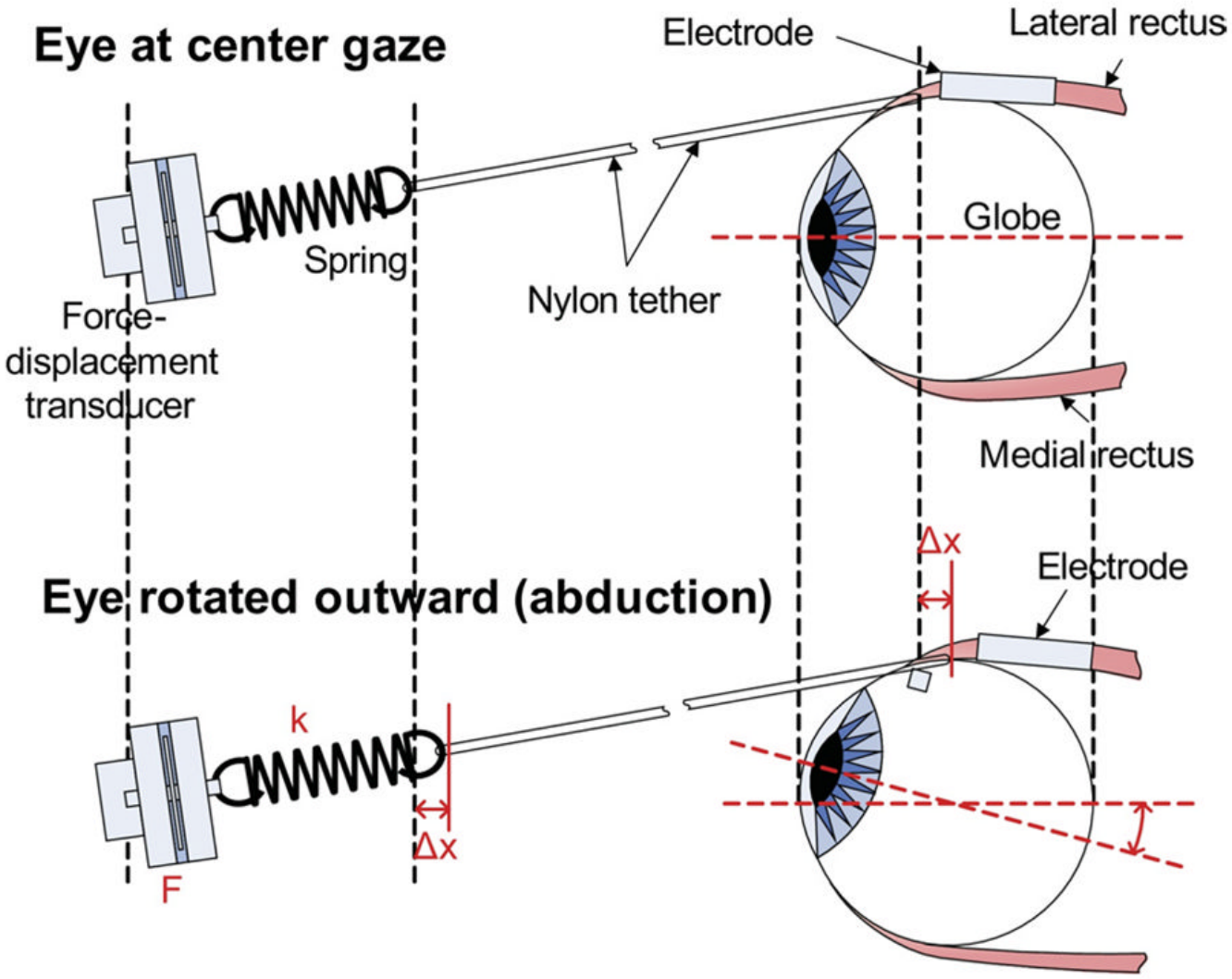

FIG 3.

The experimental setup for the feline lateral rectus muscle used a force-displacement transducer in series with a spring (0.3 g/cm) to measure eye deflection generated by the stimulated lateral rectus muscle. Values of linear displacement were obtained using Hooke's Law. A video camera also captured the movements against a ruler.

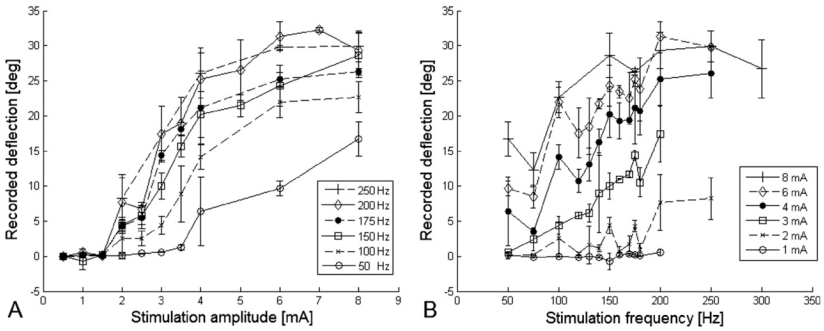

FIG 4.

Results of stimulation experiments on normal lateral rectus muscle showed that both stimulation amplitude and frequency elicited a proportional response on ocular rotation. (A) Frequencies between 100 Hz and 250 Hz responded mostly to changes in amplitude from 1 mA to 3 mA. (B) Amplitudes between 2 mA and 8 mA responded mostly to frequencies of 100–175 Hz. There was no significant change in ocular rotation when the frequency was increased >200 Hz.

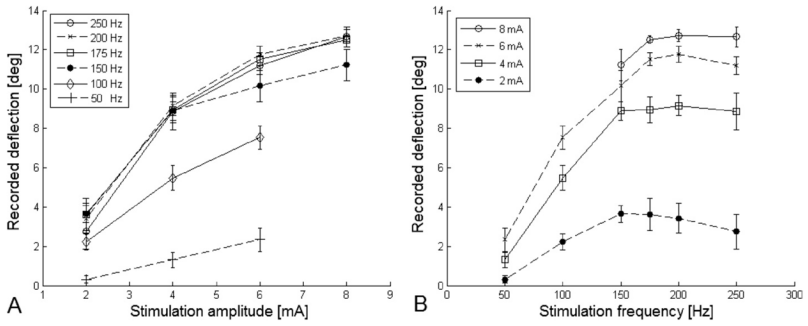

FIG 5.

Results of stimulation experiments on paralyzed lateral rectus muscles showed that most of the muscle contraction occurred when using (A) frequencies between 100 Hz and 200 Hz and (B) amplitudes between 4 mA and 8 mA. The degree of paralysis was not defined.