Activating the Levator to Elevate the Eyelid

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Abstract

Purpose: To demonstrate in an animal model the feasibility of elevating the eyelid in a functionally useful manner by chronically stimulating the levator palpebrae superioris (LPS) muscle with an implanted electrode.

Subjects & Methods: Five rabbits were implanted with electrodes designed to stimulate the nerve innervating the LPS near its entry to the muscle. Bipolar platinum electrodes in a silicone rubber envelope with silicone-sleeved, PTFE-coated platinum lead wires were used to provide long-term stimulation with bipolar square-wave pulse trains at 0.18-0.80 mA and 200 Hz, at a duty cycle of 8 s on and 2 s off. Explanted electrodes were examined for damage, and stimulated tissues were evaluated for abnormalities by light microscopy.

Results: We achieved mean lid elevation of 1.6 mm, approaching the diameter of the light-adapted pupil, with 0.5 mA stimulus. Stimulus currents below 1.0 mA produced no signs of discomfort. Three animals with which we attempted daily stimulation, averaged 16.1 hrs/wk. Experiments lasted 22 weeks, on average. Lid lifting with a well-implanted platinum electrode was stable, with no apparent tissue or electrode damage after as long as 29.1 wk.

Conclusions: Stable, functionally useful eyelid lifting was achieved with stimulation currents that caused no apparent discomfort or damage to muscles or nerves. A simple, discrete bipolar electrode was effective and survivable.
Introduction

Blepharospasm sufferers may be functionally blind despite having normal eyes, due to spasms in surrounding facial muscles and eyelid apraxia, the inability to raise the eyelids or keep them raised. It is a disorder of central control, possibly related to abnormal function of the basal ganglia, but its cause is unknown. The disorder typically affects otherwise healthy adults age 40-60y, progresses for a few months and then remains stable for decades. Unlike in congenital ptosis, muscles and nerves in the acquired ptosis of blepharospasm are generally normal, and most patients have periods of normal function, reporting that dark rooms, looking downward, even swimming under water are helpful.

Botulinum toxin injection can relieve the spasms, but eyelid apraxia often remains. Surgical lid elevation and botulinum toxin injection of the pretarsal orbicularis of the upper lid can be helpful, but static repositioning makes normal eye blinking and lid closure problematic. Functional electrical stimulation (FES) of the muscle that raises the eyelid (the levator palpebrae superioris or LPS), could provide these functionally blind patients with useful vision. Programmable binocular FES would be far superior to surgery, both functionally and cosmetically. Several studies have demonstrated feasibility of electrical stimulation of eye muscles, though not of the lid-elevating LPS. Otto et al (1986) and Somia et al (2001) studied the orbicularis oculi in dogs, and Otto (1997) and Sachs et al (2007) in rabbits. These studies produced eyelid closure (potentially therapeutic in paralysis of cranial nerve VII), suggesting that clinically useful stimulation of muscles in and around the eye is practical. FES of oculorotary and facial muscles would generally require solving the technically difficult problem of synchronous, contingent stimulation, where a control signal is derived from other, functional muscles. In contrast, binocular LPS stimulation would be clinically useful without such coordination.

Most attempts to influence eye muscle function electrically have used direct electrical stimulation of the muscle itself. Federico Velez and his group, eg, measured effects of stimulation in the denervated muscles of cats (Velez, Isobe et al. 2009). Scott (1975) developed a device to locate disinserted muscles in the orbit by direct stimulation. Using such devices we have found that direct stimulation of eye muscles to functional levels in humans requires currents an order of magnitude higher than epineural stimulation, and is impractical for chronic stimulation due to associated pain.

We herein address 3 issues that are essential preliminaries to bringing FES of the LPS to clinical practice: [1] design of an effective and survivable electrode package suitable for stimulating nerves supplying the LPS in the posterior orbit, while minimizing current density by encompassing the several nerve branches entering the muscle and spanning several nodes of Ranvier, [2] development of stimulation parameters that effectively lift the eyelid without discomfort, and [3] determination of long-term effectiveness and safety of the system under a realistic stimulation regimen.

Methods

Subjects

All experimental procedures were approved by the Animal Care and Use Committee (IACUC) of the Smith-Kettlewell Eye Research Institute (SKERI; San Francisco, CA), Pacific BioLabs (PBL; Hercules, CA) or Preclinical Medevice Innovations (PMI; San Carlos, CA), and supervised by their attending veterinarians. All work conformed to the US Animal Welfare Act of 1966 (as amended in 1985) and its implementing regulations from the USDA, the Guide for the Care and Use of Laboratory Animals (National Research Council 1996), and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (Office of Laboratory Animal Welfare 1996).

Animal were 3-4 Kg New Zealand White rabbits of either sex. Rabbits have been used for decades in oculomotor studies because their eye muscles are similar to those in humans and relatively large (Frueh, Hayes et al. 1994, McLoon, Park et al. 2011).

There being no known way to experimentally induce the central control defect of apraxia, we implanted our electrodes in normal eyes, and assessed the additional lid elevation produced by stimulation over that which was physiologic. In prospective clinical application, orbicularis spasm would be controlled with botulinum toxin injection, as now, and stimulation-produced elevation of an otherwise normal levator would proceed from relaxed closure.

Animals were monitored throughout for discomfort due to the implants, the tether, or stimulation itself, using indices that included reduced activity, postural changes, poor grooming, weight loss, self-protection, and hypersalivation.

Electrodes

Unlike recording electrodes, stimulating electrodes are highly vulnerable to electrolytic damage. Early designs using multi-strand stainless steel lead wires, though...
apparently well-sealed, failed with evidence of corrosion. We therefore switched to platinum (alloyed with 10% iridium) for both electrodes and wiring. Our final design consisted of a 0.64 mm thick silicone envelope carrying 2 parallel 0.30 mm cylindrical platinum-iridium electrodes, each 2.5 mm long, separated by 2.5 mm, bonded to PTFE-coated multi-strand 90% platinum-iridium wire leads (Medwire 10Ir9/49T), which we twisted and threaded through a 0.025 in outside-diameter protective silicone rubber sleeve. The package presented to the body only platinum and implant-grade silicone, and caused no apparent tissue reaction.

A "connector can" was designed to receive the electrode leads, seal the lead wire exit against infection, and provide reliable connection of a stimulation tether (Fig 1).

### Implantation

The connector can was affixed to the skull with screws and dental acrylic. The LPS was exposed by incising conjunctiva, and identified using electrical stimulation. The flexible envelope of the electrode package was sutured to the muscle anteriorly, with its active portion extending posteriorly so as to contact the nerve supply on the inferior surface the LPS near its origin, with position verified by delivering test stimuli. After a few weeks, connective tissue anchors the electrodes firmly in place. Wires were led under the skin, superotemporally across the brow ridge, into the connector can, and soldered to its pins. Implant grade RTV silicone inside the can created a seal. A cap protected the connector pins between stimulation sessions. Implants, and electrode movement with stimulation, were visualized by fluoroscopy (Fig 2).

### Tether

A 4-channel commutator (PlasticsOne, Roanoke VA, Model SL2+2C) was fitted to the top of the rabbit’s home cage to allow free movement during stimulation. Animals wore a “rabbit jacket” (Tomir, Quebec, Canada), to which we fitted a guide to direct the tether out of the animal's way. During stimulation sessions a spring-steel-shielded flexible tether (PlasticsOne) was connected to the commutator, passed through the guide, and plugged into the connector can.

### Stimulation

Early experiments (rabbits BNG & RXX, see Tbl 1) aimed to assess implant effectiveness and stability, and stimulation was only occasional. Other animals were scheduled to receive in-cage stimulation for up to 7 hrs/day, 5 days/week, approximating a regimen that might be adopted clinically, and this was achieved with animal T3539 (Tbl 1). Rabbit CRL32 would only tolerate the jacket for an hour or two at a time.

Stimulation equipment consisted of a WPI (Sarasota, FL) A310 Accupulser stimulus generator, two WPI A385 Stimulus Isolators, and two WPI A382 Battery Chargers, with which we delivered electrically isolated, constant-current, charge-balanced, biphasic, square-wave
stimulation trains. Charge-balanced epineural stimuli were delivered at 200 Hz, with amplitude 0.18-0.80 mA, optimized for each animal to produce as large an amplitude of eyelid elevation as possible without discomfort. Stimulus trains were 8 s long, followed by 2 s off to allow eye closure to maintain corneal hydration.

At the conclusion of each study the animal was euthanized to evaluate LPS tissue health and electrode condition.

**Results**

### Lid Elevation

Across 6 electrode implants we achieved mean lid elevation of 1.6 mm with 0.5 mA stimulus. In animals with which we attempted daily stimulation, we averaged 16.1 hrs/wk. Experiments lasted 22 weeks, on average (Tbl 1). Responses were stable, except where corrosion of stainless steel lead wires, used in early implants, led to device failure. An example of stimulation-produced lid lifting is shown in Fig 3.

### Electrodes & Stimulation

PTFE insulation and silicone encapsulation were adequate protection for materials such as stainless steel and silver solder when stimulation was infrequent (animals BNG & RXX), but not with frequent, long-term, chronic stimulation. The platinum electrodes described in Fig 1 showed no corrosion at any time.

Long-term chronic stimulation was bipolar and charge-balanced, consisting of 1 ms-wide square-wave pulse trains at 200 Hz, with a duty cycle of 8 s on (lid elevated) and 2 s off (allowing eye blinks for corneal hydration). Effective currents varied from 0.18-0.80 mA, likely depending electrode positioning. Excessive currents, generally about 50% higher than effective currents, caused lid closure, either by direct stimulation of the orbicularis oculi or as a central response to discomfort.

### Implantation & Explantation

The rabbit orbit is unlike that of the human in being shallow and containing a large venous sinus, damage to which causes bleeding that usually results in an ineffective implant.

Light-microscopic examination of muscle subject to long-term stimulation showed no abnormalities apart from slightly thickened epimysium (Fig 4).

### Discussion

Given that the light-adapted pupil is 2-4 mm in diameter, it may be possible to achieve clinically useful lid lifting with biphasic, charge-balanced, epineural stimulation currents under 1 mA, which appear to be painless and
not cause tissue or electrode damage over many months. Well-positioned, platinum electrodes with multi-strand platinum lead wires appear stable, and may function indefinitely.

In a complete system, our electrodes would be driven by an implantable pulse generator (IPG) of the type used for deep brain stimulation. Reduction of excessive orbicularis activity by surgery or toxin injection (being careful to avoid the LPS) might also be needed in blepharospasm patients to enable lid lifting. LPS stimulation would be binocular and asynchronous, as in our rabbits. A duty cycle permitting hydrating blinks (eg, 8 s on, 2 s off) could be programmed to run during the day, and be turned off at night, when the IPG might be recharged inductively.

It has also been shown in many muscle systems that chronic FES increases muscle size, normalizing the paretic muscles themselves, and tends to promote reinnervation, raising the possibility that even a limited period of FES would be therapeutic.

Similar systems could be used to activate nerves to the orbicularis to close eyes tonically or intermittently, and to a paretic extraocular muscle to provide constant muscle tone, to promote reinnervation, or to directly correct a comitant strabismic misalignment.

Our stimulation system might also be a component of a system to treat strabismus by activating a paretic oculorotary muscle, contingent on a control signal recorded from its antagonist, or from muscles in the fellow eye. Similarly, unilateral eyelid ptosis might be relieved with activation based on recordings from nerves to a normal fellow levator muscle.

Bibliography


Appendix

A short video corresponding to Fig 3 is available: https://drive.google.com/open?id=1kqo-yKjzXNaDIXxxb9dBLWM0uhkNul6x