

Activating the levator to elevate the eyelid



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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.
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 of 0.18–0.80 mA and 200 Hz at a duty cycle of 8 seconds on and 2 seconds 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 hours per week. Experiments lasted 22 weeks on average. Lid lifting with a well-implanted platinum electrodes was stable, with no apparent tissue or electrode damage after as long as 29.1 weeks.
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. (J AAPOS 2019;23:219.e1-4)



Blepharospasm sufferers may be functionally blind, despite having normal eyes, due to spasms in surrounding facial muscles and eyelid apraxia, or 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 40–60 years, 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 (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 the feasibility of electrical stimulation of eye muscles, though not of the lid-elevating LPS. Otto and colleagues¹ and Somia and colleagues² studied the orbicularis oculi in dogs; Otto³ and Sachs and colleagues⁴ in rabbits. These studies produced eyelid closure (potentially therapeutic in paralysis of the facial nerve), suggesting that clinically useful stimulation of muscles in and around the eye is practical. FES of oculomotor 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. Velez and colleagues⁵ measured the effects of stimulation in the denervated muscles of cats. Scott⁶ 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.

The purpose of this study was to investigate three issues that are essential preliminaries to bringing FES of the LPS to clinical practice: (1) design of an effective and survivable

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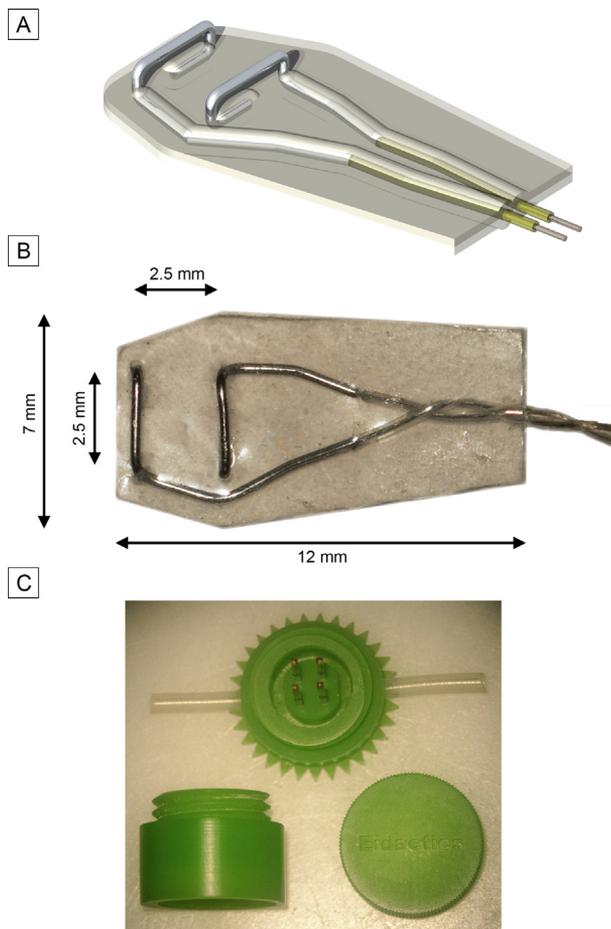


FIG 1. Functional electrical stimulation electrode package and connector can. A, CAD rendering of electrode package. B, Finished electrode with dimensions. C, Connector can, consisting of a base with connector pins and lead wire strain relief, which is mounted to the skull; a sleeve, which is fixed to the base after lead wires are soldered to the pins; and a cap, which protects the pins between stimulation sessions.

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 the potential life span of the system under a realistic stimulation regimen.

Methods

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 Medevic Innovations (PMI; San Carlos, CA) and were 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 Ani-

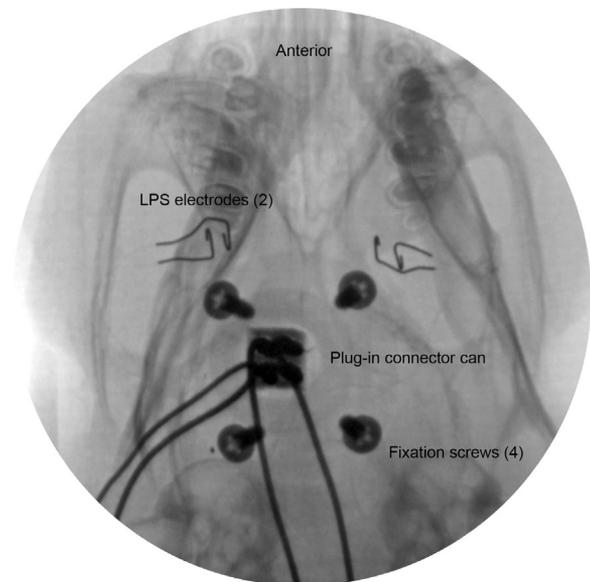


FIG 2. Implants. A fluoroscopic image in superior view shows bilateral levator palpebrae superioris electrodes, screws anchoring the connector can (faintly visible ring) to the skull with stimulating leads plugged into it, and external wiring. Electrode lead wires are faintly visible. When stimulation was applied, the electrodes could be seen to move medially, as the lids lifted.

mals (NRC 1996), and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS 1996).

Animals 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.^{7,8} Animals were monitored throughout for discomfort due to implants or stimulation.

With 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 it is now, and stimulation-produced elevation of an otherwise normal levator would proceed from relaxed closure.

Electrodes

Unlike recording electrodes, stimulating electrodes are highly vulnerable to electrolytic damage. Early designs using multi-strand stainless steel lead wires, although 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 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 multistrand 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

Table 1. Implants

Rabbit ID	Eye	Lid elevation, mm	Stimulus magnitude, mA	Stimulation sessions, hours/week	Experiment duration, weeks	Endpoint
BNG ^a	R	1.0	0.30	—	6.3	Scheduled
RXX ^a	R	2.0	0.65	—	55.5	Scheduled
R1617 ^b	L	1.6	0.21	13.0	12.9	Device failure
	R	1.8	0.18	13.0	10.0	
CRL32 ^c	R	2.2	0.5	2.6	29.1	Scheduled
T3539 ^d	L	1.0	0.80	35.8	18.1	Scheduled
Mean		1.6	0.5	16.1	22.0	

^aOccasional stimulation only.

^bCorroded stainless steel lead wires found on autopsy.

^cAnimal disliked tether, limiting stimulation session duration.

^dBinocular implant attempted but failed in one eye because of intrasurgical bleeding.

can” was designed to receive the electrode leads, seal the lead wire exit against infection, and provide reliable connection of a stimulation tether (Figure 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 of the LPS near its origin; its position was verified by delivering test stimuli. After a few weeks, connective tissue anchored 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 (Figure 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 Table 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 hours per day, 5 days per week, approximating a regimen that might be adopted clinically, and this was achieved with animal T3539 (Table 1). Rabbit CRL32 would only tolerate the jacket briefly.

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 seconds *on*, followed by 2 seconds *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 hours per week. Experiments lasted 22 weeks on average (Table 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 Figure 3 (see also Video 1, available at jaapos.org).

Electrodes and 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 Figure 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 seconds *on* (lid elevated) and 2 seconds *off* (allowing eye blinks for corneal hydration). Effective currents varied from 0.18 to 0.80 mA, likely depending on 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 and Explanation

Unlike the human orbit, the rabbit orbit is shallow and contains a large venous sinus, damage to which causes bleeding that usually results in an ineffective implant.

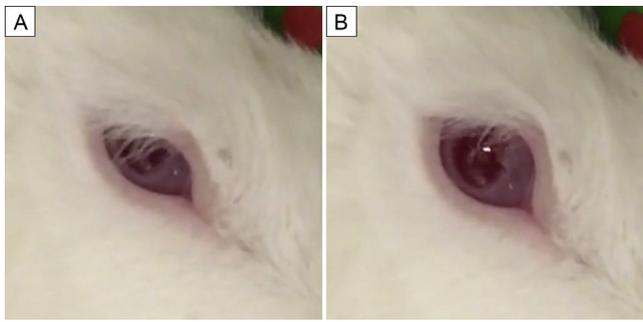


FIG 3. Typical response to LPS stimulation. A, Physiologically open eye, stimulation off. B, 200Hz 0.5 mA biphasic stimulation lifts lid an additional 2 mm.

Light-microscopic examination of muscle subject to long-term stimulation showed no abnormalities apart from slightly thickened epimysium (Figure 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 multistrand platinum lead wires appear stable and may function indefinitely.

In a complete system, our electrodes would be driven by an implantable pulse generator 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 seconds *on*, 2 seconds *off*) could be programmed to run during the day, and be turned off at night, when the implantable pulse generator 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 could 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



FIG 4. Muscle after electrode excision. The electrode of rabbit BNG had occupied the position shown. Thickened epimysium surrounding electrode is apparent in an otherwise normal muscle.

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.

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