

Bupivacaine Injection Treatment of Strabismus

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(40 min)

Why Treat Strabismus With Pharmacologic Injection?

- 注射器图标 Traditional surgical treatments restore muscle balance by means of compensatory impairment:
 - Resection removes tissue in order to stretch a muscle, increasing its elastic force.
 - Recession moves an insertion so as to reduce stretch, and so reduce elastic force.
 - Transposition moves an insertion “sideways”, sacrificing one direction of muscle action for another.
 - Posterior fixation relocates a muscle’s effective insertion to a mechanically disadvantageous position.
- 注射器图标 Pharmacologic injection treatment, in contrast, offers the possibility of directly:
 - Increasing and decreasing contractile muscle strength,
 - Increasing elastic stiffness, and
 - Increasing and decreasing muscle length,
- 注射器图标 Injection treatment does not require removing tissue or otherwise compromising extraocular mechanics.
- 注射器图标 Injection does not cause scaring, which makes followup surgeries difficult.
- 注射器图标 Injection is not greatly obstructed by prior scaring.
- 注射器图标 Injection treatment costs are much lower than surgical costs.



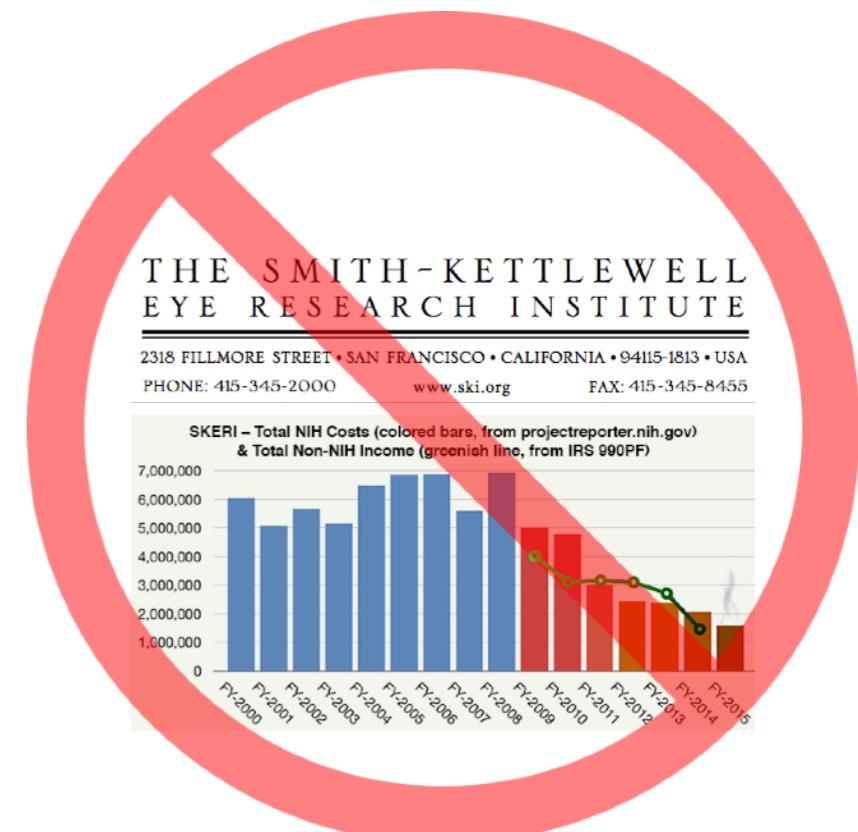
Pharmacologic Injection Treatments From Our Lab

- 💉 We have long been interested in pharmacologic injection treatments as an alternative or supplement to surgery.
- 💉 Oculinum® (now called Botox®) was originally developed in our lab to relax and lengthen abnormally short eye muscles (Scott 1980). It temporarily weakens muscles, allowing their antagonists to stretch and lengthen them.
- 💉 We've now turned our attention to the opposite problem. With bupivacaine (BPX), we've demonstrated the first practical method for strengthening eye muscles, which induces them to shorten, thereby correcting eye misalignments.
- 💉 Work continues on improving BPX injection effectiveness, extending its applicability to new populations, and better understanding its mechanism of action.



SKERI → SRF & Eidactics

- 針 For many years, Scott and Miller had their labs at the Smith-Kettlewell Eye Research Institute (SKERI).
- 針 However, sad to say, beginning about 15 years ago, this once vigorous and respected center for research in strabismus, motor control, and electrophysiology entered a period of decline, withdrawing from those areas of research, and from basic science generally.
- 針 Over the next decade, most of S-K's faculty and staff departed, and most of its research support was lost. Its physiology facility was shuttered (see: eidactics.com/projects/s-k for the full story!).
- 針 S-K no longer supports Fellows in strabismus.
- 針 But happily, the work abandoned by SKERI is continuing at The Strabismus Research Foundation (SRF, our non-profit, educational arm) and Eidactics (our facility provider).
- 針 We love hosting Brazilian Fellows (recently Iara Debert and Talita Malta e Cunha), providing them with both laboratory training and clinical experience (though we are a bit short of support funds!).



Bupivacaine (BPX) Myotoxicity

- 注射器图标 Bupivacaine injection induces calcium release from sarcoplasmic reticulum, inhibits reuptake, and sensitizes the contractile apparatus.
- 注射器图标 Within a few minutes, myofibrils hypercontract and damage to plasma membranes is evident. Within a few hours, enzymes cleave the sarcomeres, which are then digested by other enzymes. Macrophages remove the debris over 2–10 days.
- 注射器图标 Basal lamina, satellite cells, nerves & vasculature are spared.
- 注射器图标 Beginning around day 2, satellite cells are activated and regeneration begins.

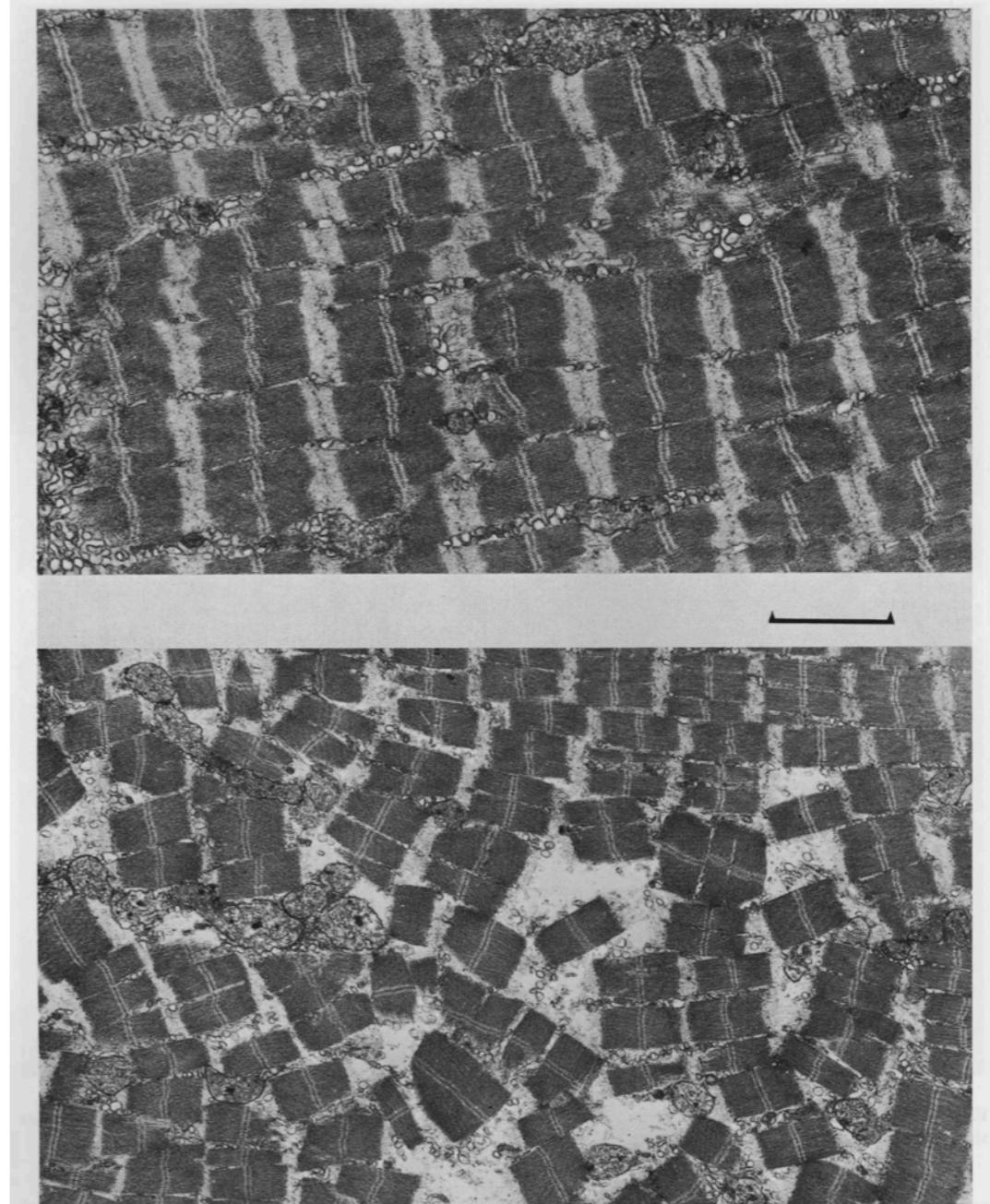


FIG. 7. Electron micrographs of rat muscle fibers 2 hr after bupivacaine injection. Top: Z-band lysis has occurred. Bottom: The myofibrils have separated into "envelopes" at the former sites of the Z-bands. Calibration bar: above 2.5 μ , below 3.5 μ .

Walter G. Bradley, 1979



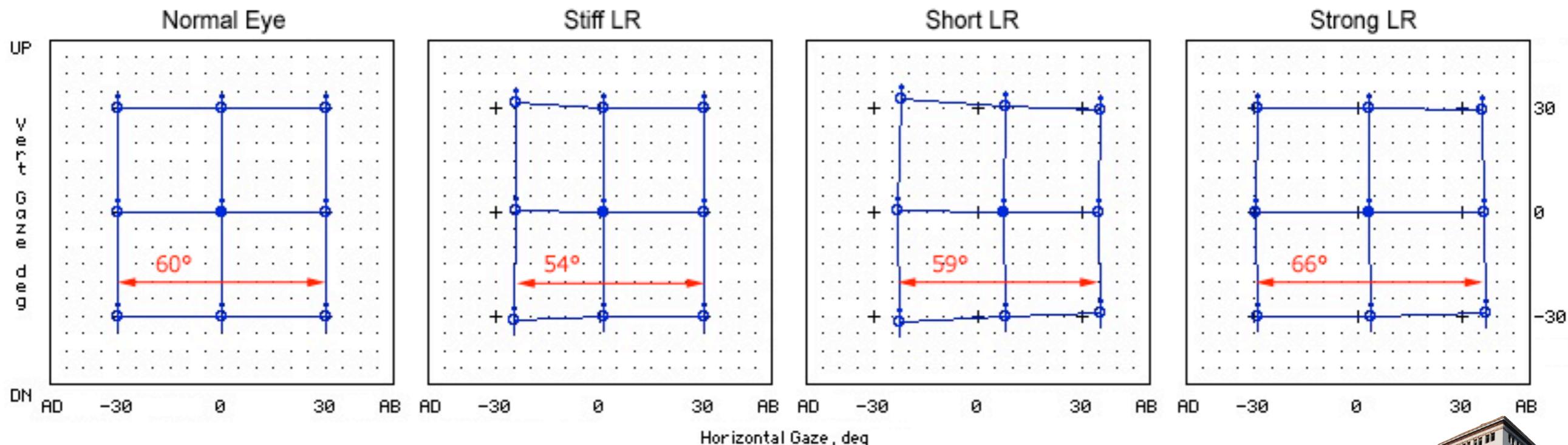
Muscle Strengthening With Bupivacaine

- 注射器图标 Bupivacaine injection is currently the only pharmacologic agent clinically shown to strengthen and shorten extraocular muscles. Myogenic growth factors IGF & FGF have been investigated, but only in animals.
- 注射器图标 Long used as an anesthetic in cataract surgery, bupivacaine, inadvertently injected into a muscle, was found to sometimes cause strabismus.
- 注射器图标 Initially attributed to simple myotoxic damage, careful observation of its clinical time course showed more complex sequelae, suggesting both increased contractility and elevated stiffness (Goldchmit & Scott 1994).
- 注射器图标 We later clarified that bupivacaine injection induces modest hypertrophy, muscle shortening, and significant, stable alignment corrections.+
- 注射器图标 Bupivacaine injection is currently an office procedure performed under topical anesthesia in cooperative adults, and has been used as an alternative to strabismus surgery to treat moderate-sized, non-paralytic, non-restrictive strabismus since 2006.
- 注射器图标 Stability of alignment correction has been documented up to 5 years.



BPX Increases Muscle Contractility, Not Just Stiffness

- 注射器图标 Inadvertent bupivacaine injection generally results, after recovery, in increased range of motion in the field of action of the injected muscle (Goldchmit & Scott 1994).
- 注射器图标 Modeling made it clear that only increased contractile force, and not increased stiffness, could increase range of motion.
- 注射器图标 (Increased stiffness alone tends to decrease range of motion.)



Might bupivacaine injection, then, be a
treatment for weak muscles?



Bupivacaine injection of eye muscles to treat strabismus

Alan B Scott, Danielle E Alexander, Joel M Miller

Br J Ophthalmol 2007;91:146–148. doi: 10.1136/bjod.2006.110619

- 注射器图标 BPX, 4.5 ml at 0.75%, was injected into the RLR of a patient with 14^Δ esotropia & diplopia.
- 注射器图标 Paresis lasted 7 days.
- 注射器图标 The RLR regained its abducting ability over the next 33 days, and alignment improved to 4^Δ esophoria.
- 注射器图标 Diplopia was resolved.
- 注射器图标 MRI showed size increase of the RLR.

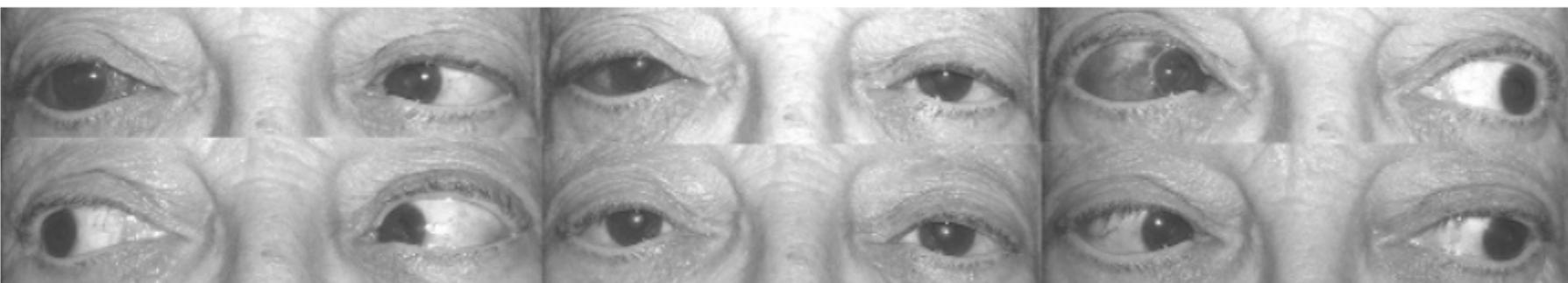


Figure 1 The patient immediately after bupivacaine injection (above), and at 33 days after injection (below). Informed patient consent was obtained for publication of this figure.



Bupivacaine injection of the lateral rectus muscle to treat esotropia

Alan B. Scott, MD, Joel M. Miller, PhD, and Kevin R. Shieh, BS

J AAPOS **2009;13:119-122**

注射器图标 Bupivacaine, in volumes 1.0 - 4.5 mL and concentrations 0.75 - 3.0%, was injected into one LR in each of 6 patients with comitant esotropia, guided by the electrical activity recorded from the needle tip.

注射器图标 Clinical alignment measures and MRI scans were collected before and at intervals after injection.

注射器图标 Four patients showed improved eye alignment, averaging 12^Δ , measured an average of 367 days after the last injection. Two were substantially unchanged.

注射器图标 Injected muscles enlarged 6.2% on average.

注射器图标 There was a modest positive correlation ($r = 0.65$) between alignment change and muscle enlargement.



FIG 2. Patient 3: preinjection, 25^Δ esotropia (A); 15^Δ esotropia before second injection, 161 days after first injection (B); and 11^Δ esotropia on day 417 after second injection (C).



Increasing the Effectiveness of BPX Injection



- 注射器图标 Injection of small dose of Botox in the antagonist muscle weakens it for a few weeks, and we theorized that would prevent stretching of the bupivacaine-injected muscle, allowing it to regenerate shorter than otherwise.
- 注射器图标 Conversely, we thought it might be possible to lengthen muscles with BPX injection in the agonist only, but this was not successful.
- 注射器图标 A few of our patients received BPX with epinephrine on the theory that vasoconstriction would increase BPX effectiveness by prolonging its contact with muscle tissue. These patients enjoyed generally larger corrections, but we cannot conclude this was an effect of the epinephrine because these patients also got higher doses of BPX and BTXA.



TREATING STRABISMUS BY INJECTING THE AGONIST MUSCLE WITH BUPIVACAINE AND THE ANTAGONIST WITH BOTULINUM TOXIN

BY Alan B. Scott MD*, Joel M. Miller PhD, AND Kevin R. Shieh BS

Trans Am Ophthalmol Soc / 107 / 2009

- 💉 We therefore treated 7 patients with comitant horizontal strabismus (2 had partial LR paralysis), injecting the agonist muscle with BPX at 0.75–3.0%, and the antagonist with Botox at about half the usual therapeutic dose.
- 💉 Correction averaged 19.7^Δ at 193 days after injection.
- 💉 Muscle volume by MRI increased by 5.8% at 158 days.
- 💉 One LR palsy patient without LR atrophy was changed 55^Δ ; the other, with LR atrophy, was corrected only 4^Δ . BPX does not appear to strengthen atrophic muscles.
- 💉 Injections of BPX & Botox yielded corrections roughly twice those reported from BPX injection alone.



Extraocular Muscle Scan Analysis

We then sought to study muscle size more carefully.

注射器图标 Scan planes were at least roughly perpendicular to the muscle's long axis

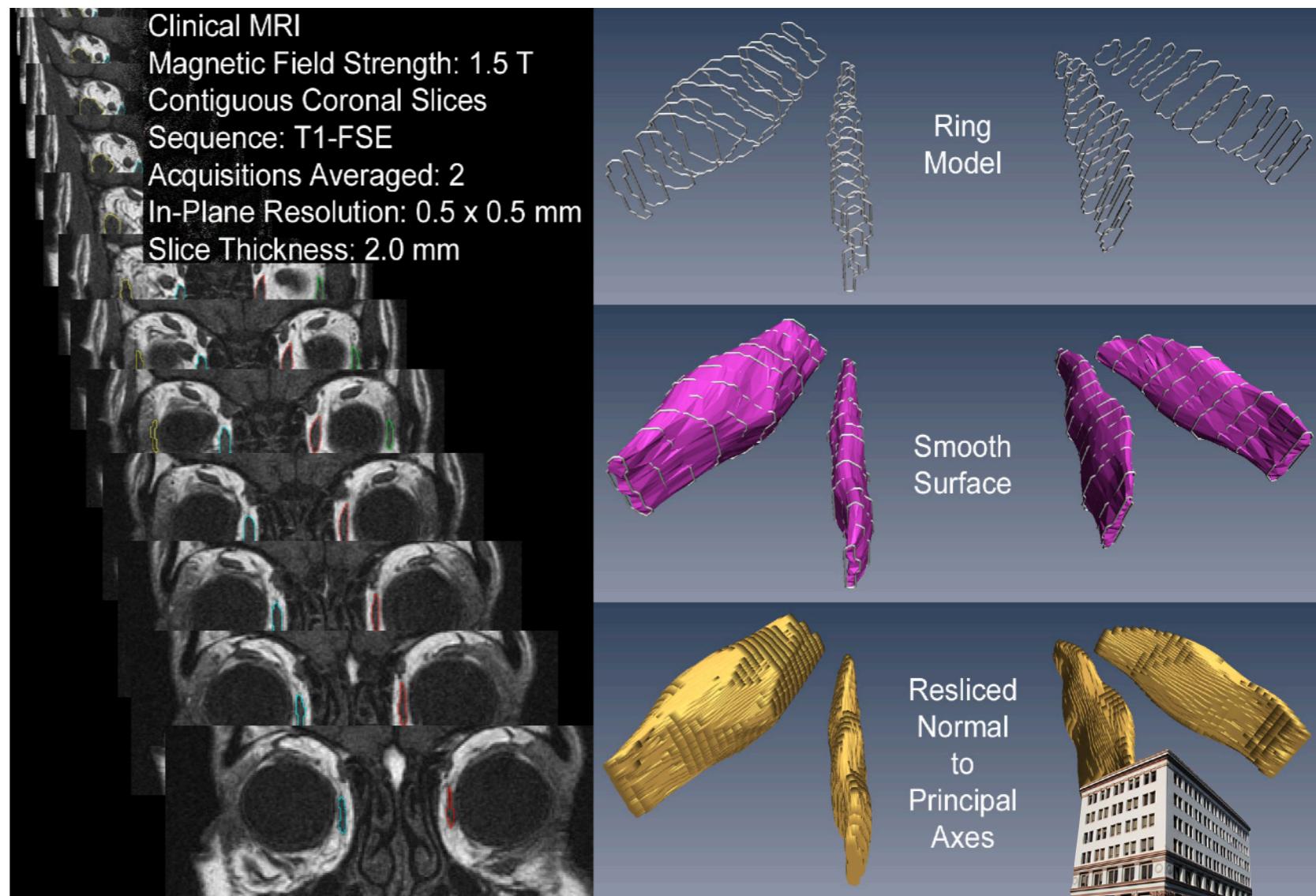
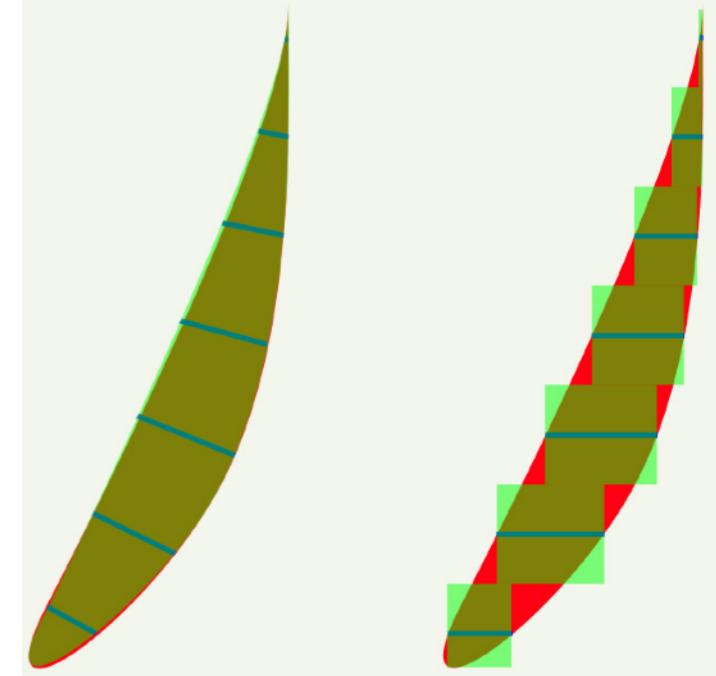
- To view muscle against contrasting orbital fat.
- To minimize volume averaging.

注射器图标 Accurate volumes were computed, and selection biases avoided, by imaging & analyzing essentially the entire muscle.

注射器图标 3D reconstruction gave accurate volume estimates

- Avoiding “stacked block” errors.
- Giving true crossections.

注射器图标 Operator errors & biases were addressed by employing multiple independent readers.



Bupivacaine Injection Remodels Extraocular Muscles and Corrects Comitant Strabismus

Joel M. Miller, PhD,¹ Alan B. Scott, MD,² Kenneth K. Danh, BS,² Dirk Strasser, BSS,² Mona Sane, MD²

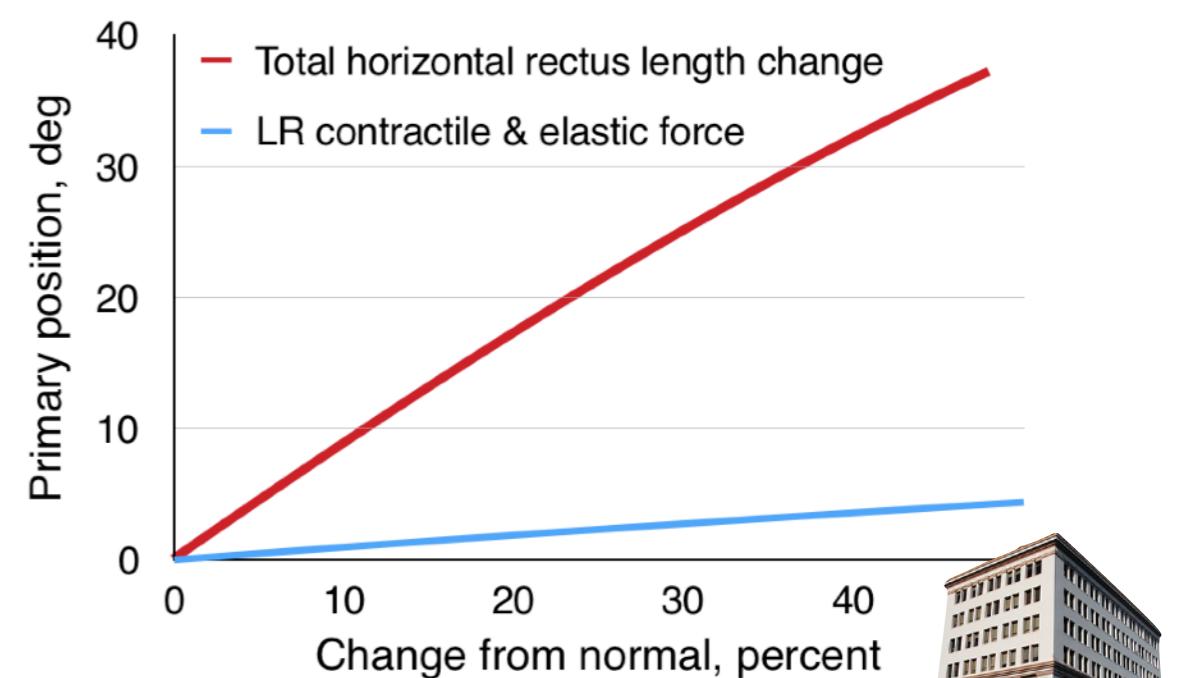
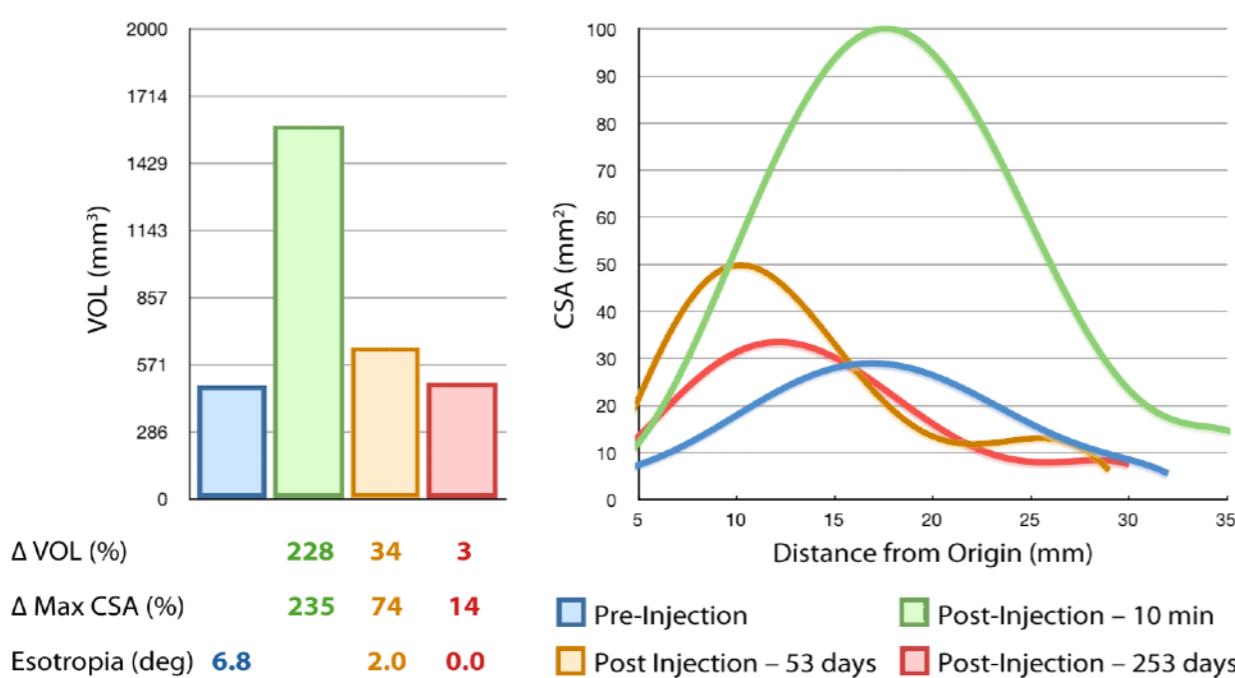
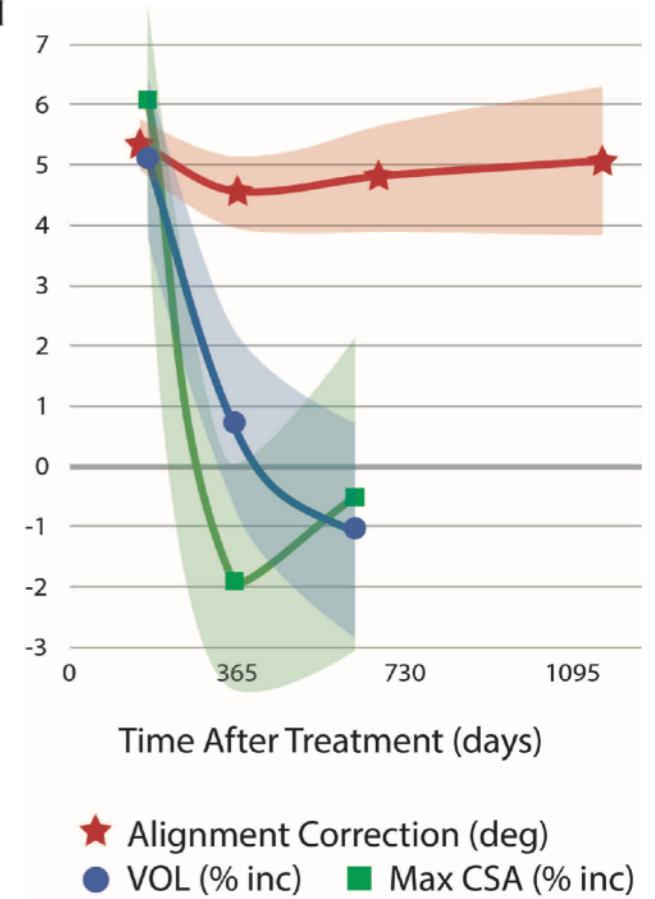
Ophthalmology 2013;120:2733-2740 © 2013 by the American Academy of Ophthalmology

Thirty one patients with comitant horizontal strabismus received BPX injections in LR or MR. Sixteen of these, with large deviations, also received Botox injections in the antagonist. Thirteen needed a 2nd treatment.

Alignment corrections were stable over 3 yrs.

Six months after injection, muscle volume had increased by 6.6%, and maximum crossectional area by 8.5%, gradually relaxing to pre-treatment values thereafter.

Orbit™ 1.8 modeling suggests that following transient increases in muscle size, BPX treatment results in stable changes in muscle lengths, without damage to extraocular biomechanics.



Pharmacologic Injection Treatment of Comitant Strabismus

Iara Debert, MD, PhD ^{1,2,3,4}, Joel M Miller, PhD ^{1,2}, Kenneth K Danh, BS ^{1,2}, Alan B Scott, MD ^{1,2}



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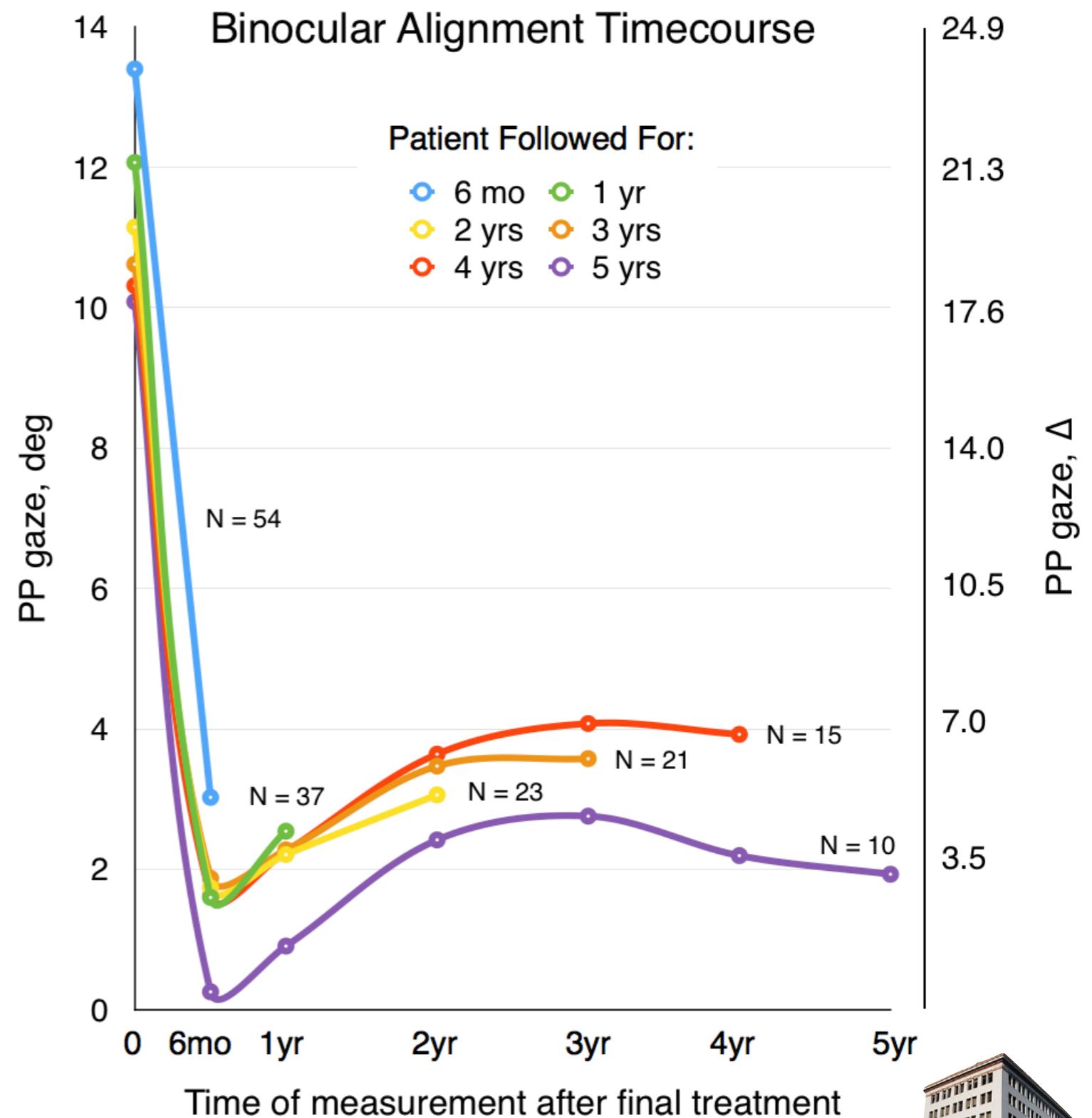
Our most recent report supports & extends earlier findings.

- 💉 55 adult comitant horizontal strabismus patients, 29 of whom had one or more unsuccessful strabismus surgeries, and 4 of whom had had other orbital surgeries.
- 💉 About half had esodeviations, and received BPX injections in an LR, some with Botox in the antagonist MR, and half with exodeviations received BPX in an MR, some with Botox in the antagonist LR.
- 💉 A second treatment (BPX, Botox, or both) was given to 27 patients who had residual strabismus after the first treatment. Five patients required additional injections.



Results

- 注射器图标 Misalignment of 23.8^Δ (13.4°) was reduced at 28 mo by 16.0^Δ (9.1°)
- 注射器图标 Successful outcomes in 56% of patients (residual deviations $\leq 10^\Delta$).
- 注射器图标 66% of patients with initial misalignments $\leq 25^\Delta$ enjoyed successful outcomes, with corrections averaging 13.2^Δ (7.5°).
- 注射器图标 40% of patients with larger misalignments had successful outcomes, with corrections averaging 20.9^Δ (11.8°).
- 注射器图标 Stability of corrections was measured to 5 years.



Clinical Notes

- 注射器图标 Marked muscle weakness due to myofibrillar destruction, and some inflammation related to fiber necrosis, diminishing over a week. (Botox in the antagonist takes effect on day 2-3, so agonist and antagonist are about equally weakened, and eye position is not greatly altered during this time).
- 注射器图标 Progressive improvement in eye alignment over 3-4 weeks.
- 注射器图标 BPX dose must be no more than to 90 mg to avoid chemosis and enduring tissue change.
- 注射器图标 In > 200 EMG-guided BPX injections, there have been no instances of globe perforation, optic nerve damage, or vision loss, and no cases of systemic toxicity.

Initial Deviation ($^{\circ}$)	BPX			BTXA (u)
	Vol (mL)	Conc (%)	Epinephrine (μ g)	
6 - 12	1.25 - 2.00	1.50 - 2.50	0	0.0
13 - 30	2.50 - 3.00	1.50 - 2.75	5 - 10	1.5 - 2.5
> 30	3.00	3.00	5 - 10	2.5 - 5.0



Repair or Regeneration?

Muscles are extraordinarily resilient, with multilevel mechanisms for repair & adaptation.

Minor Muscle Damage Is Repaired:

- 💉 Routine repairs may be done by resident myonuclei, without satellite cell (SC) involvement.
- 💉 “Microdamage” (eg, muscle strain), likely involves SC activation, adding myonuclei to existing cells.
- 💉 Optimal Therapeutic Repair?: BPX effect tuned for SC activation & addition of myonuclei, which may permanently increase a cell’s protein synthetic capacity, resulting in stable hypertrophy.

Severely Damaged Muscles Are Regenerated:

- 💉 Following sarcolemmal disruption, myofibril dissolution, invasion of macrophages, and SC activation. SCs fuse with one another, or to undamaged portions of a fiber.
- 💉 Optimal Therapeutic Regeneration? Why are regenerated fibers bigger and stronger?
 1. Perhaps growth or other factors cause replacement fibers to be abnormally large.
 2. Perhaps, instead, small weak muscle fibers are preferentially damaged, so that even if replacement fibers had a normal size distribution, mean fiber size would increase.
 - Normal overloading might preferentially damage small, weak fibers.
 - BPX injection: Small cells have a larger surface (over which to absorb BPX) relative to volume (in which to cope with the metabolic consequences).
 - There might therefore be an optimal BPX concentration, a dose that would destroy only small fibers.
- 💉 None of these mechanisms are mutually exclusive and might have clinically distinguishable effects on so inhomogeneous a tissue as EOM.



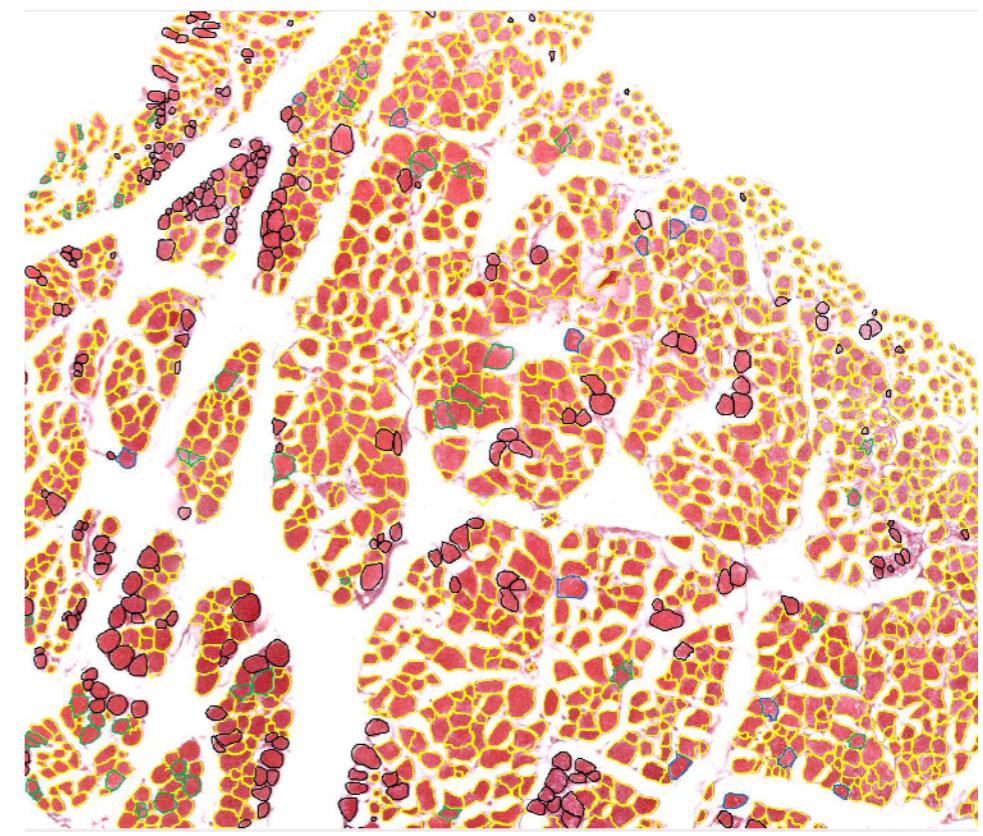
How Does BPX Change Muscle Fiber Size Distribution?

The first histological question to answer!

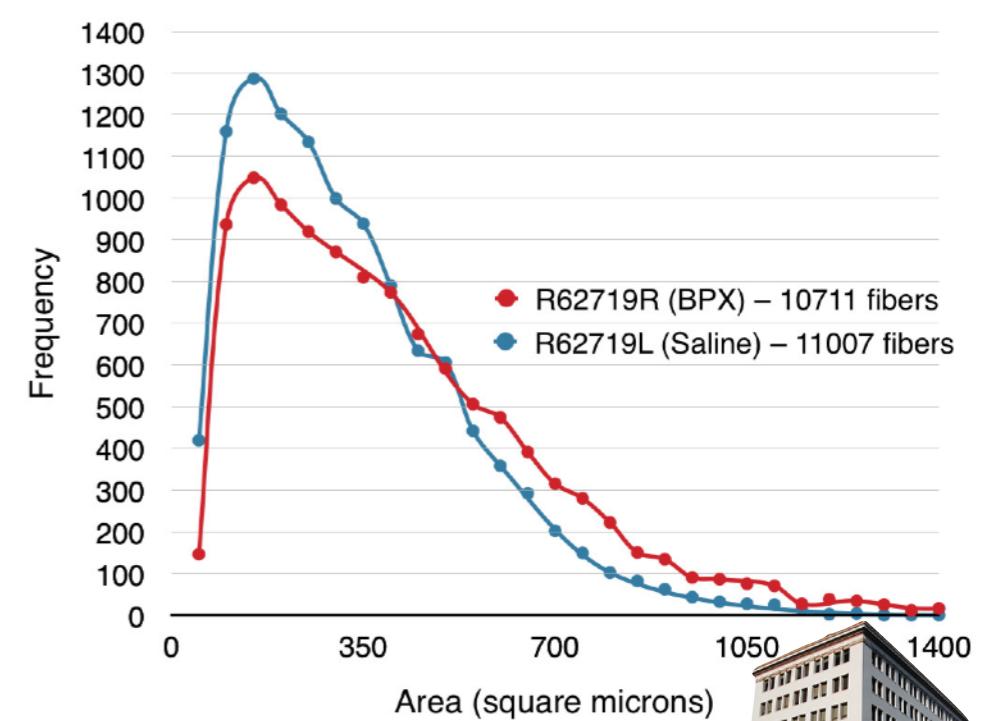
- 注射器 Quantitative EOM histology has required sampling because of the many thousands of fibers in a crossectional slice, but it is difficult to avoid bias.
- 注射器 We've developed an operator-aided automatic process to segment essentially all the fibers in a section, calculating fiber sizes and other statistics, while excluding voids, connective tissues, blood vessels, and nerves. Exhaustive measurement is achieved with only the labor normally required for sampling.
- 注射器 Early results suggest that BPX injection changes the distribution of muscle fiber diameters in favor of larger fibers, clarifying the nature of the muscle size changes and alignment corrections observed in the clinic. Time-course studies may tell if selective destruction or biased rebuilding is responsible.



注射器 Talita Malta e Cunha is working on this project.



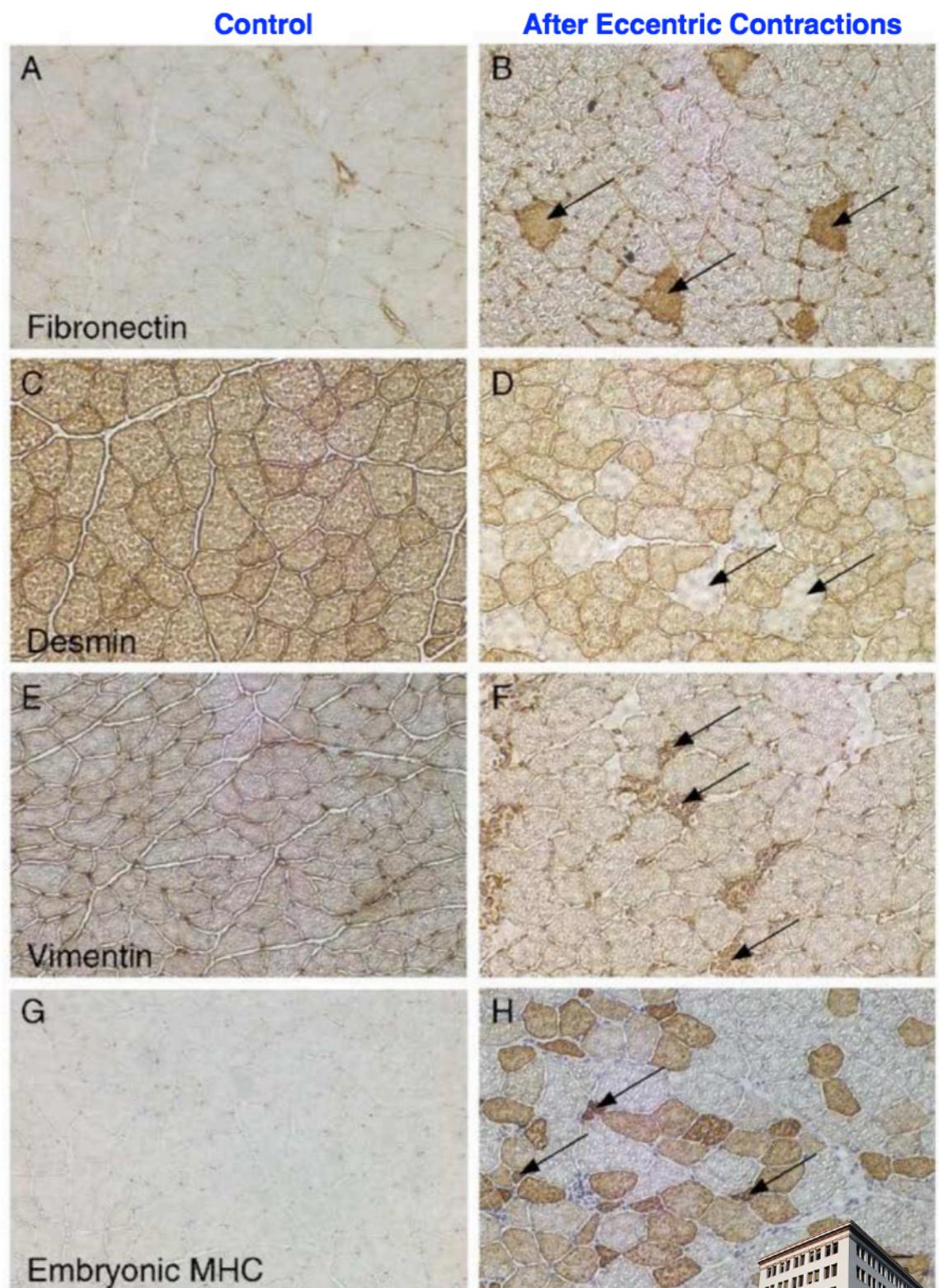
Muscle Fiber Crossections
30 Days After Injection



Identifying BPX-Damaged Muscle Fibers

Another way to detect selective damage is with immunohistochemistry.

- Cells with included fibronectin have lost their permeability barrier.
- Damaged cells that lose immunostaining for desmin.
- Inflammatory cells label positively for vimentin.
- Embryonic myosin heavy chain indicates regenerating fibers.
- Abnormal myofiber permeability can also be detected by uptake of low molecular weight dyes, such as Evans blue or procion orange.



From Peters et al 2003



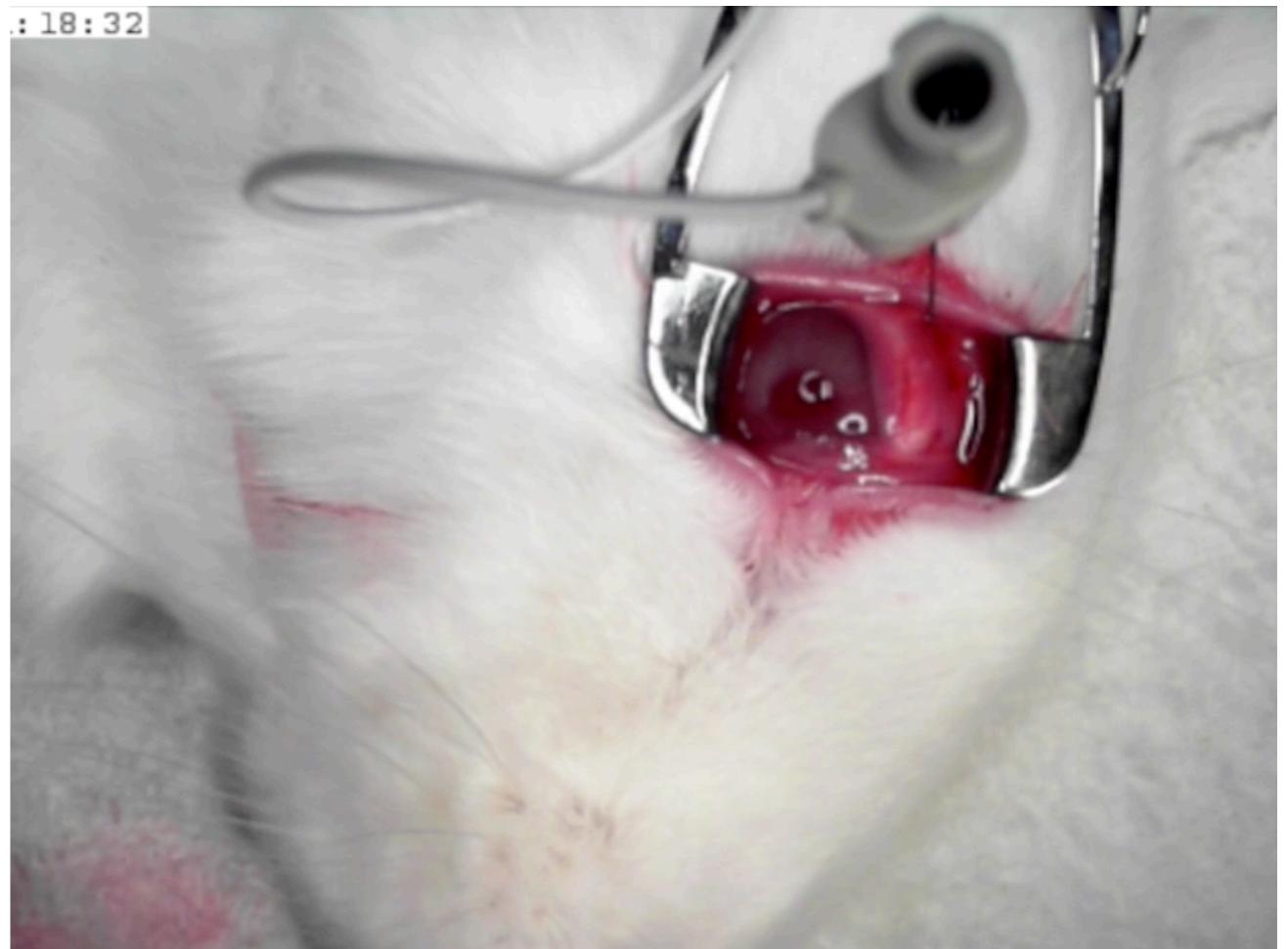
BPX Treatment Of Children

- 💉 Most strabismus patients are children, in whom early correction can facilitate normal visual and social development.
- 💉 But there is concern that such general anesthesia as is required for conventional surgery may damage the developing brain (McGowan & Davis 2008; Flick et al 2011; McCann 2011; Ing et al 2012; Stratmann et al 2014).
- 💉 It has therefore been recommended that anesthetic procedures in young children be kept brief (Good 2014).
- 💉 Botox® may be best injected using EMG guidance, which is only possible in alert, cooperative adults.
- 💉 Botox can also be effective when injected at the insertional end of a muscle, and Mendonça Forceps make it possible to inject Botox in children with minimal anesthesia.
- 💉 Bupivacaine, however, must be distributed along the length of a muscle, and an appropriate targeting technique is needed that is compatible with brief anesthesia.



Stimulation-Guided Injection

- 針 In anesthetized rabbits, we determined it was possible to tell the location of the tip of an injection needle by the stimulation-evoked eye movement.
- 針 Horizontal, vertical, and torsional movements identify muscles.
- 針 Alternatively, by holding a muscle, one can evaluate its contractile force.
- 針 Low movement thresholds, and absence of globe retraction and other signs of diffuse stimulation, indicate good needle placement.
- 針 Negative 0.5-1.5 mA pulse trains at ~200 Hz appear optimal.



SRF Stim-EMG 1.0 by Bak Electronics

- 注射器图标 Battery powered, microprocessor controlled.
- 注射器图标 EMG Mode – for conventional EMG-guided injection, with output to an onboard speaker and an external recording device.
- 注射器图标 STIM Mode – for stimulation-guided injection:
 - Negative 500 μ s wide pulses.
 - 0.2 – 5.0 mA.
 - 150 – 250 Hz.
 - Button or foot-switch stimulation control.



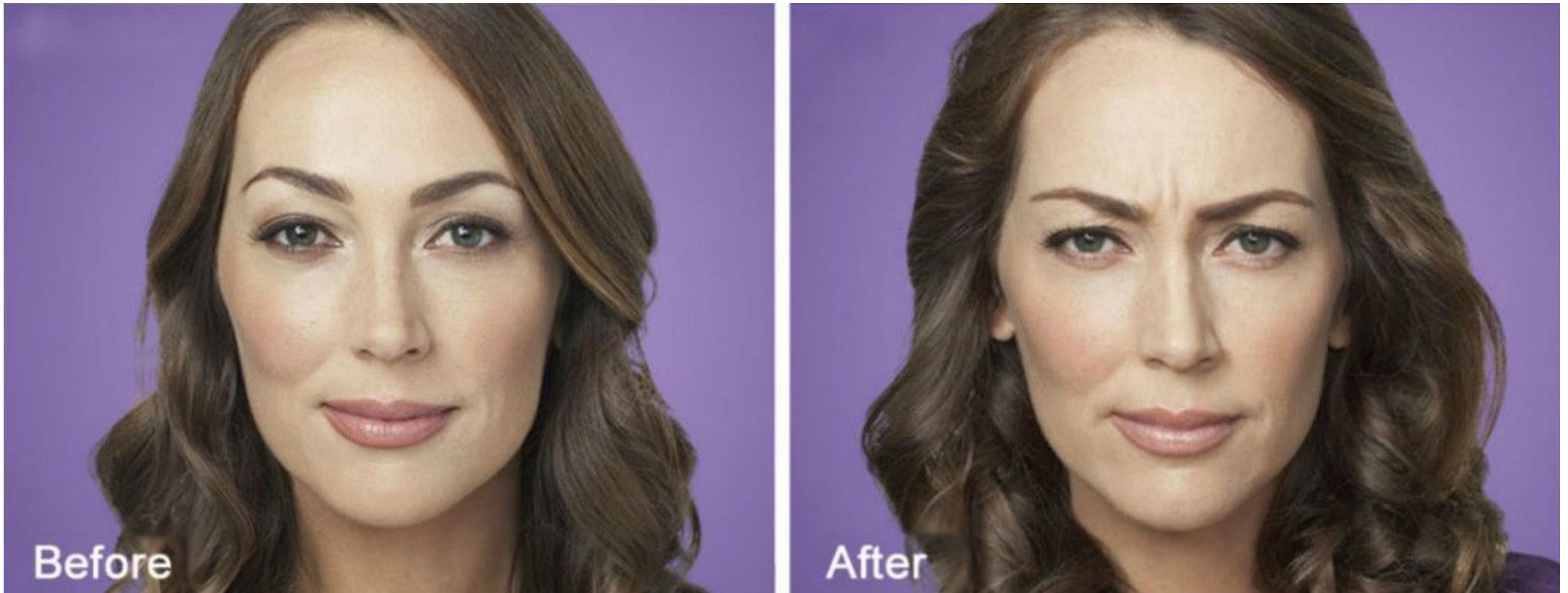
Increase & Decrease
• Stimulation Current
• Stimulation Frequency
• Speaker Volume

Stimulate!

Mode: ES or EMG
Power



Yet Another Cosmetic Neurotoxin?



Before

After

- 💉 Do your colleagues have difficulty taking you seriously?
- 💉 Do people see you as “just another pretty face”?
- 💉 Now ... you can get instant gravitas!
- 💉 Now ... there's Bupivacaine Cosmetic!!!



Questions?

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eidactics.com

eidactics.com/projects/s-k

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