# Methods and Perceptual Thresholds for Short-Term Electrical Stimulation of Human Retina with Microelectrode Arrays

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**Purpose.** To report methods for performing epiretinal electrical stimulation with microfabricated electrode arrays and determining perceptual thresholds on awake human volunteers during acute surgical trials.

**Methods.** Four hypotheses were tested: (1) epiretinal stimulation can be performed during acute experiments without obviously damaging the retina or degrading vision or the health of the eye; (2) perception can be obtained 50% of the time in blind patients with charge densities below published safety limits; (3) the minimal charge needed to induce perception would be higher in patients with more severe retinal degeneration; and (4) threshold charge would be lower at shorter stimulus durations. Five subjects with severe blindness from retinitis pigmentosa and one with normal vision (who underwent enucleation of the eye because of orbital cancer) were studied. Electrical stimulation of the retina was performed on awake volunteers by placing a single 250-$\mu$m diameter handheld needle electrode or a 10-$\mu$m thick microfabricated array of iridium oxide electrodes (400-, 100-, or 50-$\mu$m diameter) on the retina. Current sources outside the eye delivered charge to the electrodes. Assessment of damage was made by observing the clinical appearance of the eyes, comparing pre- and postoperative visual acuity, obtaining retinal histology in one case, and comparing perceptual thresholds with published safety limits.

**Results.** No clinically visible damage to the eye or loss of vision occurred. Even at sites removed from stimulation, histology revealed swollen photoreceptor inner and outer segments, which were believed to be nonspecific findings. Percepts could not be reliably elicited with 50-$\mu$m diameter electrodes using safe charges in one blind patient. With the two larger electrodes, only the normal-sighted patient had thresholds at charge densities below 0.25 and 1.0 millicoulombs (mC)/cm$^2$ for 400- and 100-$\mu$m diameter electrodes, respectively, which is one seemingly reasonable estimate of safety derived from the product of charge per phase and charge density per phase. In blind patients, thresholds always exceeded these levels, although most were close to these limits in patient 6. The range of charge density thresholds with the 400-$\mu$m electrode in blind patients was 0.28 to 2.8 mC/cm$^2$. The normal-sighted patient had a threshold of 0.08 mC/cm$^2$ with a 400-$\mu$m electrode, roughly one quarter of the lowest threshold in the blind patients. Strength–duration curves obtained in two blind patients revealed the lowest threshold charge at the 0.25- or 1.0-ms stimulus duration.

**Conclusions.** Threshold charge densities in severely blind patients were substantially higher than that in a normal-sighted patient. Charge densities in blind patients always exceeded one seemingly reasonable estimate of safe stimulation. The potential adversity of long-term stimulation of the retina by a prosthesis has yet to be determined. (*Invest Ophthalmol Vis Sci.* 2003;44:5355–5361) DOI:10.1167/iovs.02-0819

A retinal prosthesis has the potential to restore vision to patients with blindness due to retinitis pigmentosa (RP) and age-related macular degeneration.[1–10] In both conditions, there is relative sparing of ganglion cells,[6,11–13] which connect the eye to the brain. A retinal prosthesis could theoretically provide vision by artificially stimulating the epi- or subretinal surface.[4,14–19]

Our primary objective was to transfer techniques for use of ultrathin electrode arrays developed in animal experiments to humans. Our arrays contacted the retina, which provided an opportunity to obtain lower and potentially safer thresholds than previously reported.[20,21] We addressed another fundamental question—the quality of induced percepts—in a study reported in a companion paper in this issue.[22]

## Methods

An online Appendix (available at *http://www.iovs.org/cgi/content/full/44/12/5355/DC1*) provides additional information regarding methods and results, and an expanded discussion of our findings and their implications.

### Volunteer Selection

The protocol was approved by the Massachusetts Eye and Ear Infirmary and the Massachusetts Institute of Technology and adhered to the provisions of the Declaration of Helsinki. Participants could not have vision that initially exceeded hand motion perception in the worse eye, which was always the eye studied. After four experiments, the criterion was changed to 20/800 (Table 1). Volunteers underwent a medical examination and (all but one) psychiatric screening. One volunteer with normal vision whose eye was removed because of orbital cancer was studied.

### Stimulation Electronics and Electrodes

Ten current sources (Fig. 1) simultaneously distributed charge-balanced, biphasic pulses (Fig. 2) sequentially along one column of a microelectrode array (Fig. 3). Stimulation continued until the "pulse train duration" (typically 1.5 seconds, occasionally up to 4.0 seconds)

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**TABLE 1.** Demographic and Clinical Details of Volunteers

| Volunteer | Gender | Age (y) | Duration of Legal Blindness* (y) | Visual Acuity (Eye Studied) | Diagnosis | Lowest Threshold Charge Density, 400 μm Microfabricated Electrodes (4 ms Stimulus Duration) |
|---|---|---|---|---|---|---|
| 1 | M | 42 | 25 | Hand motion | Retinitis pigmentosa/Usher syndrome | — |
| 2 | M | 41 | 22 | Hand motion | Retinitis pigmentosa | — |
| 3 | F | 68 | 15 | Hand motion | Retinitis pigmentosa | 1.54 mC/cm$^2$† |
| 4 | F | 57 | — | 20/20 | Normal eye; orbital cancer | 0.08 mC/cm$^2$† |
| 5 | M | 28 | 11 | 20/1000 | Retinitis pigmentosa | 0.64 mC/cm$^2$ |
| 6 | M | 47 | 15 | 20/800 | Retinitis pigmentosa | 0.32 mC/cm$^2$ |

All blind patients had severely abnormal visual fields by Goldmann perimetry testing, with isolated islands of vision, severe constriction, or both.

* Vision of 20/200 or worse.

† These values are normalized to those of patients 5 and 6. See online Appendix for method of normalization.

had been reached (see online Appendix). All but the first experiment were initiated with a monopolar, glass-insulated, 250-μm platinum-iridium wire (Frederick Haer Co., Brunswick, ME). If definable percepts were obtained, an array was inserted (Table 2).

## Surgery

Ocular akinesia was achieved with botulinum toxin. Topical anesthesia generally sufficed, although intravenous remifentanyl was needed occasionally with some surgical manipulations. A three-port, pars plana approach was used. Array insertion required elongation of the standard 0.9-mm port to 3.5 mm (Fig. 4). A posterior vitrectomy was performed only on patients 5 and 6 to facilitate apposition of the array to the retina.

## Summary of Testing Methods

Hypothesis-driven testing was performed. The return electrode was on an arm for monopolar stimulation, and on an array for bipolar stimulation. Intraocular light was never used during testing with arrays. Trials began with a tone followed 1 second later by electrical stimulation. Thresholds with the needle electrode were obtained approximately 1-mm above the retina, whereas arrays contacted the retina. Initial stimuli were subthreshold, and amplitudes were doubled until perception was reported. "Threshold" was defined as the lowest current (for a given duration) at which percepts were reported 50% of the time or more, if higher currents also met this criterion. At least four trials were necessary to determine one threshold. Stimulus durations (negative pulse) were 100 μs to 16 ms (Table 3). Negative control trials (i.e., tone without electrical stimulation) were randomly inserted.

Experimental priorities and algorithms were established before surgery. During surgery, decisions about stimulus parameters were influenced by the reported percepts, which accounted for some technical variation across experiments, especially for testing "form" vision (i.e., the ability to distinguish one versus multiple points, lines versus points, and letters). Stimulation frequencies of 20 or 30 Hz were preferred, although other frequencies were needed for long-duration pulses (see online Appendix, Stimulation Electronics).

**FIGURE 1.** Electrical stimulation apparatus. Current sources are housed in the switch box. Each switch is connected by a multiwire cable to bonding pads on a printed circuit board (*small, square* structure, *left*), which was attached to the side of the patient's face during surgery. A microfabricated, polyimide ribbon cable connects the bonding pads to the stimulating electrodes, located at the distal end of the polyimide strip (*arrow*). Only the distal-most region of the polyimide strip containing the electrode array was inserted into the eye.

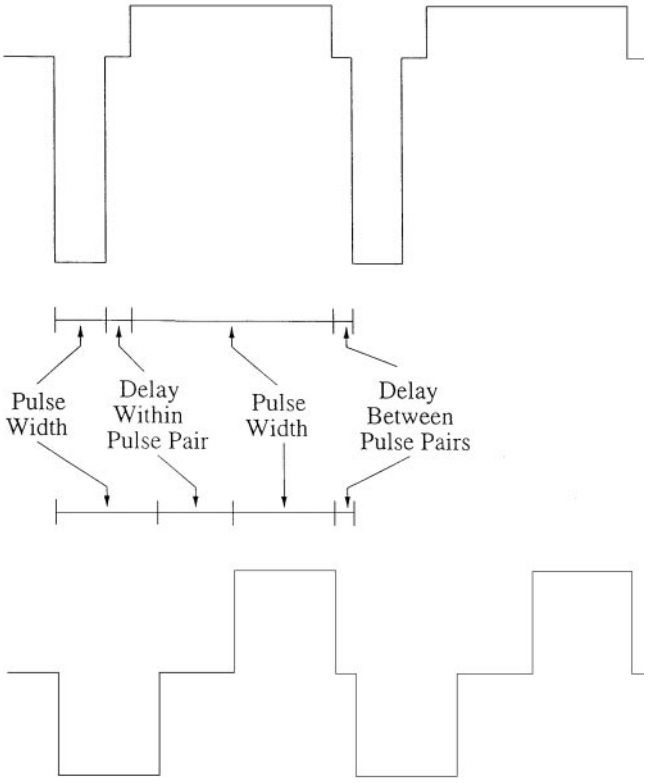


**FIGURE 2.** Stimulus current waveform 1 (*top*) and 2 (*bottom*). All stimuli were charged balanced. Waveform 1 was used in the first two experiments. In the first experiment, a 100-μs negative pulse was used. In the second experiment, the negative pulse ranged from 200 μsec to 2.5 ms. Waveform 2 was used for the other experiments (see Table 2). The delay between negative and positive pulses in a pulse pair was 10 μs in all experiments. The electronic stimulator added a 30-μs delay between pulse pairs (see Methods and online Appendix). For both waveforms, currents, thresholds, and durations (pulse duration) always are reported for the negative pulse. Current is reported per electrode.

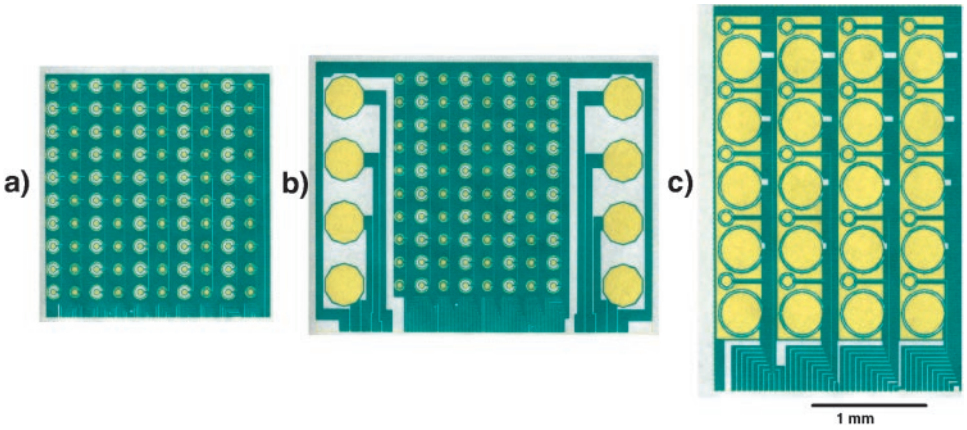


**FIGURE 3.** Geometry of the three generations of 10-$\mu$m-thick, polyimide electrode arrays. Electrode surfaces of all arrays were oxidized iridium. The first device (*left*) was a $10 \times 10$ array of 50-$\mu$m-diameter center electrodes, with center-to-center spacing of 220 $\mu$m. All center electrodes were surrounded by a concentric return electrode with an interelectrode space that alternated between columns as either a 20- or 40-$\mu$m gap. The second-generation (*middle*) device was an $8 \times 10$ array of 50-$\mu$m-diameter center electrodes, with center-to-center spacing of 220 $\mu$m. All electrodes were surrounded by a concentric return electrode with an interelectrode space that alternated between columns as either a 20- or 40-$\mu$m gap. Eight 400-$\mu$m-diameter electrodes with a vertical center-to-center spacing of 600 $\mu$m were aligned along the two end columns. These electrodes were not paired with a return electrode on the array. The third device (*right*) contained two interleaved $4 \times 5$ arrays of electrodes. The smaller electrodes were 100 $\mu$m in diameter with center-to-center spacing of 620 $\mu$m. The larger electrodes were 400 $\mu$m in diameter with center-to-center spacing of 620 $\mu$m. All electrodes were surrounded by a concentric return electrode with an interelectrode gap of 40 $\mu$m. For all electrodes except the large electrodes of the second array, center-to-center spacing between electrodes for the three generations of electrode arrays was the same vertically and horizontally. All the return electrodes were physically interconnected in each array. The *yellow* color indicates sites of electrode metal. The *teal* color indicates sites where a polyimide overlayer covered metal. The *white* color indicates sites of polyimide without underlying metal.

The goal of experiments 1 and 2 was to determine whether percepts could be induced within published charge safety limits. The goal of experiment 3 was to determine whether higher charges would yield more defined percepts; monopolar stimuli (6 or 30 Hz) were generally used. The goal of experiment 4 was to determine whether lower thresholds and better vision could be obtained in a normal-sighted volunteer; monopolar, 20-Hz, 2-ms pulses were used. The primary goal for experiments 5 and 6 was to obtain strength–duration curves; mostly monopolar, 20-Hz stimulation was used.

### Assessment of Damage from Surgery or Electrical Stimulation

We sought evidence of ocular injury by comparison of pre- and postoperative visual acuity, intraocular pressure, slit lamp evaluation and funduscopy and by retinal histology in one case. The potential for harm from electrical stimulation was judged by comparison of thresholds to published safety limits. Strength–duration curves obtained in two experiments provided a detailed assessment of threshold charge. Eye examinations were performed by us on the first 2 days after surgery and thereafter by arrangement with local ophthalmologists.

### Histology

The retina of the enucleated eye (volunteer 4) was fixed in 10% formalin, divided into eight $2 \times 2$-mm pieces taken at various eccentricities, dehydrated, and embedded in glycol methacrylate (JB-4; Polysciences, Eppelheim, Germany). Sections (2–4-$\mu$m thick) were stained with 1% neutral red and examined by light microscopy.

## RESULTS

Stimulation was monopolar unless otherwise indicated. Currents and durations are reported for negative pulses; currents are reported per electrode.

### Evolution of Experimental Technique

Experiment 1 yielded ill-defined percepts. The small electrode size too severely restricted the charge limits, which prompted us to make larger electrodes and a stronger current source. Experiment 2 produced similar results, despite the use of a much higher charge. We suspect that retinal degeneration (rather than electronics) compromised the outcome. Experiment 3 yielded some formed percepts, but thresholds were relatively high. This result motivated us to concentrate on obtaining strength–duration curves in experiments 5 and 6 to assess charge efficiency.

### Hypotheses

**Hypothesis 1.** Epiretinal stimulation can be performed during acute experiments without obviously damaging the retina or degrading vision or the health of the eye.

**TABLE 2.** Overview of Stimulation Methods

| Volunteer | Duration of Testing (min) | Single (Handheld) Electrode* | Electrode Array Generation† | Position of Electrode Array | Stimulus Waveform‡ |
|---|---|---|---|---|---|
| 1 | 14 | No | 1 | Peripheral macula | 1 |
| 2 | 79 | Yes | Array not used | — | 1 |
| 3 | 146 | Yes | 2 | Superotemporal periphery; superior macula | 2 |
| 4§ | 80 | Yes | 3 | Temporal edge of macula, along horizontal raphe | 2 |
| 5 | 265 | Yes | 3 | Temporal macula, just superior to horizontal raphe | 2 |
| 6 | 153 | Yes | 3 | Superior macula | 2 |

* Only monopolar stimulation was used for this electrode.
† See Figure 3 for details.
‡ See Figure 2 for details.
§ Normal sight; ocular cancer.

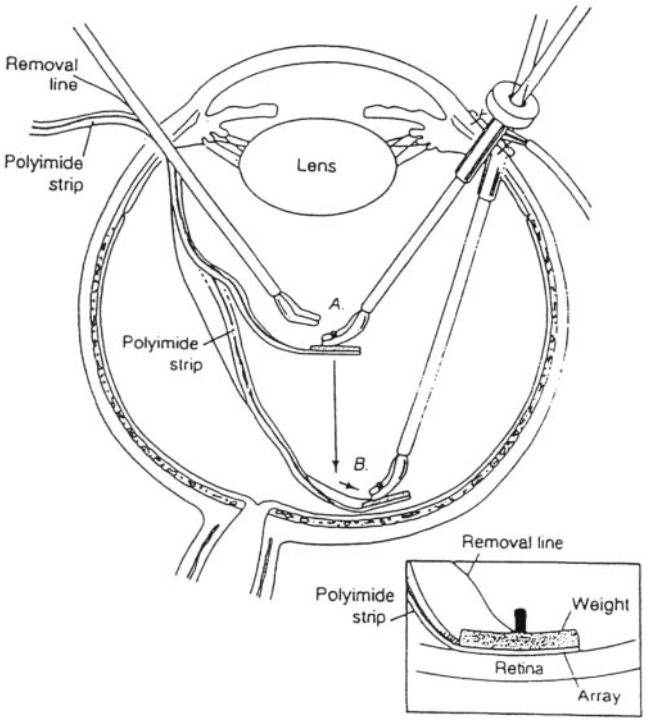


**FIGURE 4.** Cross-section schematic of an eye to illustrate the method of placement of the electrode array on the retina. The infusion port, used to maintain pressure within the open eye, is not shown. A sewn-on contact lens (Ocular Instruments Co., Bellevue, WA) and fixed fiberoptic light allowed visualization of the retina without touching the eye. The array was inserted through a pars plana incision (*top left*) and transferred to a second forceps (**A**), which was used to bring the array close to the retina (B). A thin suture attached to the end of the polyimide strip served as a removal line, which when pulled withdrew the array away from the retina safely. This maneuver precluded grasping the post with a forceps, which could inadvertently inflict damage on the retina. *Inset*: Positioning of the array on the retina after the array was gently advanced by injection of a synthetic viscoelastic made of hyaluronic acid. A gold weight (2 × 2 mm, 25 mg) glued to the array helped to maintain apposition of the array to the retina. The weight had relatively little mass and did not obviously distort the retinal surface.

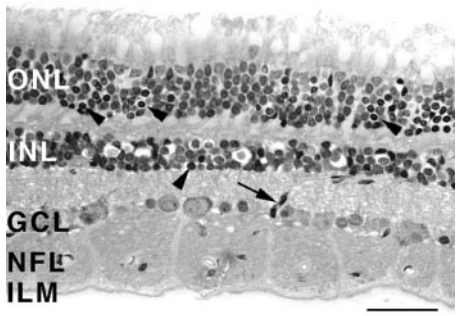


**FIGURE 5.** Retina of patient 4. The eye was removed during an exenteration for orbital cancer just after in vivo testing had been performed. This section is from the area where electrical stimulation had been performed. The region was identified by comparison of the anatomy of the major retinal blood vessels to a drawing that had been made during surgery. Swollen photoreceptor inner and outer segments and other swollen cells are seen. Numerous pyknotic nuclei (*arrowheads*) are evident. Similar appearances were observed in sections from retinal areas remote from the site of testing, which suggests that these changes were not related to electrical stimulation or placement of the array on the retina. There was no evidence of more specific damage at this site of stimulation. *Arrow* points to endothelial cells of a blood vessel. ONL, outer nuclear layer; INL, inner nuclear layer; GCL, ganglion cell layer; NFL, nerve fiber layer; ILM, inner limiting membrane. (1% neutral red stain). Bar, 50 μm.

Eye discomfort with intraocular pressure of 38 mm Hg developed after the first experiment. Medical therapy achieved normal pressure, which was verified up to day 17. One posterior subcapsular cataract advanced. No visual loss, discomfort, change in the appearance of the retina, or other potentially relevant problems were reported during a mean observation period of 32 months (range: 28–36) after surgery. Histology of the eye from the sighted patient showed swelling of photoreceptor inner and outer segments and other nonspecific changes (Fig. 5).

**Hypothesis 2.** Perception can be obtained at least 50% of the time in blind patients with charge densities below published safety limits.

Only single-electrode trials were considered. Reliable thresholds could not be obtained in the first two experiments. In experiment 3, a clear threshold was not obtained with 50-μm diameter electrodes. Accordingly, relevant data were recorded from the 100- and 400-μm diameter electrodes in

**TABLE 3.** Summary of Lowest Single-Electrode Threshold Measured during Each Experiment

| Volunteer | Electrode | 100 μs | 0.25 ms | 1 ms | 2 ms | 4 ms | 8 ms | 16 ms |
|---|---|---|---|---|---|---|---|---|
| 1 | Array | Indeterminate | | | | | | |
| 2 | Single needle | | | 3 mA (?) | | | | |
| 3 | Single needle | | | | | | 147 μA (?) | 98 μA |
| | Array, large electrode | | | | | | 441 μA | |
| | Array, 50 μm electrode | | | | | | Indeterminate up to 740 μA | |
| 4* | Single needle | | | | 500 μA | | | |
| | Array, large electrode | | | | 50 μA | | | |
| | Array, 100 μm electrode | | | | 12 μA | | | |
| 5 | Single needle | | | | 1.0 mA | | | |
| | Array, large electrode | | 1.5 mA | 800 μA | | 200 μA | | 150 μA |
| | Array, 100 μm electrode | | 1.3 mA | 435 μA | | 135–180 μA | | 60 μA |
| 6 | Array, large electrode | | 1.6 mA | 350 μA | | 100 μA | | 100 μA |
| | Array, 100 μm electrode | | | | | 150 μA | | |

Question mark indicates a value that was the best estimate for threshold, given that the criteria for threshold determination were not satisfied. All pulse durations, including the asymmetrical stimulation pulses used in experiments 1 and 2, are reported as values for the negative-phase pulse. In the last experiment, the single-needle electrode was used only qualitatively to elicit percepts and to locate more active areas of the retina prior to introducing the electrode array.

* Normal sight; orbital cancer.

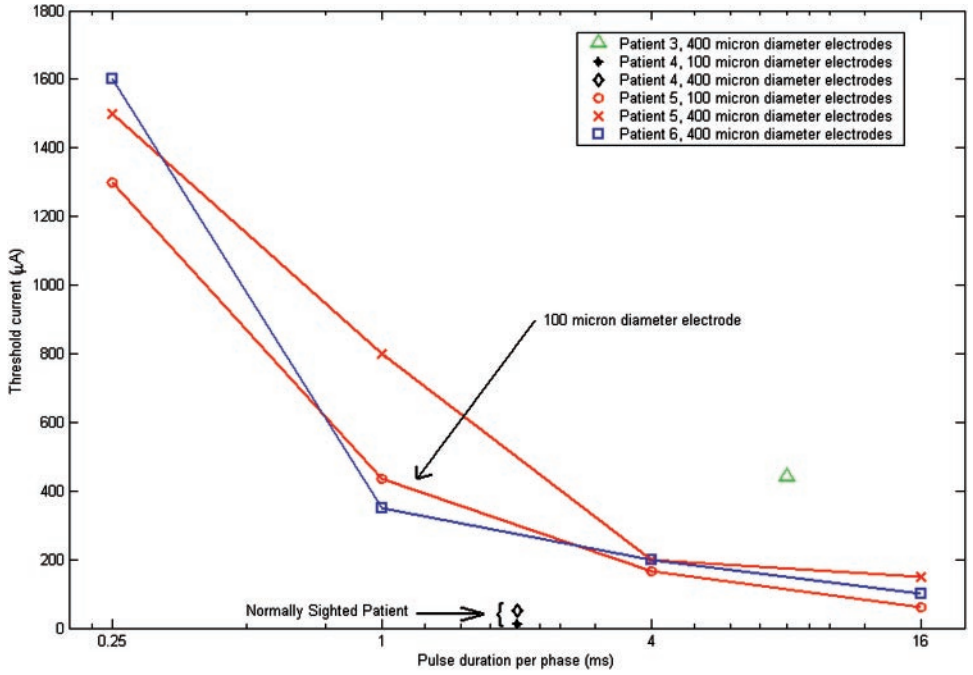


**FIGURE 6.** Strength–duration curves obtained with the third-generation array, with electrodes positioned at the temporal edge of the superior macula in experiments 5 and 6. Stimulation was monopolar at 20 Hz. Small- and large-diameter electrodes (100- and 400-$\mu$m, respectively) were used in experiment 5, whereas only the large electrode was used in experiment 6. The curves were similar with both electrode diameters. As an estimate of the rheobase (the current threshold in the limit of long-duration stimulus pulses), the measured current thresholds at 16 ms were used. The chronaxie (the pulse duration at which the threshold rises to twice the rheobase) was estimated by fitting the data by using a least-squares percentage error fit of the Hill equation as described by Ronner.[23] For the average of the two large electrode curves, the rheobase was 125 $\mu$A and the chronaxie was 2.3 ms. For the small electrode plot, the rheobase was 60 $\mu$A and the chronaxie was 4.4 ms. Strength–duration curves were not obtained in subjects 3 and 4. However, for reference, perceptual thresholds from these subjects using the same diameter electrodes are shown.

experiments 3, 5, and 6, especially the strength–duration curves (Figs. 6, 7). Threshold charge generally decreased with shorter pulses, with the lowest charge usually occurring at 0.25 ms. At this duration, charge density was 4.1 and 0.30 millicoulombs (mC)/cm$^2$ for the 100- and 400-$\mu$m electrodes, respectively. For blind patients, thresholds with 400-$\mu$m electrodes were 0.28 to 2.8 mC/cm$^2$. Safety limits are summarized in the Discussion section.

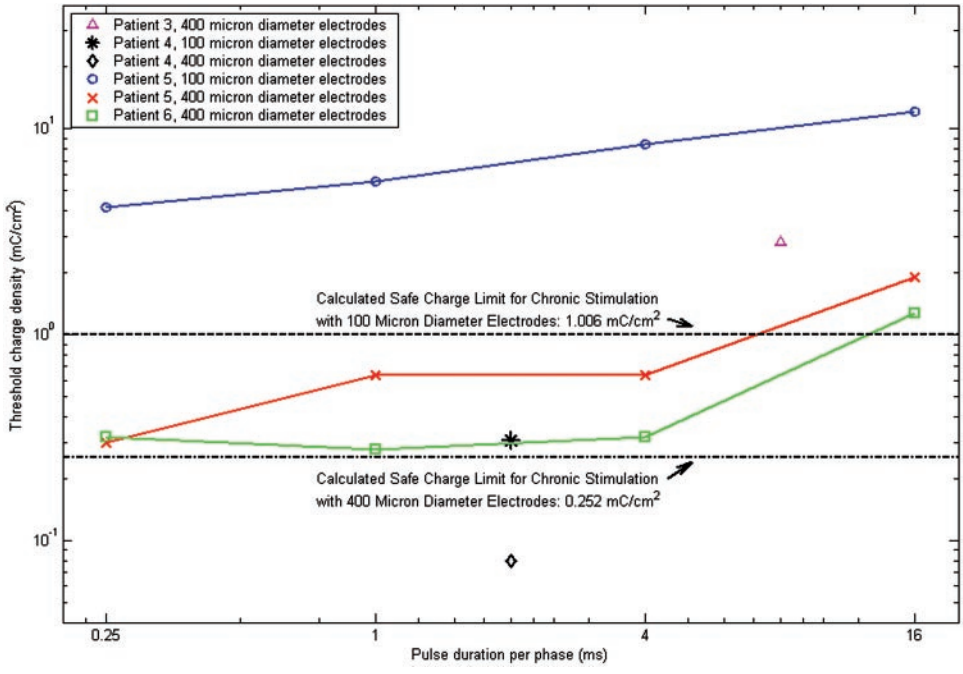


**FIGURE 7.** Strength–duration curves replotted in units of threshold charge density, which is a more relevant parameter for the assessment of safe limits for prolonged stimulation. Results were obtained with 400-$\mu$m-diameter electrodes in experiment 3, and 100- and 400-$\mu$m-diameter electrodes in experiments 4, 5, and 6. In the blind volunteers, charge density at 0.25 ms was 4.1 and 0.30 mC/cm$^2$ for the 100- and 400-$\mu$m electrodes, respectively. The two *dotted lines* represent biologically safe charge density limits calculated from one study.[26] The *upper line* is the calculated value for our small (ie, 100 $\mu$m diameter) electrode, and the *lower line* is the calculated value for our large (ie, 400 $\mu$m diameter) electrode. Other values for charge density safety have been suggested (see online Appendix and Discussion for more details).

**Hypothesis 3.** The minimal charge needed to induce perception is higher in patients with more severe retinal degeneration.

The normal-sighted patient's charge density threshold was 0.08 mC/cm$^2$ (400-$\mu$m diameter electrode, 2 ms), approximately one quarter that of any blind patient (Table 1). By comparison, threshold charge density at 4 ms was 4 times greater in the patient with 20/800 acuity and 8 and 19 times greater in the patients with 20/1000 and hand-motion vision, respectively. These results required normalization of thresholds to 4 ms, but qualitatively similar results held without normalization (see online Appendix, Part II, Data Analysis).

**Hypothesis 4.** Threshold charge is lower at shorter stimulus durations. The strength–duration curves (Fig. 7) support this hypothesis.

## Discussion

The first hypothesis asserted that epiretinal stimulation could be performed without obviously damaging the eye or degrading vision. By this definition, we succeeded, although a cataract progressed in one patient. Abnormalities were noted in the one histologically studied retina, but these changes were nonspecific and present in areas remote from stimulation. One patient developed elevated intraocular pressure, probably from high-density hyaluronic acid. Thereafter, we used standard-density material without complication. These seemingly favorable results do not preclude the possibility of occult damage.

The second hypothesis asserted that perception could be obtained 50% or more of the time in blind patients with charge densities below published safety limits. The outcome depends on the choice of a "safe" limit (see online Appendix).[24–26] One widely quoted limit, based on the electrode-to-fluid potential remaining below that which generates hydrogen or oxygen (ie, a physical versus a biological limit), is 1 mC/cm$^2$ for cathode-first stimulation with iridium oxide electrodes without DC bias,[25] which corresponds to our experiments. (That study also suggested that a positive 0.8-V bias raises the limit to 3.5 mC/cm$^2$.) Strength–duration curves of our blind patients showed thresholds below 1 mC/cm$^2$ for 400-$\mu$m diameter electrodes with 4-ms pulses or less, but above 3.5 mC/cm$^2$ for 100-$\mu$m diameter electrodes (Fig. 7).

Stimulation limits for biological safety are less well understood, and we are unaware of experimental data that closely relate to our methods. One model[26] based on electrical injury in feline cortex[24,27] predicts neural damage when the product of charge density per phase and charge per phase exceeds a certain threshold. Using a threshold of 79 $\mu$C$^2$/cm$^2$ per phase, rather than a more conservative limit of 32 $\mu$C$^2$/cm$^2$ suggested by Shannon[26] (see online Appendix), this model predicts limits of 0.25 and 1.0 mC/cm$^2$ for 400 and 100-$\mu$m diameter electrodes, respectively (Fig. 7). For both electrode sizes, only the normal-sighted patient had thresholds at charge–charge density products below these "safe" values. In blind patients, thresholds always exceeded these values, although most were close to the limits in patient 6.

The third hypothesis asserted that threshold charge increases with more severe blindness. Given the variation in stimulation parameters across experiments (see Evolution of Experimental Technique section and online Appendix), comparison of thresholds required a normalized standard (Table 1). Compared with the normal volunteer, threshold charge density for 400-$\mu$m electrodes at 4 ms was 4 times larger in the patient with 20/800 and 8 and 19 times larger in the patients with 20/1000 and hand-motion vision, respectively. Indeed, thresholds increased with the degree of blindness, which raises concern about whether severely blind patients could safely tolerate prolonged stimulation with an implanted prosthesis.

The fourth hypothesis was affirmed, with the strength–duration curves (Fig. 7) generally revealing the lowest threshold charge at 0.25 ms. This pursuit for the lowest threshold was motivated by the safety potentially gained from reduced electrochemical toxicity.

### Comparison to Prior Work

Our methods differ from those of Humayun et al.,[20] who first performed intraocular stimulation of human retina, in that we (1) used flexible, microfabricated arrays; (2) paralyzed the eye to achieve closer and more stable alignment between the electrodes and retina; (3) did not illuminate the eye during testing; (4) frequently interspersed control tests; (5) generally performed many more stimulations per subject; (6) obtained strength–duration curves; and (7) quantified the accuracy and reproducibility of responses. Humayun et al. found generally higher thresholds and a greater range of thresholds in blind patients (0.16–80 mC/cm$^2$ vs. 0.28–2.8 mC/cm$^2$ in our study), possibly due to variable separation between their handheld electrodes and the retina. Similarly disparate results were obtained in normal-sighted volunteers (the 0.8 and 4.8 mC/cm$^2$ with a 125-$\mu$m diameter wire thresholds of Humayun et al. versus 0.31 and 0.08 mC/cm$^2$ with 100 and 400 $\mu$m diameter electrodes in our study).[28] Technical factors, such as higher stimulation frequencies, sequential stimulation, or planar (versus slightly rounded) electrodes used in our study, may explain some differences in outcome. Our technique of using a paralyzed eye and our more detailed search for threshold are the most likely explanations for the less variable and lower thresholds in our study. No other data of this type are available on blind patients. By comparison, in two normal patients, Eckmiller et al. reported epiretinal thresholds (verbal communication) of 12 to 95 $\mu$A with biphasic 0.1 ms pulses, using five electrodes (500-$\mu$m diameter) (Eckmiller RE, et al. *IOVS* 2002; 43:ARVO E-Abstract 2848).

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