Factors Affecting Perceptual Thresholds in a Suprachoroidal Retinal Prosthesis

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Submitted: March 19, 2014
Accepted: August 19, 2014

PURPOSE. The suprachoroidal location for a retinal prosthesis provides advantages over other locations in terms of a simplified surgical procedure and a potentially more stable electrode-neural interface. The aim was to assess the factors affecting perceptual thresholds, and to optimize stimulus parameters to achieve the lowest thresholds in patients implanted with a suprachoroidal retinal prosthesis.

METHODS. Three patients with profound vision loss from retinitis pigmentosa were implanted with a suprachoroidal array. Perceptual thresholds measured on individual electrodes were analyzed as a function of stimulus parameters (return configuration, pulse configuration, pulse width, interphase gap, and rate), electrode (area and number of ganged electrodes), and clinical (retinal thickness and electrode–retina distance) parameters.

RESULTS. A total of 92.8% of 904 measurements made up to 680 days post implantation yielded thresholds (range, 44–436 nanocoulombs [nC]) below the safe charge limit. Thresholds were found to vary between individuals and to depend significantly on electrode–retina distance, negligibly on retinal thickness, and not on electrode area or the number of ganged electrodes. Lowest thresholds were achieved when using a monopolar return, anodic-first polarity, short pulse widths (100 µs) combined with long interphase gaps (500 µs), and high stimulation rates (≥400 pulses per second [pps]).

CONCLUSIONS. With suprachoroidal stimulation, anodic-first pulses with a monopolar return are most efficacious. To enable high rates, an appropriate combination of pulse width and interphase gap must be chosen to ensure low thresholds and electrode voltages. Electrode–retina distance needs to be monitored carefully owing to its influence on thresholds. These results inform implantable stimulator specifications for a suprachoroidal retinal prosthesis. (ClinicalTrials.gov number, NCT01603576.)

Keywords: retinal prosthesis, suprachoroidal, threshold, retinitis pigmentosa

Since the research efforts of Brindley and Lewin in the 1960s to restore vision through electrical stimulation of the visual cortex,1,2 significant advances have been made in the development of a retinal prosthesis for vision restoration in patients with retinal degeneration. Retinal prostheses work via electrical stimulation of the surviving neurons and have been approved by the Food and Drug Administration (USA) and the European Commission (European Economic Area) as a safe and effective treatment for those suffering from degenerative retinal disorders such as retinitis pigmentosa (RP). There are two devices that have proceeded to commercialization: the Argus II from Second Sight Medical Products (Sylmar, CA, USA), which has both CE certification in Europe and FDA approval in the United States3; and the Alpha IMS implant from Retina Implant AG (Reutlingen, Germany),4 which recently gained CE certification in Europe.5 These devices differ significantly in almost all aspects, but particularly in the location of implantation (epiretinal versus subretinal), the number of stimulating electrodes (60 vs. 1500), and the technology used for image capturing (camera versus photodiode array). Although fundamentally different in their technology, both devices have proven their effectiveness through multicenter long-term clinical trials (Humayun MS, et al. IOVS 2012;53:ARVO E-Abstract 6953 and Ref. 4), with several implantees being able to recognize and discriminate objects (daCruz L, et al. IOVS 2012;53:ARVO E-Abstract 5507 and Ref. 4), detect motion (Humayun MS, et al. IOVS 2012;53:ARVO E-Abstract 6953 and Ref. 5), and discriminate patterns to a fairly reasonable degree (Humayun MS, et al. IOVS 2012;53:ARVO E-Abstract 6953 and Refs. 4, 6). Some patients are even able to use the devices to navigate independently,4,7 read large print,4,8 and perform tasks involving activities of daily living,4 which is a testament to the usefulness of the technology.

Despite the positive outcomes with the present devices, there have been reports of several clinical complications during clinical trials, including conjunctival erosion, hypotony, retinal detachment, endophthalmitis in patients with epiretinal devices (Humayun MS, et al. IOVS 2012;53:ARVO E-Abstract 6953), and a sustained increase in the number of microaneurysms in patients with subretinal devices.9 Moreover, the surgical
Factors Affecting Retinal Prosthesis Thresholds

The research followed the tenets of the Declaration of Helsinki, and informed consent was obtained from all participants upon explanation of the nature and possible consequences of the study. All procedures were approved by the Human Research Ethics committee of the Royal Victorian Eye and Ear Hospital, and the clinical trial was registered at www.clinicaltrials.gov (trial NCT01603576). Three patients with end-stage RP (one 53-year-old female [P1] and two males aged 50 [P2] and 63 years [P3]) were selected for implantation after a comprehensive screening process involving 95 people with RP. The patients had between 8 to 10 years (P2) and 20 years (P1 and P3) of light perception-only vision. The worse-seeing eye was selected for implantation and had bare light perception acuity in all three patients. This was determined during three separate preoperative clinical assessments, which included a range of tests such as visual acuity, electroretinography, and perimetry. Between May and August 2012, all patients were implanted with a prototype suprachoroidal retinal prosthesis developed by the Bionics Institute through Bionic Vision Australia. The prosthesis consisted of an intracocular electrode array made of medical-grade silicone (19 × 8 mm) containing 35 platinum disc electrodes (Fig. 1A; 3 × 400-μm diameter, 30 × 800-μm diameter, and 2 × 2000-μm diameter). The electrodes on the top, bottom, and leadwire ends of the array were shorted together to form a “guard ring” return electrode (Fig. 1B). The largest-diameter electrodes were placed at the leadwire end of the array and acted as additional return electrodes (Fig. 1A). A platinum pin implanted subcutaneously behind the ear served as the fourth extracocular return electrode (Fig. 1C). Thus there were 20 stimulating electrodes and four choices of return electrodes. Each electrode was attached to a single 20-μm-diameter platinum-iridium wire. The helically coiled leadwire (150 mm long, 1.5-mm diameter) exited the eye and connected the electrode array to a titanium percutaneous plug that exited the skin behind the ear (Fig. 1C). The use of a percutaneous plug enabled direct access to the electrodes via an external stimulator, thus eliminating the need for implantable electronics and providing maximum flexibility in the use of different electrode configurations and parameters for stimulation.

Surgical Procedure

The surgical procedures were similar to those performed in preclinical studies both in felines (intraocular component only) and in cadaver humans. Briefly, a curved incision was made behind the ear through the posterior temporalis muscle to expose a flat section of temporal bone. A tunnel was created beneath the temporalis fascia up to the orbital rim. After performing a lateral canthotomy, disinserting the lateral rectus muscle, and making the required scleral incision, the device was tunneled from behind the ear using a custom trocar up to the lateral orbital margin. The percutaneous plug was secured to the temporal bone with self-tapping screws. A pocket was made within the suprachoroidal space using a lens glide, and the electrode array was inserted. A lateral orbitotomy was created using 10-mm burrs to stabilize the lead. Upon closure of the lateral wound, the superotemporal conjunctiva, stabilization of the leadwire, and reattachment of the lateral rectus muscle, an indirect ophthalmoscope was used to check parameters is ideal in order to obtain the lowest perceptual thresholds.

MATERIALS AND METHODS

Patient Selection and Device Description

The main goals of this study were to provide further evidence of successful stimulation of the retina via an electrode array placed in the suprachoroidal space of blind humans with advanced RP; assess thresholds required to elicit photic percepts; assess which stimulus parameters affect thresholds the most; and provide insights on what combination of procedures to implant these devices require multiple manipulations to the eye before the intraocular device is implanted, for example, a pars plana vitrectomy for both epiretinal and subretinal approaches, and an obligatory cataract operation and creation of a subretinal bleb with the subretinal approach. Finally, long-term device stability may become an issue with the use of retinal tacks for the epiretinal approach. Despite this safety profile, these devices have been approved by regulatory agencies with the benefits currently outweighing the risks and are commercially available for implantation. In order to alleviate some of the complications and significantly simplify the surgical procedure, our group has been developing a suprachoroidal approach whereby the electrode array component of the prosthesis is inserted into the space between the sclera and choroid. The most significant advantage of this surgical approach is that the electrode array is held stable within the natural cleavage plane of the suprachoroidal space, thus eliminating the need for external elements such as retinal tacks to fixate the device to the retina. Moreover, the surgery requires only one layer of the eye (the sclera) to be breached for insertion of the electrode array, thus making it less invasive and reducing the risks of adverse events compared to the other approaches.

It is thought that while the suprachoroidal location may provide a more stable electrode–tissue interface, significantly higher levels of charge will be necessary to elicit visual percepts, owing to the greater distance between the electrode array and the target retinal ganglion cells (RGCs) compared to epiretinal and subretinal placements. The increased charge may further result in unwanted current spreading to the retina. Moreover, the surgery requires only one layer of the eye (the sclera) to be breached for insertion of the electrode array, thus making it less invasive and reducing the risks of adverse events compared to the other approaches.

Through numerous preclinical studies (Nayagam D, et al. IOVS 2013;54:ARVO E-Abstract 1053 and Refs. 13,19–21), our group validated the safety and efficacy of suprachoroidal stimulation, which led to commencement of a phase 1 clinical trial (www.clinicaltrials.gov, trial NCT01603576) in three RP patients in 2012 (Blamey P, et al. IOVS 2013;54:ARVO E-Abstract 1044; Allen P, et al. IOVS 2013;54:ARVO E-Abstract 1031; and Ref. 14). Since then, we have monitored perceptual thresholds over nearly 24 months and have therefore had more time to assess the effects of varying stimulus parameters. The main goals of this study were to provide further evidence of successful stimulation of the retina via an electrode array placed in the suprachoroidal space of blind humans with advanced RP; assess thresholds required to elicit photic percepts; assess which stimulus parameters affect thresholds the most; and provide insights on what combination of procedures to implant these devices require multiple manipulations to the eye before the intraocular device is implanted, for example, a pars plana vitrectomy for both epiretinal and subretinal approaches, and an obligatory cataract operation and creation of a subretinal bleb with the subretinal approach. Finally, long-term device stability may become an issue with the use of retinal tacks for the epiretinal approach. Despite this safety profile, these devices have been approved by regulatory agencies with the benefits currently outweighing the risks and are commercially available for implantation. In order to alleviate some of the complications and significantly simplify the surgical procedure, our group has been developing a suprachoroidal approach whereby the electrode array component of the prosthesis is inserted into the space between the sclera and choroid. The most significant advantage of this surgical approach is that the electrode array is held stable within the natural cleavage plane of the suprachoroidal space, thus eliminating the need for external elements such as retinal tacks to fixate the device to the retina. Moreover, the surgery requires only one layer of the eye (the sclera) to be breached for insertion of the electrode array, thus making it less invasive and reducing the risks of adverse events compared to the other approaches.

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the position of the electrode array in relation to the optic disc and the macula. An electrode connectivity test was performed immediately after surgery to confirm that all wires/electrodes were intact by passing a small test biphasic current pulse (75 μA, 25 μs per phase) and measuring the electrode voltage. Patients remained in the hospital for 4 to 5 days post surgery and were given topical steroids, antibiotic eye drops, and systemic analgesia as required. More details regarding the surgical procedures will be the subject of another manuscript.

**Clinical and Psychophysical Sessions**

Upon discharge from the hospital, patients underwent clinical assessment every week, during which images were taken using color fundus photography (TRC-50Dx; Topcon Medical Systems, Oakland, NJ, USA) and spectral-domain optical coherence tomography (OCT; Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany). Using the images from the weekly OCT scans, retinal thickness as well as the distance...
between individual electrodes on the array and the retina (taken from the anterior surface of each disc to the retinal pigment epithelium) was measured (Fig. 2). In addition, the percutaneous plug and wound were closely examined and cleaned as necessary, and intraocular pressure measurements were made using contact tonometry (TonoPen XL; Reichert Technologies, Depew, NY, USA). Postsurgical follow-ups were completed on a monthly basis to check ocular health; x-ray images were taken monthly for the first 6 months and at 12 months; and a full-head computed tomography scan was performed at 1 and 12 months.

All patients experienced a combined suprachoroidal and subretinal hemorrhage post surgery, which resolved without a need for intervention in all cases (Fig. 3). The extent of the hemorrhage was limited to the area covered by the electrode array. In P2, a fibrotic tissue reaction occurred, most likely due to hemorrhage at the temporal end of the implant, and remained following hemorrhage resolution; but this should not have affected device efficacy and did not cause complications such as retinal detachment. Patient 1 and P3 commenced weekly psychophysics sessions of 2 to 4 hours at the Bionics Institute between 1 and 2 months post implantation. Sessions with P2 commenced approximately 3 months post implantation due to a slower postsurgical recovery. While it was possible to start psychophysical testing much earlier, the subretinal and suprachoroidal hemorrhage was not something we had experienced in preclinical studies, and it was the first time that electrodes had been inserted into the suprachoroidal space of blind humans. While Fujikado et al. \cite{15} also described their technique as suprachoroidal, since their electrodes were in fact intrascleral and not in direct contact with the choroid, this may explain why they did not report any hemorrhage. The hemorrhage seen in our study also impeded the visualization of electrodes under OCT. Therefore, as a precaution it was decided by the clinical team to begin testing only once the hemorrhage had cleared.

At each psychophysics session, the patient was connected to an in-house–designed and manufactured external benchtop stimulator (neuroBi) using a custom flexible cable. The neuroBi stimulator is completely electrically isolated via a Universal Serial Bus (USB) connection to a laptop computer and consists of a single current source. The current source is routed through a multiplexer to allow flexible stimulation of any single or ganged combination of electrodes on the array. The stimulator is capable of delivering charge-balanced symmetric biphasic pulses using currents up to 10 mA and pulse widths ranging from 20 to 3000 $\mu$s per phase, at frequencies of up to 6250 pulses per second (pps), within a 40-V voltage compliance. To ensure that overstimulation above safe charge and charge density levels was not performed, the charge on each electrode was capped to 447 and 298 nanocoulombs (nC) (equating to an upper limit of charge density of 158 $\mu$C/cm$^2$ and 237 $\mu$C/cm$^2$) for the 600-$\mu$m- and 400-$\mu$m-diameter electrodes, respectively. This charge limit was based on the data presented in Merrill et al. \cite{23} and calculated using the well-accepted Shannon equation, \cite{24} with a conservative value of $k = 1.85$. In addition to being connected to the stimulator, the patient also wore a pair of glasses that contained an eye tracker (Arrington Research, Inc., Scottsdale, AZ, USA) and head motion detection system (Ascension Technology Corp., Shelburne, VT, USA). Finally, to avoid any static discharge, the patient and the operator wore elastic wrist bands that were grounded to static shielded floor mats, which were in turn connected to the earth. More details regarding the flexible psychophysics system will be the subject of another manuscript.

**Threshold Measurement Technique**

The threshold measurement technique was based on a well-established adaptive up–down staircase procedure that has been used extensively for psychophysics. \cite{25} The procedure...
involved presenting multiple trials and detecting turning points (Fig. 4). For any given threshold measurement, the electrode being stimulated, return configuration, pulse polarity, pulse width, interphase gap, stimulation rate, and duration of each trial were kept constant with only the charge per phase allowed to vary. The threshold procedure began with selecting an initial value of charge (100 nC by default) to be delivered. Each trial was a train of biphasic pulses with a total duration of 2 seconds. The duration between trials was kept to approximately 3 seconds.

Patients were told when the threshold procedure began and were asked to respond “yes” whenever they saw a phosphene. However, with the exception of P3 (details below), patients were not told explicitly exactly when each trial began within the procedure. Upon presentation of each trial, the operator would pause for approximately 3 seconds, and if there was no response from the patient, the operator would enter a “no” response. Each “yes” or “no” response automatically determined a charge per phase to be delivered for the next trial. During the “up” phase, the charge per phase was increased until a “yes” response was encountered. The next trial following the first “yes” response during the “up” phase was presented using the same charge per phase as in the previous trial. If two consecutive “yes” responses were encountered, the “down” phase of the procedure began in which the charge per phase was decreased until a “no” response was encountered. Turning points were defined as either the second of two consecutive “yes” responses using the same charge per phase during the “up” phase, or the first “no” response during the “down” phase. Threshold (yellow line) was defined as the average charge per phase across the last six turning points (in this case 140 nC).

FIGURE 4. An example of the up–down staircase procedure used for threshold measurements. Each trial consisted of a pulse train lasting 2 seconds. Subjects were asked to verbally respond “yes” (green bars) if they saw anything. If the subject did not respond within a few seconds after each trial, a response of “no” (red bars) was entered. Turning points (asterisk) were defined as either the second of two consecutive “yes” responses using the same charge per phase during the “up” phase, or the first “no” response during the “down” phase. Threshold (yellow line) was defined as the average charge per phase across the last six turning points (in this case 140 nC).
Electrode Configurations and Stimulus Parameters

Stimulus parameters were systematically varied to assess their effects on thresholds. One of six return configurations (Fig. 5) was chosen in decreasing order of the likelihood of current spread: monopolar, using one of the 2-mm discs as a return; common ground, where the return electrode consisted of all electrodes shorted together except for the stimulating electrode; bipolar, where an electrode adjacent to the stimulating electrode was the return; tripolar, where two electrodes adjacent to the stimulating electrode were shorted to form the return; and hexagonal, where five or six electrodes surrounding the active electrode were shorted together as the return. A special case of pseudo-hexagonal was also tested, in which one of the 2-mm discs was shorted to the six electrodes surrounding the stimulating electrode, thus approximating a 50% monopolar and 50% hexagonal situation. In addition, the pulse polarity (cathodic first or anodic first; CF or AF), pulse width (PW, up to 500 μs per phase), interphase gap (IPG, up to 500 μs), and stimulation rate (up to 500 pps) were varied.

Statistical Analyses

All thresholds were expressed in nanocoulombs charge per phase per pulse. Statistical analysis was performed in Minitab (State College, PA, USA). The effects of number of days post implantation, electrode–retina distance, and retinal thickness on perceptual thresholds were assessed using linear regression analyses. The effects of all other factors on thresholds were tested using separate general linear models (GLM) with number of days post implantation designated as a covariate and the patient number designated as a random factor. Data from P1 and P2 were included in most analyses. Data from P3 were analyzed separately due to previously mentioned issues and the inability to test a large range of stimulus parameters. When assessing the effect of one factor on thresholds, all the other parameters were kept constant. As the distribution of thresholds was found to violate normality (Anderson-Darling test, $P < 0.01$), data were logarithmically transformed before GLM and regression analyses were performed. Most data were plotted using box plots, where outliers were defined as threshold values that were at least 1.5 times above or below the interquartile range (defined as the difference between the third and first quartiles). Outliers were marked on the plots for display purposes only and not removed from the dataset prior to statistical analyses.

RESULTS

Threshold Yield

The threshold yield was defined as the percentage of electrodes at which a reliable threshold was reached below the safe charge limit ($447 \text{ nC}$ for 600-μm-diameter electrodes, $298 \text{ nC}$ for 400-μm-diameter electrodes). Table 1 summarizes the efficacy of eliciting phosphenes on individual electrodes and indicates stimulus parameters that were most effective in obtaining a valid threshold. Most data were collected using a stimulation rate of 50 pps using a 500 μs per phase PW and a 500-μs IPG. Using these parameters, valid thresholds could be obtained on all electrodes tested in P1 using both pulse polarities with the exception of hexagonal CF stimulation, where only 50% of the electrodes tested yielded a threshold within the safe charge limit. When P2 commenced psychophysics sessions, there were some difficulties in obtaining thresholds on 100% of electrodes, even with monopolar stimulation. Moreover, although a valid threshold could be measured with P2 using a stimulation rate of 50 pps, he would describe the phosphenes as two quick flashes, one appearing at the onset of stimulation and the other appearing at the offset with no percept in between. In addition, the onset and offset flashes were described as being in different locations, which was very confusing for the patient. This led us to explore high-rate stimulation with P2. Using high-rate stimulation (500 pps) with the same PW and IPG not only made P2’s phosphene appearance complete, but also enabled a 100% success rate of valid thresholds. When the PW and IPG were considerably shortened to 148 μs per phase and 20 μs, respectively, and the rate was slightly decreased to 400 pps to allow for sequential stimulation of multiple electrodes during other psychophysical tests (details not included in present manuscript), the yield in P2 was reduced, with a valid threshold obtained in 85% of electrodes tested using AF stimulation (Table 1).

We first began testing high-rate stimulation on P3 as it had already been shown to be of benefit to P2. Although thresholds could be measured on 12 of 14 single electrodes tested with AF stimulation, the threshold values were found to be very high ($>300 \text{ nC}$), leaving only ~100 nC of headroom below the safe charge limit. In order to alleviate this problem, we switched to testing ganged pairs of adjacent electrodes, in which two adjacent electrodes were shorted together as the stimulating active electrode, as opposed to single electrode stimulation. Using ganged pairs increased the maximum safe charge per phase because of the larger total electrode area, thus increasing the available headroom, as well as the yield compared to...
Factors Affecting Retinal Prosthesis Thresholds

Table 1. Number of Single Electrodes or Ganged Pairs for Which a Valid Threshold Was Measured, Out of the Total Number of Single Electrodes or Ganged Pairs Tested, for Each Combination of Stimulus Pulse Parameters and in Each of the Three Patients

<table>
<thead>
<tr>
<th>Electrode Threshold Yield</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return configuration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monopolar, 500 μs PW, 500 μs IPG, 50 pps</td>
<td>20/20 CF, 20/20 AF</td>
<td>4/4 CF, 18/20 AF</td>
<td>CF* AF*</td>
</tr>
<tr>
<td>Common ground, 500 μs PW, 500 μs IPG, 50 pps</td>
<td>19/19 CF, 19/19 AF</td>
<td>2/3 CF, 18/20 AF</td>
<td>CF* AF*</td>
</tr>
<tr>
<td>Hexagonal, 500 μs PW, 500 μs IPG, 50 pps</td>
<td>4/8 CF, 8/8 AF</td>
<td>CF* 1/8 AF</td>
<td>CF* AF*</td>
</tr>
<tr>
<td>High rate, long pulses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monopolar, 500 μs PW, 500 μs IPG, 50 pps</td>
<td>6/6 CF AF*</td>
<td>CF* 20/20 AF</td>
<td>CF* 12/14 AF</td>
</tr>
<tr>
<td>High rate, short pulses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monopolar, 148 μs PW, 20 μs IPG, 400 pps</td>
<td>CF* 20/20 AF</td>
<td>2/2 CF, 17/20 AF</td>
<td>CF* AF*</td>
</tr>
<tr>
<td>High-rate ganged pairs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monopolar ganged pairs, 500 μs PW, 500 μs IPG, 500 pps</td>
<td>CF* AF*</td>
<td>CF* AF*</td>
<td>CF* 9/9 AF</td>
</tr>
<tr>
<td>Monopolar ganged pairs, 200 μs PW, 200 μs IPG, 200 pps</td>
<td>CF* AF*</td>
<td>CF* AF*</td>
<td>CF* 21/21 AF</td>
</tr>
</tbody>
</table>

Maximum of 20 possible single electrodes. Stimulus duration was fixed at 2 seconds in all cases. For patient 3, the threshold procedure had to be altered to a three-alternative forced choice method (see text for details).
* Those parameters for which no electrodes were tested.

With the number of days post implantation. For P2, not only were absolute thresholds higher than those for P1, but also his threshold increases over time occurred at a much faster rate compared to P1’s (less than 100 nC increase for P1 over almost 700 days versus more than doubled for P2 over approximately 400 days of measurements). Electrode-retina distance increases over time were also higher for P2 and nearly doubled in a span of 3 to 4 months, compared to P1, in whom there was only a ~100- to 150-μm increase in just under 2 years. However, it should be noted that P2 had significant nystagmus, which led to increased difficulty in obtaining high-quality OCT scans; hence a smaller number of data points were available for P2 than for P1. Since both thresholds and electrode-retina distance were found to increase with time, thresholds were found to correlate significantly with electrode-retina distance (Fig. 6C). There was also a small but significant correlation between thresholds and retinal thickness in P1 (Fig. 6D). For analyzing the effects of all other parameters on thresholds, the number of days post implantation was chosen as a covariate.

Effect of Electrode Area and Number of Electrodes Stimulated

Surprisingly, thresholds were not dependent on the electrode area or the number of ganged electrodes stimulated. A GLM analysis using data from P1 and P2 (Fig. 7A) showed that thresholds for single electrodes were not dependent on the electrode diameter (400 μm, x̄ = 124.2 nC, n = 26 vs. 600 μm, x̄ = 174.2 nC, n = 211, P = 0.260), after accounting for differences due to the number of days post implantation. Further, while there was a trend of lower thresholds with ganged pairs compared to single electrodes, a separate GLM analysis (Fig. 7B) for P3 revealed that thresholds for single electrodes (x̄ = 331.3 nC, n = 20), were not significantly different (P = 0.781) from those for ganged pairs (x̄ = 288.7 nC, n = 27) after accounting for the number of days post implantation. When further analyzing thresholds for P1 and P2, data from both electrode diameters were pooled together.

Effect of Return Configuration

As expected, the monopolar return configuration was found to elicit phosphenes with the lowest thresholds, regardless of the pulse polarity used, for P1 and P2 (Fig. 8). For the same return...
configuration, thresholds were higher for P2 compared to P1, and generally higher for CF stimulation compared to AF stimulation. Also, in a small number of measurements, changing the monopolar return to the extraocular pin (electrode 24) did not significantly change threshold (data not shown). Compared to monopolar stimulation, thresholds were found to increase with use of the common ground configuration, followed by the pseudo-hexagonal, bipolar,
tripolar, and finally the hexagonal configuration, which elicited phosphenes with the highest thresholds. Interestingly, threshold values using the pseudo-hexagonal configuration (where approximately each half of the current would flow through the monopolar and hexagonal return electrodes) were approximately halfway between the values using the pure monopolar and pure hexagonal configurations. The yield of threshold values below the safe charge limit also largely depended on the return configuration. A GLM analysis revealed that after accounting for number of days post implantation and differences between patients, thresholds using the monopolar ($\bar{x} = 119.4$ nC) and common ground ($\bar{x} = 151.4$ nC) configurations were significantly different ($P < 0.001$). The only other significant difference ($P < 0.001$) found was between thresholds using the pseudo-hexagonal configuration ($\bar{x} = 206.5$ nC) and those using the pure hexagonal configuration ($\bar{x} = 292.3$ nC). For further analysis of the effects of other parameters on thresholds, only data using the monopolar configuration were included.

**Effect of Active Electrode and Pulse Polarity**

A GLM analysis was conducted with active electrode and pulse polarity as the factors, number of days post implantation and differences between patients, thresholds using the monopolar ($\bar{x} = 119.4$ nC) and common ground ($\bar{x} = 151.4$ nC) configurations were significantly different ($P < 0.001$) from those using all other configurations. The only other significant difference ($P < 0.001$) found was between thresholds using the pseudo-hexagonal configuration ($\bar{x} = 206.5$ nC) and those using the pure hexagonal configuration ($\bar{x} = 292.3$ nC). For further analysis of the effects of other parameters on thresholds, only data using the monopolar configuration were included.

**Effect of Pulse Width and Interphase Gap**

Figure 10 summarizes the effects of varying PW and IPG on thresholds in P1 (Fig. 10A) and P2 (Fig. 10B). Generally, larger IPGs resulted in lower perceptual thresholds, but this was more evident at shorter values of PW. A GLM analysis with PW and IPG as factors and number of days post implantation as the covariate revealed that thresholds using a PW of 100 µs per phase (“narrow”) were marginally lower (~20 nC on average, $P < 0.05$) than those using a PW of 500 µs per phase (“wide”). Thresholds using a 200 µs per phase PW were not different from narrow or wide pulses ($P > 0.05$). Post hoc analysis of IPG revealed that only thresholds using an IPG of 500 µs were marginally lower (~20–30 nC on average, $P < 0.05$) than those using shorter IPGs (20, 100, and 200 µs).

**Effect of Stimulation Rate**

Along with the return configuration, stimulation rate was found to have the most significant influence on perceptual thresholds of all stimulus pulse parameters, with decreasing thresholds as a function of increasing stimulation rate (Fig. 11). In all three patients, the highest rate tested resulted in significantly reduced perceptual thresholds, by 34% to 43% on average, compared to a rate of 50 pps. Interestingly, in both P1 and P2, there was a trend for single pulses to induce phosphenes percepts with lower thresholds compared to a 5-
pps pulse train, but this was not significant after accounting for number of days post implantation.

**DISCUSSION**

The main goals of this study were to provide evidence of successful stimulation of the retina via an electrode array placed in the suprachoroidal space of profoundly vision-impaired humans, assess thresholds required to elicit phosphene percepts, and discover what stimulus parameters and other associated factors affected thresholds the most. Our study monitored thresholds over a duration of just under 2 years in three patients with profound vision loss from RP. We found that apart from electrode area, the number of ganged electrodes stimulated, and retinal thickness, all factors tested had a significant influence on perceptual thresholds. Charge per phase thresholds were found to be lowest when using short duration AF biphasic pulses with a long IPG, in a monopolar return configuration, at high rates of stimulation. Other factors that affected thresholds were the individual patient, active electrode chosen for stimulation, time after implantation, and electrode–retina distance.

**Threshold Range and Patient Influence on Thresholds**

The perceptual thresholds for single electrodes recorded in this study ranged widely from as low as 44 nC per phase in P1 (monopolar, CE 500 μs PW, 500 μs IPG, 500 pps) to as high as 436 nC per phase in P2 (monopolar, AF 148 μs PW, 20 μs IPG, 400 pps). This type of variability and the large range of thresholds across patients seen in our study have also been seen with epiretinal stimulation. Presumably, the factor likely responsible for the greatest variability among patients in our study was the electrode–retina distance (over the duration of the study, electrode–retina distances ranged between 253 and 780 μm in P1, 422 and 1420 μm in P2, and 279 and 1296 μm in P3); but there could be other unknown factors involved, including the density and health of surviving neurons in the retina. Nevertheless, the fact that we were able to obtain thresholds in all three patients through careful optimization of stimulus parameters provides a proof of concept that suprachoroidal stimulation is a viable option for a retinal prosthesis.

When compared with the thresholds reported for chronic epiretinal stimulation in humans using similar stimulus parameters, the thresholds in our study were found to be higher (Table 2). However, the difference was not as extreme as previously expected, based on an in vivo study showing that suprachoroidal stimulation required ~15 times on average higher charge to reach the threshold of cortical activity compared to subretinal stimulation. When compared to a previous study testing stimulation of the retina via intrascleral electrodes, thresholds in our study were found to be significantly lower (Table 2).

**Stimulus Parameter Influence on Thresholds**

**Effect of Return Configuration.** The influence of return configuration has been well documented in both animal and clinical studies with cochlear implants. Narrower electric fields in the cochlea using common ground, bipolar, and tripolar stimulation result in higher thresholds of either recorded brain activity or perception, and the monopolar return configuration has been shown to produce percepts with the lowest thresholds. An important difference to note between cochlear and retinal implants is that the latter make use of a two-dimensional electrode array as opposed to a linear array, thus allowing one to test even more spatially restricted configurations compared to bipolar and tripolar stimulation. One such configuration we assessed was the hexagonal return, first proposed by Lovell et al. Perceptual thresholds in our study with the hexagonal return were found to be on average 2.5 times higher than those using the monopolar return. In addition to being the first report of hexagonal stimulation in humans, this result is consistent with what has been seen in preclinical retinal implant studies, where between two times and six times higher thresholds for hexagonal stimulation compared to monopolar stimulation have been reported. Although our preclinical study showed that return configurations such as common ground and hexagonal produce a narrower spread of activation in the retina compared to monopolar stimulation, the benefits of using such return configurations for retinal stimulation are at present unclear. Apart from the threshold rise, our subjects did not report any systematic or significant noticeable effects on phosphene percepts as the return configuration was varied, but this was not quantified. Perhaps the benefits of return configurations with spatially restricted fields of excitation will be more evident with performance of simultaneous or sequential stimulation of electrodes, where electrode interactions will significantly influence the resultant percept (albeit with the known limitation of requiring 2.5 times higher charge levels).
Factors Affecting Retinal Prosthesis Thresholds

Effect of Pulse Polarity. Clinically, compared to the return configuration, the influence of pulse polarity on perceptual threshold is still debatable. Cochlear implants typically have been shown to produce activation with similar thresholds for CF and AF stimulation, during both electrophysiology and psychophysics testing. However, there are also studies using pulses with long IPGs or monophasic pulses, which have shown that anodic currents result in more efficient activation of the cochlea; but this can also be species dependent. In the retinal implant field, studies by Jensen and Rizzo using subretinal stimulation showed that AF pulses resulted in lower thresholds for activation of RGCs compared to CF pulses, but the opposite was true for epiretinal stimulation. Our preclinical study using suprachoroidal stimulation showed that for the same amount of cortical activation, AF stimulation required less charge per phase compared to CF stimulation, which is consistent with the results reported in the current study. The most likely explanation for the relatively small benefit seen with AF stimulation in our study comes from the notion that anodic currents tend to excite neurons that are distal to the stimulating electrode, which would most likely be the case with our electrodes being suprachoroidal and the RGCs being hundreds of microns away. This notion is further supported by a study that performed recordings in both superficial and deeper layers of the motor cortex in response to electrical stimulation of the cortical surface; neurons in deeper layers were found to be more sensitive to AF stimuli. Thus clinically, at least for suprachoroidal prostheses, AF stimulation is recommended when using symmetric biphasic pulses.

Effect of Pulse Width, Interphase Gap, and Stimulation Rate. Our study showed a marked reduction in perceptual threshold when using short-duration PWs combined with long IPGs compared to other PW–IPG combinations. While this result is well established in the cochlear implant literature, recent reports with epiretinal stimulation have also demonstrated the beneficial effects of using an IPG with biphasic pulses compared to pulses without any IPG. In fact, the study by Weitz et al. showed an improvement of ~10% in perceptual threshold when using IPGs of ≥500 μs compared to no gap with the PW set to 450 μs per phase, a result very closely matched with what we found when using a PW of 500 μs per phase. The effect of PW alone on threshold is also well established; longer PWs have been shown to increase threshold charge per phase and decrease threshold current (strength–duration curve) with both cochlear implants and retinal implants. In our study, although we tested only a limited number of PW and IPG combinations due to time constraints, the data support the present literature.

While the benefit of high stimulation rates on perceptual threshold is well known with cochlear implants, it has not been extensively reported in humans with retinal stimulation. A study by Horsager et al. showed some promise for high-rate epiretinal stimulation, with significantly reduced threshold currents for rates up to 135 pps using long-duration pulse trains, and up to 3000 pps using short-duration pulse trains. However, when their data were converted to total charge delivered over a 500-ms pulse train and fitted using their model, they predicted that high stimulation rates required more total charge to reach threshold for a given PW. These results led to their conclusion that the most effective rate for epiretinal stimulation is 50 pps. It is likely that the duration of stimulation will govern the most effective stimulus rate in terms of lower total charge delivered due to differences in the number of pulses. At longer durations, a 50-pps pulse train may require less total charge compared to a 400-pps pulse train; however, for short-duration stimulation (more likely to occur when using a camera-based strategy), a higher rate will be preferential as the charge per pulse is significantly reduced.

A problem to consider with high-rate stimulation is the possibility of phosphene fading, occurring within a few seconds after stimulation onset, but sometimes much more quickly. There have been reports with both epiretinal and subretinal stimulation that higher stimulation rates cause faster fading than lower rates; but the opposite can also be true, so the data are not consistent across subjects. However,
Factors Affecting Retinal Prosthesis Thresholds

**Influence of Other Factors on Thresholds**

Apart from stimulus parameters, we found that thresholds depended significantly on electrode-retina distance but negligibly on retinal thickness. A study using the Argus I epiretinal prosthesis also found that retinal thickness was not a determinant factor of threshold.\(^{23}\) One reason for the weak correlation could be that while visual acuity in RP patients depends on the preservation of macular photoreceptors, the level of preservation may not be proportional to the overall retinal thickness, as it has been shown that visual acuity and foveal retinal thickness do not correlate in all RP patients.\(^{70}\) Also, the macular volume does not highly correlate with threshold, similar to the findings of the present study. Interestingly, in our study the electrode-retina distance was highly variable, not only across patients but even among electrodes within each patient. Therefore, it is also possible that the high variability in electrode-retina distance across the electrode array was responsible for the weak correlation between threshold and the retinal thickness directly above each electrode due to confounding measurements between electrode-retina distance and retinal thickness. The variability seen within each patient was partly attributed to limitations with the measurement tool on the OCT equipment and partly the typical rates used to test phosphene fading have been up to only tens of pps as opposed to the hundreds of pps that we tested. Our patients reported no major fading of phosphenes and were able to see the phosphene for the total duration of stimulation (2 seconds in this study), but we did not systematically quantify the effects of fading. P3, who only saw a quick flash at the onset of stimulation, was an exception, but this was not stimulus or electrode dependent.

There are two mechanisms that may be responsible for the lower thresholds seen with the use of high rates. Several in vitro studies using epiretinal and subretinal stimulation have shown that most types of RGCs are typically “desensitized” at high stimulation rates (beyond 200 pps), such that they may fail to “follow” each pulse within a high-rate pulse train or produce no spiking at all.\(^{53-65}\) However, there are some types of RGCs that can follow even 600-pps stimulation,\(^{66}\) and a recent study performing epiretinal stimulation showed robust responses in ON–OFF directionally sensitive RGCs when stimulation was applied at 2000 pps.\(^{67}\) It is possible that higher rates may provide exclusive activation of RGCs as opposed to the remaining neural network, thus bringing down thresholds and eliciting clearer phosphenes. Alternatively, the reason for high-rate stimulation to work well could simply be a central mechanism: Integration of multiple pulses within a short temporal window could significantly increase detectability of the stimulus, a feature prominent in both the visual\(^{68}\) and auditory\(^{69}\) systems.

Ultimately, the decision to use high rates will be partly governed by the threshold charge level required, electrode impedances, and voltage and current limitations of the stimulator. High rates will likely require short PWs for sequential stimulation of multiple electrodes and therefore large currents and voltages to evoke percepts. In addition, one must bear in mind that the prosthesis in normal operation is expected to be stimulating at levels up to 1.5 to 2 times above threshold, so the stimulator design would need to supply large currents and voltages—a challenge when using miniature components. In such situations, perhaps a low stimulation rate with long pulses would be more suitable.

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due to the location of the electrodes on the array. Measurement error could easily be 10 to 20 μm, and this would lead to fluctuations in measurement values. In addition, the electrodes on the outer edge of the array always tended to be closer to the retina, as the area of presumed fibrosis overlying the array was thinner in the middle, causing more elevation of the retina compared to the edges. However, there was a clear trend for increasing electrode-to-retina distance with time, despite these limitations.

The electrode diameter or the number of ganged electrodes stimulated also did not affect thresholds, seen when comparing thresholds from single electrodes (two different electrode diameters) in P1 and P2 and when comparing single electrodes versus ganged pairs (600 μm diameter only) in P3. The finding related to electrode area is consistent with what we have previously reported in a preclinical study measuring evoked potential thresholds, and is also consistent with findings from patients with epiretinal implants. While larger electrodes may be expected to result in higher thresholds, it is possible that the 600-μm-diameter electrodes in our study have more uneven current distribution across the electrode surface compared to the 400-μm-diameter electrodes, with more current density around the edges, thus accounting for similar thresholds. It must be noted, however, that the only way to change the electrode diameter was to change the active electrode on the array being stimulated; thus electrode diameter and electrode location always covaried. Therefore, it is also possible that we were not able to isolate the effects of electrode diameter alone on threshold. The second finding may be a little surprising at first, as one may expect a larger retinal area covered by two ganged 600-μm electrodes to elicit a lower perceptual threshold than a single electrode if one assumes the higher probability of exciting more neurons with ganged pair stimulation. However, if edge effects of current distribution play a role, then ganging two electrodes may not have the same effect as increasing the area of retina being stimulated. Taking into account the above two findings, it may be beneficial for a suprachoroidal retinal prosthesis to use larger-diameter electrodes as opposed to smaller electrodes to take advantage of the significantly lower impedances and lower charge densities that larger electrodes offer. Also, as learned from the experience with P3, ganged pairs of electrodes can be used as a fallback in case single electrode stimulation is unable to elicit phosphenes, since the effects of stimulus parameters on thresholds are likely to be similar with single electrode and ganged pair stimulation.

The increase in thresholds over time is of some concern. With the Argus 1 prosthesis, thresholds also increased with time, and this was suggested to be a result of the electrode’s lifting off the retina after surgery, thus increasing the electrode-retina distance. It is well known that threshold is strongly correlated with electrode-retina distance, both in vitro and in vivo. In our study, we also observed an increase in electrode-retina distances over time, and therefore this may explain the increase in threshold over time. At this stage, it is unclear what exactly caused the longitudinal increase in electrode-retina distances, and this is currently under further investigation. Many factors could be responsible, but it is likely to be associated with the formation of fibrous tissue around the array. The rate of increase varied between patients, which may be related to the time taken for the initial hemorrhage to resolve in each patient or the level of nystagmus. For example, P2 had the largest electrode-retina distances and the most severe nystagmus, while P1 had almost no nystagmus and the smallest change in distance. The rate of fibrous growth could also have possibly depended on stimulus levels used (P2 and P3 had higher thresholds compared to P1). Studies are currently being conducted to identify the exact cause of the increase observed; but this issue highlights the need to carefully monitor electrode-retina distances over the long term when using suprachoroidal stimulation, as this is likely to be an important factor governing the success of this implant.

CONCLUSIONS

Our study is the first of its kind to report the factors affecting perceptual thresholds with suprachoroidal stimulation over long-term implantation. Firstly, we showed that through careful optimization of stimulus parameters, it was possible to obtain reliable thresholds and phosphenes perceive in all three patients, thus proving that suprachoroidal stimulation can be effective. Secondly, we showed that for suprachoroidal stimulation, using the monopolar return configuration and AF polarity, along with short PWs combined with long IPIs and high stimulation rates, we can maximally reduce perceptual thresholds. Lastly, future investigations will need to carefully monitor electrode-retina distances and attempt to elucidate the cause of increasing thresholds over time.

Acknowledgments

Supported by the Australian Research Council through its Special Research Initiative in Bionic Vision Science and Technology awarded to Bionic Vision Australia and by the Bertalli Family Foundation to the Bionics Institute. The Bionics Institute and the Centre for Eye Research Australia (CERA) acknowledge the support received from the Victorian Government through its Operational Infrastructure Program. CERA is also supported by National Health and Medical Research Council Centre for Clinical Research Excellence Award 529923.

Disclosure: M.N. Shivdasani, None; N.C. Sinclair, None; P.N. Dimitrov, None; M. Varsamidis, None; L.N. Ayton, None; C.D. Luu, None; T. Perera, None; H.J. McDermott, None; P.J. Blamey, None.

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Factors Affecting Retinal Prosthesis Thresholds


APPENDIX

The Bionic Vision Australia Consortium

The Bionic Vision Australia Consortium consists of five member organizations (Centre for Eye Research Australia, Bionics Institute, NICTA, University of Melbourne and University of New South Wales) and three partner organizations (The Royal Victorian Eye and Ear Hospital, National Vision Research Institute of Australia and the University of Western Sydney). For this publication, the consortium members consist of (in alphabetical order): Penelope J. Allen, Tamara-Leigh E. Brawn, Robert Briggs, Anthony N. Burkitt, Owen Burns, James B. Fallon, Lisa Gillespie, Robyn H. Guymer, Wilson Heriot, Nigel H. Lovell, Mark McCombe, Michelle McPhedran, Rodney Millard, David A.X. Nayagam, Nicholas L. Opie, Matthew A. Petoe, Alexia Saunders, Peter M. Seligman, Kyle Slater, Robert K. Shepherd, Gregg J. Suanning, Joel Villalobos, Chris E. Williams, and Jonathan Yeo.