

Effect of the Electrode Array-Retina Gap Distance on Visual Function in Patients with the Argus II Retinal Prosthesis

Abhishek Naidu (✉ abhishek.naidu@stonybrookmedicine.edu)

Stony Brook University Renaissance School of Medicine

Nimra Ghani

Stony Brook University Renaissance School of Medicine

Mohammad Saad Yazdanie

Stony Brook University Renaissance School of Medicine

Khurram Chaudhary

Stony Brook University Renaissance School of Medicine

Research article

Keywords: Argus II, Argus II Retinal Prosthesis, Direction of Motion, Electrode array-retina gap, distance, Gap distance, Low vision, Optical Coherence Tomography (OCT), Retinitis, Pigmentosa, Square Localization, Visual Function

Posted Date: June 13th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-32698/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on September 17th, 2020. See the published version at <https://doi.org/10.1186/s12886-020-01631-6>.

Abstract

Background

Post-implantation visual outcomes in patients with the Argus II Retinal Prosthesis is dependent on a multitude of factors including the positioning of the electrode array on the retina. The purpose of this study is to determine whether the average electrode array-retina gap distance correlates with objective visual function outcomes and sensitivity detection thresholds in patients implanted with the Argus II Retinal Prosthesis.

Methods

5 patients with implantation of the Argus II Retinal Prosthesis were enrolled in this single-institution retrospective study. Patient demographics were collected from medical records. Visual function data (Square Localization [SL] and Direction of Motion [DOM]) and Optical Coherence Tomography (Cirrus HD-OCT) images were extracted retrospectively from the Argus II Retinal Prosthesis Post-Approval study. Visual function tests were performed with the device OFF and ON at each study visit. Electrode array-retina gap distances were measured at each of the array's 60 electrodes using the Cirrus HD-OCT software in both the nasotemporal and superoinferior planes. Data was obtained at baseline, and post-operative month 1, month 3, month 6, and year 1. Sensitivity detection thresholds were obtained at the initial programming visit and each reprogramming session.

Results

1 of 5 patients had a significant average improvement in the SL visual function test and 0 of 5 had a significant average improvement in the DOM visual when the device was ON compared to OFF ($p < 0.05$). Electrode array-retina gap distance did not show a significant correlation with changes in SL visual function ($r = 0.20$; $p = > 0.05$) or DOM visual function ($r = -0.18$; $p = > 0.05$). In addition, electrode array-retina gap distance did not show a significant correlation with sensitivity detection threshold ($r = -0.01$; $p = 0.98$).

Conclusion

Our results demonstrate that the average electrode array-retina gap distance does not correlate with changes in objective visual acuity function or sensitivity detection thresholds in a cohort of patients implanted with the Argus II Retinal Prosthesis. Therefore, complete apposition between the electrode array and retina may not always be necessary to achieve optimal visual outcomes.

Background

Retinitis Pigmentosa (RP) is an inherited degenerative disorder resulting in the loss of photoreceptor cells of the outer retina. Over 1 million patients worldwide suffer from RP, which leads to progressive vision loss that can pose significant challenges in many facets of their lives. More than 190 genes have been implicated in the pathogenesis of RP and all mutations inevitably result in degeneration of the photoreceptor layer¹. However, the inner retinal cells are largely preserved in RP, serving as a target for direct electrical stimulation in order to generate phosphenes that may be perceivable by the patient². Producing and manipulating these phosphenes to accurately reflect the surrounding visual environment is the common objective for electric stimulation-based visual prostheses.

The Argus II Retinal Prosthesis System (Second Sight Medical Products Inc., Sylmar, California, USA) was developed for the purpose of providing artificial vision in patients with outer retinal degenerative diseases such as RP. It became commercially available after receiving FDA approval as a humanitarian device in 2013. Roughly, the Argus II consists of an implantable epiretinal 60-channel electrode array connected wirelessly to a portable computer (Visual Processing Unit, VPU). The VPU receives real-time images from a video camera mounted onto glasses worn by the patient. Wireless connection between the electrode array and the VPU occurs via an external coil (side arm of the glasses) and an internal coil (housed in the internal unit) that utilize radiofrequency telemetry. An application-specific-integrated-circuit (ASIC) within the internal unit generates electrical impulses in accordance with the VPU output. These impulses are relayed to the electrode array, ultimately stimulating the inner retina in order to produce an artificial image^{1,2}.

Surgical techniques for implantation of the Argus II retinal prosthesis may vary depending on patient factors, globe anatomy, and surgeon preferences. Array positioning over the macular region is a requisite for optimal visual outcomes³. Normally, a spring-tensioned titanium retinal tack is used to affix the electrode at the posterior pole in order to ensure close apposition of the electrode to the retinal surface. However, even with the concavity of the electrode, complete apposition of the electrode array against the retina may not occur. Ahuja et al³ demonstrated that complete or near complete apposition results in a lower perceptual threshold. The effect of the electrode array-retina gap distance on objective visual function outcomes has not been elucidated. This study aims to determine how the electrode array-retina gap distance influences postoperative visual outcomes in patients with RP implanted with the Argus II retinal prosthesis, with the hypothesis that smaller gap distances correlate with more significant visual improvement.

Methods

Patient Eligibility and Demographics

Patients enrolled in the Argus II Post-Approval Study (PAS) were invited to join this study. Eligibility criteria included a diagnosis of outer retinal dystrophy, some residual light perception, ability to undergo surgery under anesthesia, and ability and willingness to comply with post-operative follow-up and testing.

Exclusion criteria included co-morbid ocular conditions (e.g. advanced glaucoma, optic glioma) that could compromise the functional optic nerves and tracts. Pretesting at the baseline visit included visual function testing, general slit lamp examination, Optical Coherence Tomography imaging (Cirrus HD-OCT Machine, Carl Zeiss Meditec, Dublin, Calif.) and fundus photography. A total of 5 patients with implantation of the Argus II device were enrolled in the study (Table 1). All patient recruitment, study investigations and surgeries were conducted at Stony Brook University Hospital and its affiliated sites. Surgeries were performed by one vitreoretinal surgeon under general anesthesia at the Stony Brook University Hospital.

Table 1
Demographics of patients included in the study at baseline.

Patient #	Gender	Age Range	Diagnosis	Years since Diagnosis	Visual Acuity at Presentation
01	F	60–70	Leber’s Congenital Amaurosis	Unknown	Bare Light Perception (BLP)
02	F	50–60	Retinitis Pigmentosa	19	Bare Light Perception (BLP)
03	M	70–80	Retinitis Pigmentosa	28	Bare Light Perception (BLP)
04	M	70–80	Retinitis Pigmentosa	48	Bare Light Perception (BLP)
05	M	60–70	Retinitis Pigmentosa	33	Light Perception (LP)

Data Collection

Data was collected from patient visits at baseline prior to implantation, post-operative month 1 (M1), month 3 (M3), month 6 (M6), and year 1 (Y1). At M1, activation and programming of the device took place and visual function testing was deferred. Visual function testing was performed at M3, M6 and Y1. Sensitivity detection thresholds (to be defined later) were collected when possible at M1, M3, M6 and Y1. Gap distances were measured from Optical Coherence Tomography (OCT) images at M1, M3, M6, and Y1. All data was collected by two authors, cross-checked for accuracy and thoroughness, and independently reviewed by two other authors. Microsoft Excel was utilized for data collection.

Visual Function

The visual function of patients with the Argus II retinal implant were assessed using Square Localization (SL) and Direction of Motion (DOM) measures which were developed by Second Sight. SL involves locating and touching a white square set against a black background on a touchscreen monitor with the device ON and OFF. The distance (measured in number of pixels) between the true center of the square and the location at which the patient touches the monitor where they perceive the center of the square to be is measured, with smaller pixel distances indicating higher accuracy². DOM testing utilizes a white bar that moves across a black screen in a particular direction, and the patient attempts to determine the

direction of motion of the white bar. The angle between the true direction of motion and the patient's perceived direction of motion is measured, with smaller angles indicating higher accuracy² All testing was performed under controlled conditions and overseen by trained personnel. Visual function data was extracted retrospectively from the Argus II Post-Approval Study.

Sensitivity Detection Threshold

The Argus II device is programmed at M1 for initial programming prior to turning on the camera in order to find stimulation levels that are suitable for the patient to be set on their Video Processing Unit (VPU)^{4,5}. During the first session, the electrodes whose resistances are too high are disabled and the electrodes that are functional and usable are determined. A quick scan of the array is done using various stimulation amplitudes to determine which electrodes are able to produce a percept or phosphene. The minimum current that is needed for the patient to see a phosphene fifty percent of the time is defined for each electrode^{1,4}. The video signal from the camera is mapped to the electrical signal for individual or groups of electrodes, determining which electrodes are being stimulated and at what respective frequency. These values are set to the patients VPU to be used in different conditions¹. Programming for this study included use of the "Programming Assistant" software that is designed to streamline the programming process to measure general sensitivity^{1,4}. Through use of this software, the camera alignment process is simplified and comfort is determined under more real-world stimulation conditions¹. Depending on the patient experience, the device can be reprogrammed on a regular basis for a readjustment in response to changes to the array or the patient's responses to the electrode stimulation^{5,6}. The brightness of perception and the number of electrodes that give the patient a perception may decrease over time. Patients may need several reprogramming sessions in order to fully optimize the use of the device⁵. The sensitivity detection from each programming session for each patient was provided by from the programming technician from Second Sight where the values for sensitivity (μA) of each electrode for each session and the maximum current (μA) of each electrode per stimulation were collected and analyzed.

Electrode Array-Retina Apposition Distance (Gap Distance)

A Cirrus HD-OCT Machine was utilized by the PAS study to capture images during each patient visit. Parameters for capture at each visit included a 6 mm x 6 mm macular cube image (acquiring 512 nasotemporal scans x 128 superoinferior scans) which were utilized for study purposes. Images were located using unique patient identifiers and analyzed using Zeiss OCT analytical software. Eligible scans included a majority of the 60 electrodes and a surrounding portion of retina, the ability to visualize or estimate the precise location of each electrode, and a signal strength of at least 5 out of 10 (determined by the Zeiss software). While in the macular cube view of the software, the perpendicular nasotemporal and superoinferior raster lines were placed directly over the center of each visualized electrodes (Fig. 1). On the associated horizontal and vertical tomograms, the built-in caliper measurement tool was used to measure the vertical distance (in μm) between the electrode array and retina (Fig. 2). These measurements were taken for each patient at M3, M6 and Y1. The electrodes were designated a label (A-

F, 1–10) to ensure consistency of measurements at each visit. Out of 1200 electrodes, 1124 (93.7%) were able to be measured.

Statistical Analysis

At each visit for SL testing, the difference in pixel distance with the device OFF and ON (OFF – ON) was calculated, with positive values indicating an improvement with the device ON. Similarly, at each visit for DOM testing, the difference in degrees with the device OFF and ON (OFF – ON) was measured, with positive values indicating an improvement with the device ON. For patients that demonstrated an average improvement in SL and DOM testing, a two-tailed paired t-test was performed. To correlate visual function with gap distance, Regression analysis between the average OFF – ON measurements and gap distances (with R = -1 indicating an overall improvement in visual function with smaller gap distances) was performed. Regression analysis was also used to determine the correlation between sensitivity detection threshold and change in visual function (average OFF – ON measurements). Statistical analyses were performed on Microsoft Excel.

Results

Correlation of electrode-retina gap with sensitivity detection threshold

The mean sensitivity threshold detection from all programming and reprogramming sessions (Table 2) were analyzed in relation to the average electrode array-retina gap distance from all 5 patients. No significant correlation with sensitivity detection threshold and the electrode array-retina gap distance was found ($p > 0.05$, 0.98).

Table 2
Sensitivity Detection Thresholds measured at four sessions.

Sensitivity (µA)					
Patient #	Session 1	Session 2	Session 3	Session 4	Average
01	120.41	—	—	—	120.41
02	66.13	136.8	156.2	—	119.71
03	141.05	—	—	—	141.05
04	143.35	—	—	—	143.35
05	130.96	190.73	218.62	197.89	184.55

Visual Function Outcomes

In SL testing, 3 out of 5 patients demonstrated an improvement in visual function at M3, M6 and Y1 with the device ON (Table 3, Fig. 3). 1 out of these 3 patients had a statistically significant average improvement in visual function ($p < 0.05$) using a two-tailed paired t-test. 1 patient demonstrated a marginal improvement at M3 (0.90 pixels), but this improvement was not seen at M6 or Y1. In DOM testing, 2 patients demonstrated an improvement in visual function when averaged over the three visits, with 1 patient having an improvement at M3, M6, and Y1 (Table 3, Fig. 4). 1 patient showed an improvement at M6, but this improvement was not seen at other visits. None of the improvements in DOM testing were found to be statistically significant ($p > 0.05$).

Table 3

Results of Square Localization (SL) and Direction of Motion (DOM) Testing at month 3 (M3), month 6 (M6), and year 1 (Y1) measured as a change in pixels (SL) or degrees (DOM) between testing with the device OFF and ON. A positive number indicates an improvement with the device ON.

Square Localization Testing					Direction of Motion Testing			
Device OFF – ON (pixels)					Device OFF – ON (degrees)			
Patient #	M3	M6	Y1	Average	M3	M6	Y1	Average
01	18.67	81.47	71.14	57.09	2.39	14.74	14.20	10.45
02	0.90	-37.71	-81.36	-39.39	-15.58	-13.87	-43.74	-24.39
03	-52.20	-71.52	-52.72	-58.81	-10.03	-19.02	-8.94	-12.66
04	111.50	113.72	100.17	108.46	-2.10	0.63	-21.80	-7.76
05	27.96	18.35	108.99	51.76	1.32	8.54	-3.21	2.22

Correlation of Visual Function with Gap Distance

The mean change in visual function with the device OFF and ON over the 3 testing visits was analyzed in relation to the average electrode array-retina gap distance from all 5 patients (Fig. 5). No significant correlation was found between SL measures and electrode array-retina gap distance ($r = 0.20$, $p = 0.74$). No significant correlation was found between DOM measures and electrode array-retina gap distance ($r = -0.18$, $p = 0.77$).

Discussion

The Argus II retinal prosthesis is a relatively novel medical device that can marginally restore some functional vision in patients suffering from retinal dystrophies. Numerous studies have demonstrated that a statistically significant improvement in visual function can occur in some patients, and it can no doubt impact their lives tremendously^{7,8,9,10}. Our study’s analysis of SL results in patients with the device further demonstrates that a significant improvement in visual function is possible, with 1 patients performing better with the device ON. An exploration of the factors that influence these positive or

negative outcomes is crucial to our understanding of how to further improve visual prosthetic technology. Ahuja et al³ determined that the electrode array-retina gap distance strongly affects electrical threshold in patients implanted with the Argus II retinal prosthesis, with complete apposition correlating with lower perceptual thresholds. Our study aimed to determine how the gap distance correlates with functional measures of visual acuity such as Square Localization and Direction of Motion testing.

As our results demonstrate, there does not seem to be a correlation between the electrode-array retina gap distance and visual outcome as determined by SL and DOM testing. The patient with the largest average gap distance (patient 04, Avg = 399.37 μm) had the greatest average improvement in SL testing (108.46 pixels). Conversely, the patient with complete apposition of the electrode (patient 02, Avg = 0 μm) at all visits demonstrated decreased visual functions in both SL and DOM testing. While there may not be a correlation between gap distance and visual function, this leads us to hypothesize that complete apposition of the electrode array on the retina may not be necessary for optimal visual outcomes in all patients. This becomes a crucial element in determining patient eligibility for patients with anatomical defects that could affect apposition. Rizzo et al² and Delyfer et al¹¹ have demonstrated that complete apposition of the electrode array on the retina may not be possible in patients with a posterior staphyloma. However, our results demonstrate that patients with staphylomas may not necessarily be precluded from implantation of the Argus II retinal prosthesis, as visual improvement may still occur in the presence of an electrode array-retina gap. An improvement in visual function in patients with a posterior pole staphyloma implanted with the Argus II retinal prosthesis has been demonstrated by Seider et al.¹² It is possible that other staphyloma factors such as size, shape, and location may affect visual function outcomes rather than its presence alone.

One patient with almost complete apposition of the electrode array on the retina (average gap distance 0.38 μm , 0.27 μm , 8.70 μm at M3, M6, Y1, respectively) developed clinically significant retinoschisis. It is possible that complete apposition of the array may increase the risk of adverse postoperative outcomes due to traction, overstimulation of the retina, and inflammatory changes resulting in remodeling of the inner retinal layers.

SL and DOM testing are inherently arduous and time consuming, requiring patients to remain focused and motivated in order to perform optimally. Testing results may be influenced by frustration and avolition, although all attempts were made to ensure that patients completed testing in a comfortable environment. One patient (03) was on an SSRI antidepressant during all testing visits and seemed more motivated to perform well. SL and DOM testing although requires some degree of hand-eye coordination, a skill which may have slightly regressed in these patients due to a long-standing history of blindness. Testing methods that are less time consuming and easier for low-vision patients to perform would allow for a more accurate determination of post-operative visual function. Subjective measures that allow for a better assessment of what patient goals for the device may be and how they hope the device could be used to achieve them would also provide more crucial information for the device's potential for patient benefit. Furthermore, optimal utilization of the Argus II retinal prosthesis requires visual rehabilitation and self-learning by the patient during their day-to-day life. Depending on the quality and quantity of visual

rehabilitation, and the amount of time a patient spends with the device turned ON, their ability to interpret the generated phosphenes would be affected. It is also possible that overuse of the device could negatively impact visual function through constant electrical stimulation. These factors could ultimately influence performance on SL and DOM testing. Lastly, we noted that gap distances changed over time, with three patients having changes of over 50 μm between testing visits. This may be due to the positioning tack coming into contact with extraocular muscles at the scleral interface, or anatomical changes post-operatively. Our study is also limited by a small sample size ($n = 5$). Future studies with a larger data set may provide any opportunity to further explore the relationship between electrode-retina gap distance and visual outcomes.

Conclusion

Our study demonstrates that the post-operative electrode array-retina gap distance may not affect objective visual function outcomes in all patients implanted with the Argus II retinal prosthesis. This finding is an important consideration in patient selection criteria and surgical method as complete apposition of the electrode array on the retina is likely not necessary in all patients for optimal post-operative visual outcomes. In fact, complete apposition could possibly lead to adverse effects due to traction placed on the retina or overstimulation of the inner retinal cell layers. Positioning of the electrode array in relation to the macula may be a more crucial factor in providing benefit to patients implanted with the Argus II retinal prosthesis.

Abbreviations

SL

Square Localization

DOM

Direction of Motion

HD-OCT

High Definition-Optical Coherence Tomography

RP

Retinitis Pigmentosa

VPU

Video Processing Unit

OCT

Optical Coherence Tomography

M1

Month 1

M3

Month 3

M6

Month 6

Y1

Year 1

Declarations

Ethics approval and consent to participate

Approval from the Institutional Review Board (IRB) of Stony Brook University was obtained prior to initiation of the study. Written informed consent was obtained from all participants prior to their inclusion in the study. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on request.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was received for this study.

Authors' contributions

AN and NG extracted and analyzed visual function data, electrode array-retina gap distances and sensitivity detection thresholds. Data analysis was independently reviewed by MY and KC. All authors prepared, read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Ghodasra DH, Chen A, Arevalo JF, et al. Worldwide Argus II implantation: recommendations to optimize patient outcomes. *BMC Ophthalmol.* 2016;16:52.
2. Rizzo S, Belting C, Cinelli L, et al. The Argus II Retinal Prosthesis: 12-Month Outcomes from a Single-Study Center. *Am J Ophthalmol.* 2014;157(6):1282–90.
3. Ahuja AK, Yeoh J, Dorn JD, et al. Factors Affecting Perceptual Threshold in Argus II Retinal Prosthesis Subjects. *Trans Vis Sci Tech.* 2013;2(4):1.
4. Farvardin M, Afarid M, Attarzadeh A, et al. The Argus-II Retinal Prosthesis Implantation; From the Global to Local Successful Experience. *Frontiers in Neuroscience.* 2018;12:584.
5. Sight S. Argus. II Retinal Prosthesis System Fitting Manual 2013; 090002–004.
6. Gregori N, Callaway N, Hoepfner C, et al. Retinal Anatomy and Electrode Array Position in Retinitis Pigmentosa Patients After Argus II Implantation: An International Study. *Am J Ophthalmol.* 2018;193:87–99.
7. da Cruz L, Coley BF, Dorn J, et al. The Argus II epiretinal prosthesis system allows letter and word reading and long-term function in patients with profound vision loss. *Br J Ophthalmol.* 2013;97(5):632–6.
8. Kotecha A, Zhong J, Stewart D, da Cruz L. The Argus II prosthesis facilitates reaching and grasping tasks: a case series. *BMC Ophthalmol.* 2014;14(71):1–8.
9. Humayun MS, Dorn JD, Da Cruz L, et al. Interim results from the international trial of second sight's visual prosthesis. *Ophthalmology.* 2012;119(4):779–88.
10. Ahuja AK, Dorn JD, Caspi A, et al. Blind subjects implanted with the Argus II retinal prosthesis are able to improve performance in a spatial-motor task. *Br J Ophthalmol.* 2011;95(4):539–43.
11. Delyfer MN, Gaucher D, Govare M, et al. Adapted Surgical Procedure for Argus II Retinal Implantation: Feasibility, Safety, Efficiency, and Postoperative Anatomic Findings. *Ophthalmology Retina.* 2018;2(4):276–87.
12. Seider MI, Hahn P. Argus II retinal prosthesis malrotation and repositioning with intraoperative optical coherence tomography in a posterior staphyloma. *Clinical ophthalmology.* 2015;9:2213–6.

Figures

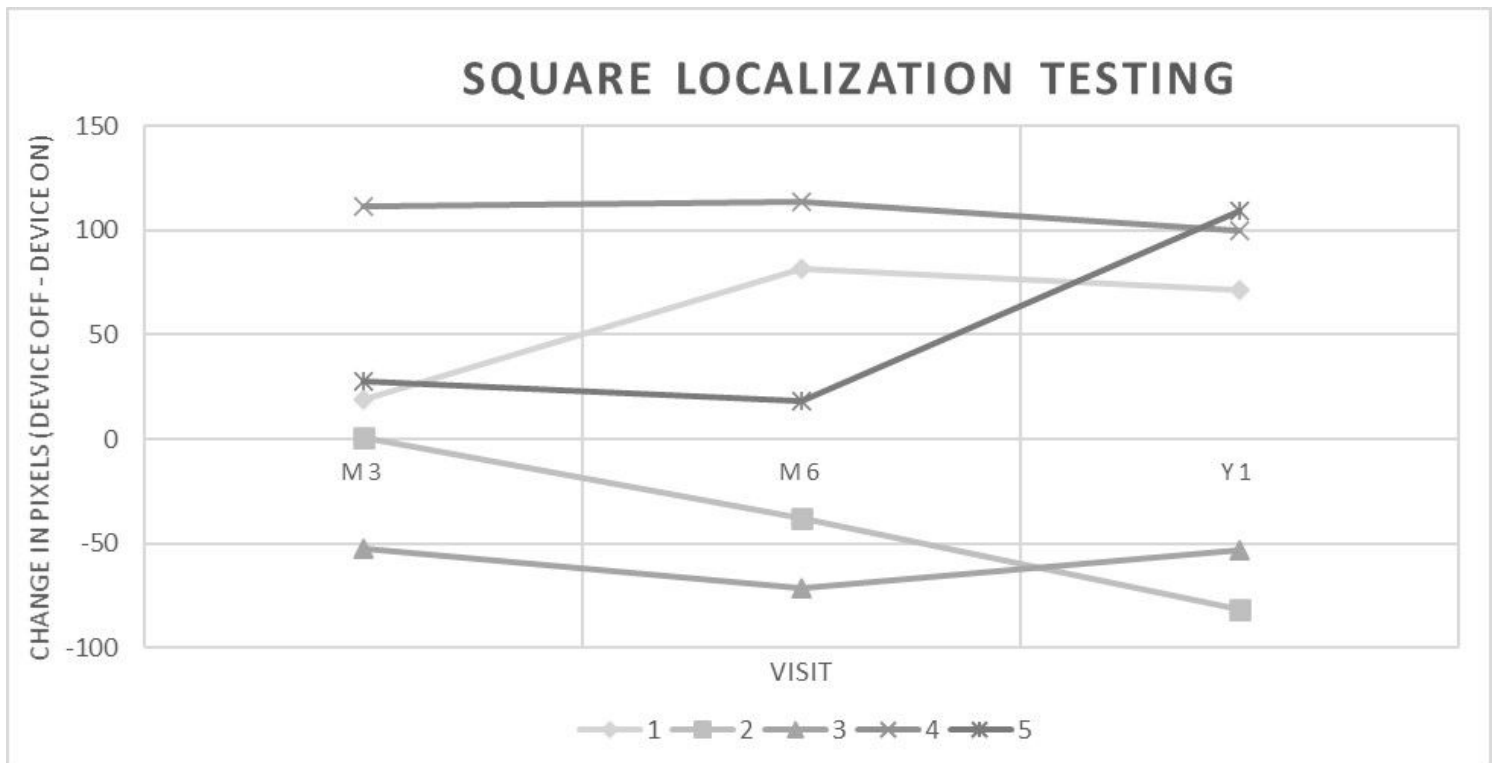


Figure 1

Square Localization Testing results for study patients at month 3, month 6, and year 1 measured as a change in pixels between testing with the device OFF and ON. A positive number indicates an improvement with the device ON.

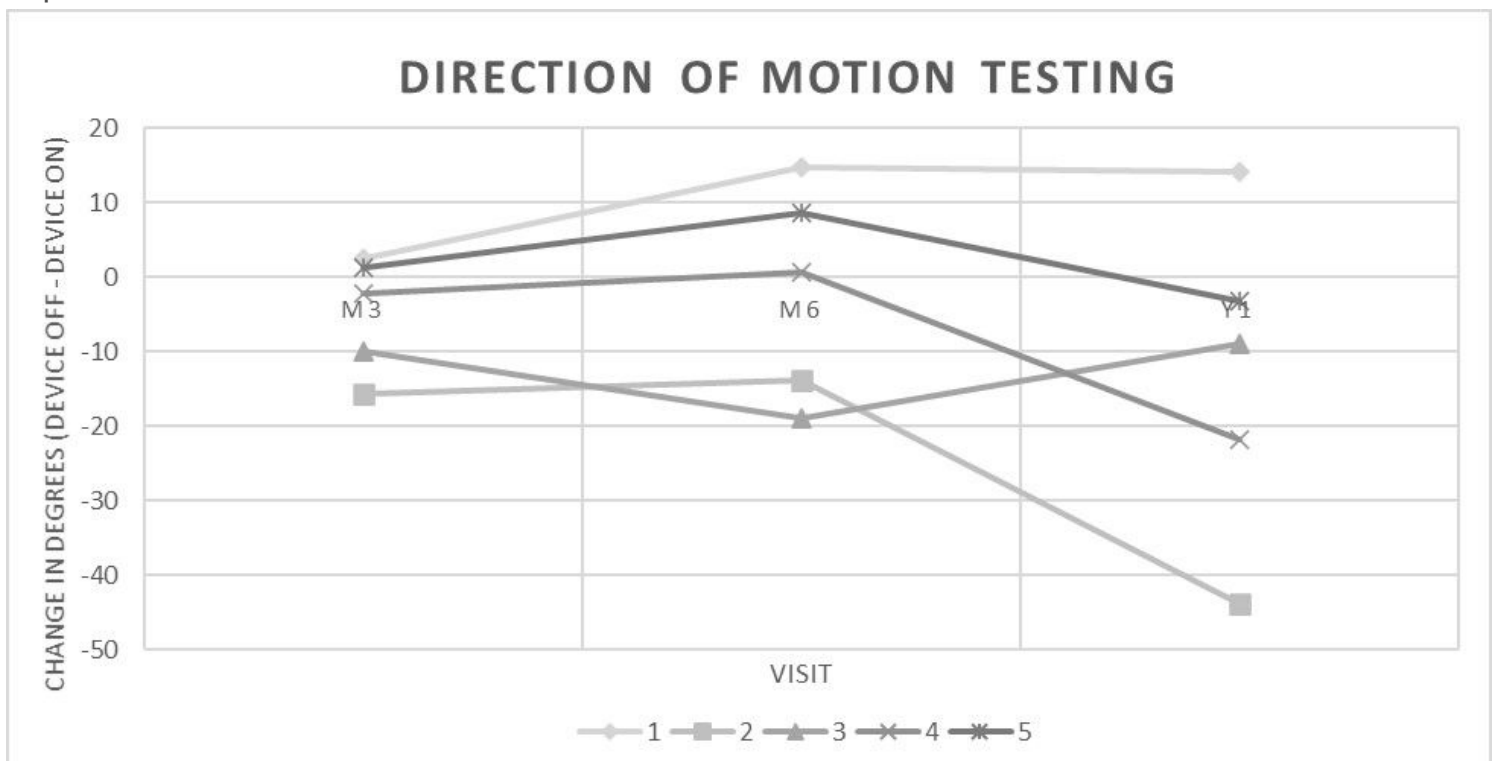


Figure 2

Direction of Motion Testing results for study patients at month 3, month 6, and year 1 measured as a change in degrees between testing with the device OFF and ON. A positive number indicates an improvement with the device ON.

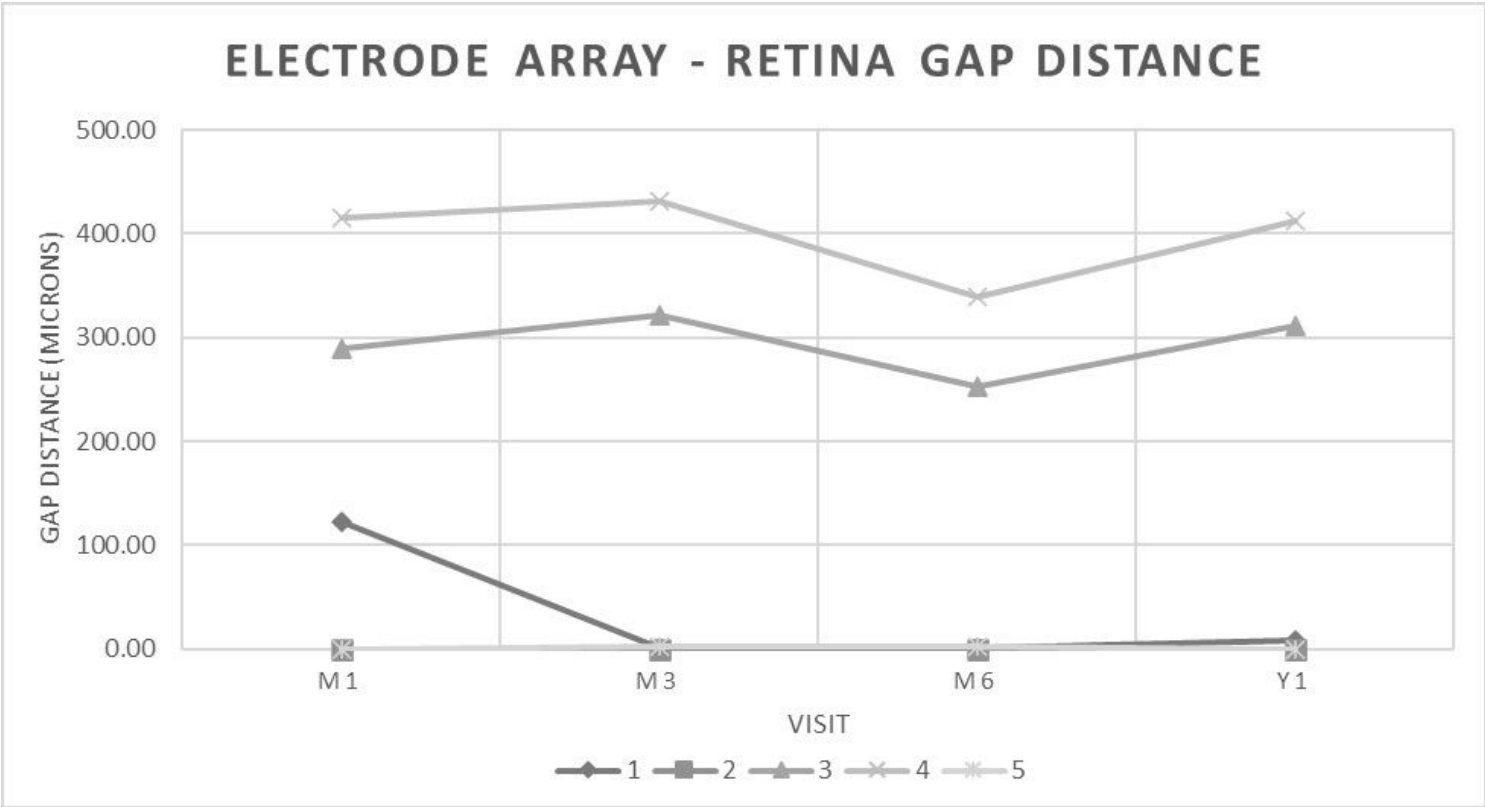


Figure 3

Post-implantation electrode array-retina gap distances of study patients averaged over all measured electrodes at month 1, month 3, month 6 and year 1.

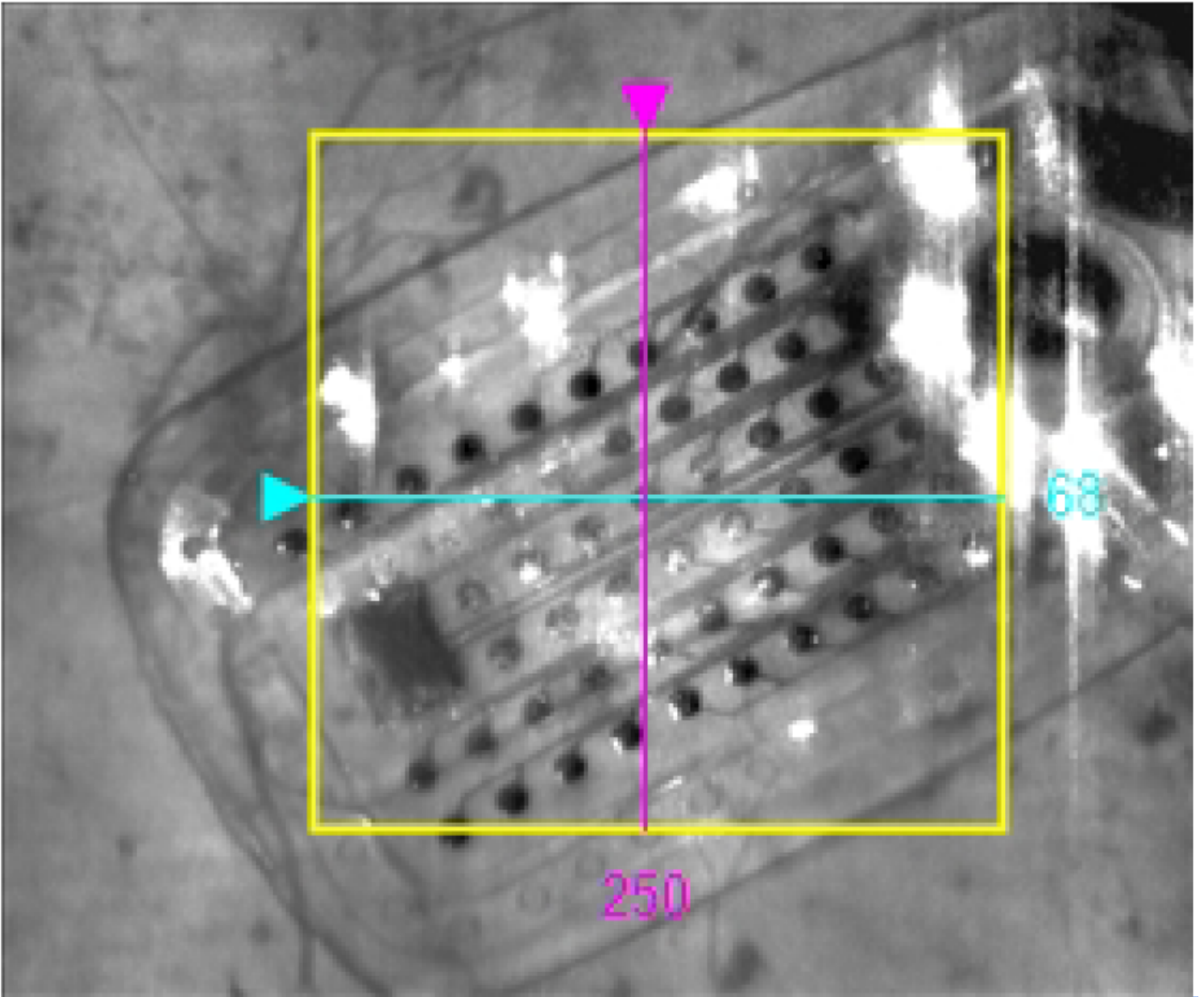


Figure 4

OCT macular cube fundus view depicting electrode array positioned over macula. The macular cube scan in the Zeiss OCT software was used to measure the electrode array-retina gap distance at each individual electrode. 60 electrodes per array in a 6x10 grid were labeled as A-F and 1-10. Perpendicular nasotemporal and superoinferior raster lines were positioned to intersect at the center of the desired electrode using the fundus view.

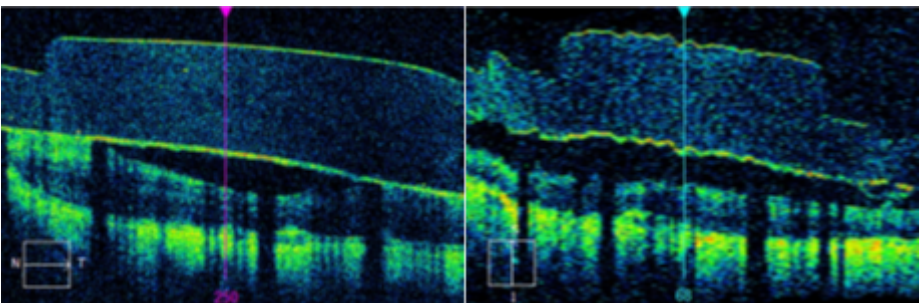


Figure 5

OCT macular cube horizontal and vertical tomograms. After targeting a specific electrode with the raster lines, the software's caliper measurement tool was used to measure the distance along the raster lines between the electrode array and the surface of the retina on the associated horizontal and vertical tomograms.