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Retinal Anatomy and Electrode Array Position in Retinitis Pigmentosa Patients after Argus II Implantation: an International Study

Ninel Z. Gregori¹, Natalia F. Callaway¹, Catherine Hoepfner¹, Alex Yuan², Aleksandra Rachitskaya², William Feuer¹, Hossein Ameri³, J. Fernando Arevalo⁴, Albert J. Augustin⁵, David G. Birch⁶, Gislin Dagnelie⁷, Salvatore Grisanti⁸, Janet L. Davis¹, Paul Hahn⁹, James T. Handa⁴, Allen C. Ho¹⁰, Suber S. Huang^{1,11}, Mark S. Humayun^{3,21}, Raymond Iezzi Jr.¹², K. Thiran Jayasundera¹³, Gregg T. Kokame¹⁴, Byron L. Lam¹, Jennifer I. Lim¹⁵, Naresh Mandava¹⁶, Sandra R. Montezuma¹⁷, Lisa Olmos de Koo³, Peter Szurman¹⁸, Lejla Vajzovic⁹, Peter Wiedemann¹⁹, James Weiland¹³, Jiong Yan²⁰, and David N. Zacks¹³

¹Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL, USA

²Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA

³USC Roski Eye Institute, University of Southern California, Los Angeles, CA, USA

⁴The Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA

⁵Städtisches Klinikum, Augenklinik, Karlsruhe, Germany

⁶Retina Foundation of the Southwest, Dallas, TX, USA

⁷Lions Vision Research and Rehabilitation Center, The Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA

⁸University Eye Clinic Luebeck at the University Hospital Schleswig-Holstein, Lübeck, Germany

⁹Duke University Eye Center, Durham, NC, USA

¹⁰Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA, USA

¹¹Retina Center of Ohio, Cleveland, OH, USA

¹²Mayo Clinic, Rochester, MN, USA

¹³Kellogg Eye Center, University of Michigan, Ann Arbor, MI, USA

¹⁴Retina Consultants of Hawaii, Aiea, Hawaii, USA

Corresponding author: Ninel Z. Gregori, MD, Bascom Palmer Eye Institute, 900 NW 17th St., Miami, FL 33136. Telephone: 305-326-6312, Fax: 305-326-6417, ngregori@med.miami.edu.

Dr. Lisa Olmos de Koo is currently at the University of Washington, Seattle, WA, USA

Dr. Paul Hahn is currently at New Jersey Retina, Teaneck, NJ, USA

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¹⁵University of Illinois at Chicago, Chicago, IL, USA

¹⁶University of Colorado, Aurora, CO, USA

¹⁷University of Minnesota, Minneapolis, MN, USA

¹⁸Eye Clinic Sulzbach, Knappschaft Hospital Saar, Sulzbach, Germany

¹⁹Klinik und Poliklinik für Augenheilkunde, Universitätsklinikum Leipzig, Leipzig, Germany

²⁰Emory Eye Center, Emory University, Atlanta, GA, USA

²¹USC Ginsburg Institute for Biomedical therapeutics

Abstract

Purpose: To assess the retinal anatomy and array position in the Argus II Retinal Prosthesis recipients.

Design: Prospective, non-comparative cohort study

Methods: Setting: international multicenter study

Patients: Argus II recipients enrolled in the Post-Market Surveillance Studies.

Procedures: Spectral-domain Optical Coherence Tomography images collected for the Surveillance Studies (NCT01860092 and NCT01490827) were reviewed. Baseline and postoperative macular thickness, electrode-retina distance (gap), optic disc-array overlap, and preretinal membrane presence were recorded at 1, 3, 6, and 12 months.

Main Outcome Measures: Axial retinal thickness and axial gap along the array's long axis (a line between the tack and handle), maximal retinal thickness and maximal gap along a B-scan near the tack, midline, and handle.

Results: Thirty-three patients from 16 surgical sites in the United States and Germany were included. Mean axial retinal thickness increased from month 1 through month 12 at each location, but reached statistical significance only at the array midline (p -value=0.007). The rate of maximal thickness increase was highest near the array midline (slope=6.02, p =0.004), compared to the tack (slope=3.60, p <0.001) or the handle (slope=1.93, p =0.368). The mean axial and maximal gaps decreased over the study period, and the mean maximal gap size decrease was significant at midline (p =0.032). Optic disc-array overlap was seen in the minority of patients. Preretinal membranes were common before and after implantation.

Conclusion: Progressive macular thickening under the array was common and corresponded to decreased electrode-retina gap over time. By month 12, the array was completely apposed to the macula in approximately half of the eyes.

INTRODUCTION

The Argus II retinal prosthesis system (Second Sight Medical Products, Inc., Sylmar, CA) is the first U.S. Food and Drug Administration (FDA)-approved epiretinal implant that electrically stimulates the surviving inner retinal cells to induce visual perception in patients with severe retinitis pigmentosa (RP) and bare light perception or no light perception in both

eyes.¹ RP causes a gradual destruction of photoreceptor cells, however some bipolar, amacrine, and ganglion cells and their exons survive in these patients.¹⁻⁴ The Argus II prosthesis provides most recipients with some functional vision, useful in orientation and mobility tasks, and improves quality of life.^{1,5,6}

The Argus II retinal prosthesis consists of external components the patient wears, namely a pair of glasses with a camera on the bridge of the nose and a video processing unit (VPU), which sends a digitized signal to the implant in the eye.⁴ The implant contains an electrode array with sixty 200- μ m platinum electrodes that deliver electrical stimulation to the surviving inner retina cells.⁴ The electrode array is affixed to the macula with a spring-loaded titanium tack. According to the surgeon's manual, the array should be centered over the fovea with electrodes oriented approximately 45 degrees diagonal to the horizontal meridian, aiming for either no overlap of the optic disc or overlap by the non-electrode portion of the array only.⁷ On the distal end of the array, opposite to the tack, is a handle, which consists of a circular tubing used for surgical manipulation of the array. Each electrode has an associated stimulation threshold, which quantifies the current required for the individual to perceive a phosphene.⁴

Previously published studies have focused on the implant's safety and efficacy. The landmark trial (Argus II Retinal Stimulation System Feasibility Protocol, NCT00407602) followed 30 patients throughout the United States, Europe and Mexico, and reported an acceptable adverse events profile and improved ability to localize large objects and movement presented on a computer screen and to perform daily functions in a majority of patients up to 5 years after implantation.¹ Other studies have focused on factors that affect the perceptual thresholds. A significant correlation has been shown between stimulation threshold for perceiving phosphenes and the electrode-retina distance.⁴

There is however a paucity of data regarding changes in retinal anatomy after implantation, position of the electrode array relative to the retinal surface, and stability of the array position over time. A recent study of 18 eyes reported slight rotation of the array over time and variable electrode-retina distance with a surgical procedure adapted in France utilizing scleral flaps and temporalis fascia autograft. Full apposition of the array was seen in a minority of patients.⁸ Position of the electrode array is dependent on the patient's anatomy, surgeon's technique, and relative difficulty in controlling the distance of the array from the retinal surface especially in cases of high myopia or staphyloma.^{8,9}

The goal of this collaborative effort was to evaluate the Spectral-Domain Optical Coherence Tomography (SD-OCT) images of the Argus II recipients enrolled in Post-Market Approval studies in the United States and international sites in order to assess the retinal anatomy and the array position in these patients. Based on clinical observations, we tested the hypothesis that with time the retina thickens in many patients, and the array-retina distance decreases, improving apposition of the array. This multi-center data analysis represents the largest longitudinal macular anatomy study in Argus II patients, and the procured information would aid in surgical planning, follow-up, and the development of future implant models with the overarching goal of improving artificial vision for patients with severe vision loss due to outer retinal degeneration.

METHODS

The current study is a collaborative effort of the United States and international surgical sites participating in two of three Post-Market Surveillance Studies of the Argus II retinal prosthesis, which are prospective, interventional, open-label protocols ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01860092) Identifiers NCT01860092 and NCT01490827). The aim of the current analysis was to review the Spectral-domain OCT images collected as part of Post-Market Surveillance Studies in order to evaluate the macular anatomy and electrode array position in these patients. All investigators of the three Post-Market Approval studies were invited, and only those centers who agreed to participate in this collaborative analysis were included (United States and German sites). Only data from patients who consented to participate in the Post-Market Surveillance Study in these centers were included. All subjects included in the current study had signed a consent form to be enrolled in the Post-Market Surveillance Study at their institution. Second Sight Medical Products, Inc. provided access to deidentified images collected prospectively from baseline to month 12 after implantation as part of the Post-Market Study, which had been approved as a prospective study by an Institutional Review Board or Ethics Committee at each institution and was compliant with the Health Insurance Portability and Accountability Act (HIPAA) or equivalent. All research was conducted in accordance with human subjects research standards and tenets of the Declaration of Helsinki.

Images were accessed via Second Sight's HIPAA-compliant, secure, encrypted account used in the Post-Market Surveillance Studies. The same spectral-domain OCT (Spectralis OCT, Heidelberg Engineering, Inc., Germany or Cirrus OCT, Carl Zeiss Meditec Inc., Dublin, CA) was used to collect images at baseline and postoperatively for each individual patient. Retinal thickness and electrode-retina distance (the electrode-retina gap) were measured using the caliper tool on the respective SD-OCT system software. Measurement protocol was designed and deidentified OCT images were reviewed at the Bascom Palmer Eye Institute and Cole Eye Institute. The following parameters were investigated during 12 months after Argus II implantation: macular thickness changes; location (under or adjacent to the array) of macular thickening if present; evolution of the retina-electrode distance through 1 year after implantation; correlation of the retina-electrode distance with the axial length; proximity of the array to the optic disc and the frequency and degree of optic nerve overlap; prevalence and characteristics of preretinal membranes before and after implantation.

Descriptive data were reviewed to study whether the retina was thickest under the array or outside of the array; how many eyes had retinal edema at baseline and how many developed retinal thickening after implantation of the Argus II; how often the preretinal membranes were present at baseline and how frequently they developed after implantation; whether the membranes caused tractional detachment or array misalignment; and whether the presence of the optic nerve overlap caused any optic nerve swelling.

A standardized approach to image evaluation and measurements was developed and strictly followed, as described below.

Preoperative Maximal Macular Thickness

Retinal thickness was measured as the distance from the inner retinal surface to the top of the hyperreflective layer under the retina, which anatomically represents the retinal pigment epithelium. Baseline maximal macular thickness was measured as the largest retinal thickness along a B-scan, in three locations: superior macula, foveal scan, and inferior macula. These locations approximated the location of the tack, array midline, and the handle as close as possible. Baseline maximal thicknesses at superior macula, through the fovea, and inferior macula were compared to the maximal retinal thicknesses at the tack, midline, and handle respectively at 1, 3, 6, and 12 months post-implantation.

Postoperative Axial and Maximal Macular Thickness Measurements

Postoperative SD-OCTs at 1, 3, 6, and 12 months were analyzed. Retinal thickness was measured the same as preoperatively. The *axial* retinal thickness was measured on the best quality OCT B-scan taken near the tack, midline and the handle at a point where the B-scan intersected the long axis of the array (a line running from the tack to the handle as shown in Figure 1). In addition, the *maximal* retinal thickness was measured along these same B-scans in each of these three locations. It was documented whether the maximal measurement was located under the array and/or adjacent to the array. For all follow-up visits, a B-scan at a similar location with respect to the array anatomy was measured. If no scan of acceptable quality or correct location was available at a particular follow-up visit, no measurement was recorded to keep measurements consistent between visits.

Macular Thickening

Macular thickening was assessed as either present or absent at each follow-up visit by judging the appearance of retinal layers compared to baseline and earlier postoperative visits, and the location of thickening (quantified by the maximal macular thickness measurements) was documented as under the array and/or adjacent to the array. If the quality of the scan resolution under the array was sufficient, an attempt was made to distinguish whether intraretinal fluid (IRF) cysts were present. For all follow-up visits, a B-scan at a similar location was chosen at months 1, 3, 6, and 12.

Axial and Maximal Electrode-retina Gap Measurements

The electrode-retina gap was defined as the distance between the inner retinal surface and the lower hyperreflective surface of the array marked by the shadows under the electrodes. The *axial* gap was measured on the same best quality B-scans used for axial retinal thickness measurements near the tack, midline and the handle at a point where the B-scan intersected the long axis of the array (a line running from the tack to the handle, Figure 1). In addition, the *maximal* gap under the electrodes was measured on each of these B-scans at months 1, 3, 6, and 12.

Optic Disc Overlap

The optic disc to array relationship was examined on the *en face* OCT images at each follow-up visit. Any presence or absence of optic nerve overlap was noted.

Among those with optic nerve overlap, the images were also assessed to determine if the disc was overlapped by the electrode-free polymer rim of the array (bumper) solely or also by the electrodes. The images were evaluated for evidence of optic nerve swelling by inspecting the appearance of the nerve rim on the *en face* images.

Preretinal Membrane Evaluation

All available B-scans through the array at each visit were evaluated to detect any preretinal membranes. When a preretinal membrane was identified, it was classified as focal versus diffuse. Diffuse was defined as a membrane present on five or more contiguous B-scans. The membrane was also characterized as completely adherent versus focally adherent, i.e. separated from the inner retinal surface (off-the-retina), if any separation was seen on any B-scan. Finally, the location of the preretinal membrane was described by quadrant (temporal, inferior, etc), hemi-field if two contiguous quadrants, or diffuse if present in more than two macular quadrants, as much as possible depending on the quality of OCT images.

Statistical Analysis

Statistical analysis was performed using SPSS Version 24.0 (IBM Corp., Armonk, NY, USA). A p-value of 0.05 or less was considered statistically significant. The Generalized Estimating Equations (GEE) models employing a first order autoregressive correlation structure were used to assess changes in thickness and gap size over time.

RESULTS

Baseline Participant Data

Spectral-domain Optical Coherence Tomography (SD-OCT) images of 33 patients from 16 surgical sites located in the United States and Germany were reviewed from preoperative visit through month 12 after implantation as available from Second Sight Medical Products, Inc. The baseline demographic information of participants is shown in Table 1. SD-OCT images were available for review as follows: 28 (85%) eyes had OCTs available at preoperative visit, 26 (79%) of patients had OCTs from at least two postoperative visits, 17 (52%) of patients had OCTs from at least three visits, and 9 (27%) of patients had OCTs from all 4 postoperative visits.

Axial Macular Thickness Along the Array's Long Axis

In order to assess the macular thickness evolution under the array, the axial macular thicknesses along the long axis of the array, a line between the tack and the handle, were explored with spaghetti plots for each patient (data not shown), boxplots (Figure 2), and the mean axial thickness measurements near the handle, midline, and tack at different follow-up points (Table 2). Spaghetti plots and boxplots of the measurements at different follow-up points demonstrate a high variability between patients at each location (Figure 2). The median values in the boxplots are indicated by the horizontal line in the boxes encompassing data points in the 25th to the 75th quartiles. The median values remained fairly unchanged at the tack and the handle, however steadily increased at midline from month 1 through month 12. These findings were corroborated by the mean axial macular thicknesses (Table 2),

which increase from month 1 through month 12 at each location, but reached statistical significance only at the array midline (p -value=0.007).

Maximal Macular Thickness by Location

The maximal macular thicknesses near the tack, midline, and the handle levels were measured along the same B-scan used to assess the axial macular thickness at these locations. Evolution of the maximal macular thickness after implantation was explored by spaghetti plots for each patient (data not shown), boxplots (Figure 3), and the mean maximal thicknesses at the handle, midline, and tack at different follow-up points (Table 2). The spaghetti plots and boxplots show large variability between patients. The median maximal macular thickness, represented by the horizontal line within boxes, increased from baseline through month 12 at each location, especially near the array midline (Figure 3). The mean maximal macular thicknesses increased from baseline at each location, and reached statistical significance near the tack ($p<0.001$) and midline ($p=0.004$, Table 2). The rate of maximal thickness increase was highest near the array midline (slope=6.02, $p=0.004$), compared to the tack (slope=3.60, $p<0.001$) or the handle (slope=1.93, $p=0.368$).

Macular Thickening

Macular thickening was assessed as either present or absent at each follow-up visit by judging the appearance of retinal layers compared to baseline and earlier postoperative visits. Based on the appearance of the retinal layers and presence of cystic changes, 6 eyes out of 28 available baseline OCTs (21.4%) were classified as having macular edema prior to implantation. Five of 6 eyes had diffuse thickening, i.e. present on more than 5 contiguous scans. After implantation, the macula appeared thickened in 11 of 21 (52%) eyes at month 1, 19 of 27 (70%) eyes at month 3, 13 of 19 (68%) eyes at month 6, and 16 of 18 (89%) eyes at month 12. To determine whether the retina thickened only under the array or also adjacent to the array, the location of the maximal macular thickness was recorded as under the array or outside, adjacent to the array in each OCT analyzed. Over the study period, the retina was thickest under the array in the majority of eyes (73% to 96%), however in up to a quarter of OCTs, namely 4% to 27% of eyes depending on the follow-up time point, the retina was thickest adjacent to the array, mostly in the nasal macula where the retina is naturally thicker than within the central macula at baseline or where the array appeared to press on the adjacent retina causing it to heap up immediately adjacent to the array edge, a “snowplow effect” (Figure 6, Bottom Left). Resolution of many OCT scans was poor under the array, making it difficult to assess for the presence of cysts, thus these data are not reported. Almost none of the scans with adequate resolution showed cystic changes, but the retina appeared boggy. This was consistent throughout 12 months, with no specific trend noted at any location along the array.

Electrode-Retina Gap

In order to assess the distance between the electrodes and the inner retina, the electrode-retina gap measurements were taken along the array’s long axis near the tack, midline, and handle. In addition, the maximal gap measurements under the electrodes along the same B-scan near the tack, midline, and handle were recorded (Table 3). The boxplots demonstrate variability between eyes in the axial and maximal gap measurements (Figure 4, 5). Along

the long axis, the median axial gap was zero at all follow-up points near the tack and handle, while the median gap at midline was 165 microns at month 1 and steadily decreased to zero by month 12 (Figure 4). The median maximal electrode-retina gap was under 100 microns near the tack and the handle at month 1 and zero at other time points (Figure 5). The median maximal gap at midline was 214 microns at month 1 and steadily decreased to 40 microns by month 12 (Figure 5).

The majority of eyes had complete touch of the electrodes and the retina (zero gap) at the tack and the handle (Table 4). The percentage of eyes with zero axial and maximal gap increased significantly across the follow-up visits at the midline but not at the tack or the handle, which corresponds to the significant macular thickening at array midline seen postoperatively. While the mean axial and maximal gaps decreased over the study period, the decrease in mean maximal gap size at midline was the only significant trend observed ($p=0.032$, Table 3).

A negative correlation between the electrode-retina gap change and macular thickness change along long axis of the array was observed from month 1 to month 3 ($n=11$, $r=-0.69$, $p=0.019$), from month 1 to month 6 ($n=10$, $r=-0.79$, $p=0.007$), and from month 1 to month 12 ($n=9$, $r=-0.83$, $p=0.006$).

Correlation of Electrode-Retina Gap with Axial Length and Tack Appearance

Axial length ranged from 21.8 mm to 25.9 mm with the median of 23.2 mm. Axial length was not correlated with large maximal gap. Axial lengths as small as 22.0 mm and as large as 25.91 mm were represented among the eyes with a maximal gap larger than 150 microns and larger than 200 microns at any location. Moreover, the 22.0 mm eye had larger gaps at the tack, midline, and handle than the 25.91 mm eye.

Out of 10 eyes with the maximal electrode-retina gap of 150 microns or more at the midline or the handle at month 1, five had zero axial gap at the tack, i.e. no separation between the array and the retina at the tack. Interestingly, 3 of these 5 eyes had a large maximal gap of 85, 108, and 185 microns near the tack at month 1, indicating a degree of tilt of the array around the long axis. The five remaining eyes demonstrated tack gaps between 32 and 395 microns at month 1. The eye with a 395-micron gap at the tack had the largest axial gap and maximal gap at the midline (both 483 microns). Two eyes had a steep curvature of the macula, but axial lengths of 24.2 and 23.7 mm and no obvious staphyloma on preoperative examination, with a large maximal electrode-retina gap of 433 and 483 microns at the midline respectively (Figure 6, Middle Right). Thus, it appears that in some eyes incomplete tacking was responsible for the large electrode-retina gap, in other eyes the curvature of the array and the retina did not follow the same radius, while in some eyes the array appeared tilted in such a way that one edge lifted off the retina.

Optic Nerve-Array Overlap

Optic disc overlap was observed in 8 of 19 (42%) OCTs at month 1, 8 of 26 (31%) at month 3, 3 of 18 (17%) at month 6, and 5 of 18 (28%) OCTs at month 12. In the majority of eyes the overlap was by the electrode-free polymer rim only. A single electrode was seen over the optic nerve in two eyes at month 1, one eye at months 3 (one of the two eyes from month 1)

and one eye at month 12 (a different eye which was not imaged earlier). No evidence of optic nerve edema was visible in any of the images.

Preretinal Hyperreflective Membranes

Completely adherent, very fine, hyperreflective membranes were seen in 25/28 (89%) eyes at baseline (Figure 6, Top Left), 14/15 (93%) eyes at month 1, 19/21 (90%) eyes at month 3, 12/13 (92%) at month 6, and 13/14 (93%) eyes at month 12. These adherent membranes were diffusely present in 5 or more contiguous B-scans in 20/25 (80%) eyes at baseline, 13/14 (93%) eyes at month 1, 18/19 (95%) at month 3, 11/12 (92%) eyes at month 6, and 11/12 (92%) eyes at month 12. These fine, completely adherent membranes were seen everywhere in the macula in 76%, 57%, 65%, 67%, and 58% at baseline and month 1, 3, 6, and 12 respectively.

Off-the-retina focally adherent membranes were seen in 10/28 (36%) eyes at baseline, 6/15 (40%) eyes at month 1, 9/21 (43%) eyes at month 3, 5/13 (38%) eyes at month 6, and 10/14 (71%) eyes at month 12 (Figure 6, Middle Left). These membranes were diffusely present in 5/9 (56%) eyes at baseline, 4/6 (67%) eyes at month 1, 4/9 (44%) at month 3, 4/5 (80%) at month 6, and 8/9 (89%) eyes at month 12. The off-the-retina membranes were seen in one or two quadrants only in 67% eyes at baseline and all eyes at months 1 through 12 postoperatively.

Preoperatively only 4 eyes demonstrated a thick focally adherent off-the-retina preretinal membrane resembling a true epiretinal membrane or thick hyaloid (Figure 6, Top Center), and these were no longer present after vitrectomy and implantation surgery. Postoperative all completely adherent and most off-the-retina focally adherent membranes were very fine and were not seen to affect the position of the array (Figure 6, Middle Left), with only one eye showing an off-the-retina membrane elevating an edge of the array off the retina. No tractional membranes were seen. Two eyes with peculiar hyperreflective layer adherent to the posterior surface of the array separate from the retina were seen, which may represent either fibrosis or inflammatory material (Figure 6, Middle Center). No membranes encapsulating the array were seen in any eyes.

DISCUSSION

Progressive macular thickening under the array was commonly seen and corresponded to decreased electrode-retina gap from month 1 to month 12 after implantation. By month 12, the array was well apposed to the macula, with no gap from the tack to the handle, in approximately half of the eyes. In the majority of eyes the retina was thickest under the array but in some eyes at each follow-up period the retina was thickest adjacent to the array due to a “snowplow” effect of the array’s edge pressing against the retina. Since a significant correlation has been shown between electrode thresholds for eliciting visual percepts and the electrode-retina distance,⁴ the current needed to create a phosphene would be expected to be lower the closer the implant is to the retina. Ahuja et al studied 22 Argus II patients and showed that placing the array in close proximity to the retinal surface produced a high percentage of electrodes with lower thresholds.⁴ De Balthasar et al studied 6 patients with an earlier version of the Argus implant and demonstrated direct correlation of stimulation

thresholds with the distance from the retinal surface but not with electrode size, electrode impedance, or retinal thickness.¹⁰

It would have been informative to study a correlation between the electrode-retina gaps and the electrode thresholds in this study; however, the Post-market Surveillance Studies do not require rechecking of electrode thresholds at any point. The patients were reprogrammed on an “as needed” basis as requested by individual sites, whenever a patient reported discomfort, declining visual function, or did not respond well to the current settings. Thus, we were unable to collect and systematically analyze device functional data in relation to the changes in anatomy.

We also considered comparing thresholds between patients with and without complete apposition, however that analysis would be inconclusive since thresholds in each individual depend on many factors: the apposition gap between the retina and the array, the health of the residual cells, possible membranes under the array, time given between stimulations (cell recovery time), patient fatigue during a testing session, and possibly age and number of years of blindness. Moreover, comparing visual function, as measured by 3 custom-designed primary end points used in the Surveillance Studies (square localization, direction of motion, and grating visual acuity),¹ would introduce a bias of blind rehabilitation training over time.

Based on the imaging results of the current study, it appears prudent to monitor the array position and macular anatomy in the Retinal Prosthesis recipients over time with OCT. Since the initial programming usually occurs at 2–4 weeks after implantation, if a significant change in the retina-electrode distance or a new membrane is detected, it may be helpful to reprogram the device, for example at 6–12 months, to adjust the currents based on the anatomy of the patient. Patient comfort and quality of phosphenes may improve after reprogramming, and should be a subject of a future study looking specifically at device function in relation to retinal anatomy and array positioning.

Optic disc-array overlap by the polymer rim was seen in up to 40% eyes depending on the time-point, with a single electrode visible over the optic nerve in a total of three eyes only, and no optic nerve edema was detected. Thus, the surgical placement appears to follow surgical manual adequately without obvious optic nerve compromise.

Preretinal membranes were present in almost all OCT scans at baseline and all postoperative follow-up periods. A third or more of eyes also had membranes separated from the retina before and after surgery. The adherent and off-the-retina membranes were present with similar frequency and characteristics at all postoperative follow-up periods, and no tractional or encapsulating membranes were seen. Based on our surgical experience, RP patients have a very adherent cortical vitreous, which fragments into wisps and may be difficult to remove completely; thus, the preretinal membranes may represent the adherent hyaloid and its postoperative remnants.

Two eyes with “subclinical staphyloma” evident as a steep macular concavity on preoperative OCT had large electrode-retina gaps, which did not prevent functionality of the device in these two patients. Both patients performed better with the device ON than OFF on Square Localization testing. Large electrode-retina gap under the array’s midline was seen in

eyes with incomplete tacking, steep macular concavity, or tilting of the array with one edge lifting off the retina. The currently approved Argus II epiretinal prosthesis contains a semi-rigid polymer array which has some flexibility but may not follow the curvature of the posterior retina completely, resulting in variability of the electrode-retina distance.¹¹

At the time when the current study was planned and collaborative group was formed, no large-scale published studies evaluated the macular anatomy and array position in the Retinal Prosthesis recipients. The idea for this collaborative project was born during an investigators meeting held at ARVO in 2016. The current study was designed to assess the macula and the array position as a variable of time with an overarching goal to understand whether the current design of the array allows close contact between the electrodes and the retina or whether a modification of the current array is necessary.

Our data demonstrated that the current array is able to appose the retina in about half of the patients; however, more flexible design may improve the electrode-retina proximity in patients with steep maculae. A recent report from three French implanting sites, utilizing a modified surgical implantation technique involving construction of a scleral flap, showed complete apposition of the Argus II array to the retina in only 4/18 (22.22%) eyes, partial apposition in 9/18 (50%), and lack of apposition in 5 eyes (27.78%), four of which had a posterior staphyloma and one had a concave macula without an obvious staphyloma.⁸ The mean electrode-retina distances in that study were between 100 and 450 microns in patients with partial apposition, with the largest gap seen in the eye with incomplete insertion of the retinal tack.⁸ In the current study, a concave macula and poor insertion of the retinal tack were also associated with the largest electrode-retina gaps. We further explored a possibility that long axial lengths may make it difficult for the surgeon to handle the array over the retina, however large electrode-retina gaps did not correlate with the long axial lengths, as long as 25.9 mm, in our cohort.

The OCT has been shown an essential tool for screening potential Retinal Prosthesis candidates, mainly to identify a posterior staphyloma or significant epiretinal membrane, and more recently as an intraoperative tool to guide the surgeon during array tacking.^{9,11,12} We utilized SD-OCT to examine changes in the macular thickness after Argus II implantation. In our cohort, 21 % of eyes demonstrated cystic macular edema prior to implantation. By 12 months, 89% of eyes had some degree of macular thickening compared to baseline retinal appearance and thickness, which may be due to long-term mechanical or electric stimulation of the retina, and may be non-pathologic. Interestingly, electrical stimulation to the retina has been shown to lead to preservation of the retinal cells via generalized neurotrophic effect. For example, transcorneal electrical stimulation was found neuroprotective against light-induced retinal degeneration in rodents, with cell preservation seen in the inner and outer retinal layers, including increased survival of ganglion cells.¹³⁻¹⁵ Subretinal electrical stimulation by the artificial silicon retina microchip with 5000 microelectrodes has been shown to improve visual field size, visual acuity, and subjective visual function distant to the implant in a pilot study with 6 patients followed for over 1 year.¹⁵ Electrical stimulation of the retina has been shown to lead to downregulation of pro-apoptotic factors and release of neurotrophic factors.^{14,16,17} Moreover, electrical stimulation can promote ganglion cell growth and regeneration in vitro and in vivo.¹⁸ Increase in the

retinal thickness in response to electric stimulation has been shown in an in-vivo rabbit model with platinum/iridium disk electrodes.¹⁹ The authors demonstrated retinal swelling after 30-minutes of high-density electrical stimulation at 1.22 and 1.63 mC/cm² but not with lower charge densities of 0.92 and 1.02 mC/cm².¹⁹ The Argus II stimulation limit is 0.35 mC/cm², which is well within the safety limits of up to 1 mC/cm² shown safe with the Argus II implant.⁴ Thus, the nature of macular thickening observed in the Retinal Prosthesis recipients is not clear and should be studied further, possibly by clinicopathologic correlations as opportunities arise.

There are inherent limitations to our study. Baseline macular thickness was measured in the superior macula, through the fovea, and inferior macula, approximating the locations of the tack, midline, and the handle. Direct correlation of the locations was not possible due to inability to register fundus images and OCT images before and after implantation. Other limitations to note are relatively small sample size and the impact of potential loss to follow-up on the data making it difficult to assess longitudinal outcomes over time. The reader should keep in mind that each point is a cross sectional survey of the available measurements and not the data from all 33 patients.

Another limitation of the current study is inconsistent quality of the OCT images. Given poor fixation, significant nystagmus, and high reflectivity of the array, obtaining good quality scans is not trivial in these patients. Due to inconsistent quality of the images, it was not possible to adequately visualize the retinal layers and evaluate for possible cysts in many scans. The 6 mm × 6 mm images obtained with a commercially available spectral-domain OCT systems may not produce a clear view of the underlying retina or capture the entire nasal-to-temporal view of the array. The swept-source OCT has been shown to produce superior images of the Argus II array and the underlying retina due to higher image acquisition speed, deeper penetration into the retina, longer wavelength with better signal-to-noise ratio, and wide-field 12 mm × 12 mm images.²⁰ Unfortunately, swept-source OCT devices are not widely available and were not utilized in the Surveillance Studies. Moreover, no standardized OCT protocol was required in the Surveillance Studies.

In conclusion, we demonstrate significant macular thickening under the array midline and corresponding significant decrease in the maximal retina-electrode gap over 12 months after Argus II implantation. The gap diminished with time in many eyes and became zero in approximately half of the eyes at 1 year. While the current study was not able to evaluate the effects of the retina-electrode positioning on the electrode function, it described a dynamic nature of the anatomy in the Retinal Prosthesis recipients. Monitoring the array position and macular anatomy in these patients provides the clinician valuable information regarding the array positioning, which may suggest an appropriate time for reprogramming of the electrode currents and increase our understanding of the biomechanics of the retinal implants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Jennifer I. Lim:

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Naresh Mandava:

- Shapetech LLC, founder, equity
- Shape Ophthalmics LLC, founder, equity
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Sandra R. Montezuma:

- Second Sight Medical Products, Inc (consultant)
- Spark Therapeutics: Advisory board

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Highlights

- Progressive macular thickening under the array was commonly seen and corresponded to decreased electrode-retina distance over time
- The rate of maximal thickness increase was highest near the array midline compared to the tack or handle
- By month 12, the array was completely apposed to the macula near the tack, midline and handle in approximately half of the eyes.
- No optic disc swelling was present
- Preretinal membranes were commonly seen before and after implantation, however no tractional or encapsulating membranes were present.

Figure 1. Measurement of Argus II Optical Coherence Tomography Characteristics

Top: En face OCT view of Argus II retinal prosthesis implant (Second Sight Medical Products, Inc., Sylmar, CA) with B-scan near the tack (top left), midline (top middle), and the handle (top right). Middle: Illustration of the Argus II implant from the Surgeon's manual labeled with the tack, midline, handle, and the array's long axis (red line) shown. The red line represents the long axis of the array used to measure axial thickness and gap. Bottom: An OCT B-scan near the handle demonstrates how axial and maximal retinal thickness and electrode-retina gap were measured, and an example of an adherent preretinal hyperreflective membrane (asterisk *). The B-scan cuts through the array diagonally and thus the handle is not visible. The A-scan through the array's long axis is shown as a red vertical line. The blue line represents the axial macular thickness measurement. The yellow line represents the axial electrode-retina gap. The purple line shows the maximal retinal

thickness along the B-scan. The pink line shows the maximal electrode-retina gap along the B-scan. Measurements were taken using the Heidelberg software program.

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Figure 2. Axial Macular Thicknesses Along Array's Long Axis by Location through Month 12 after Argus II Implantation.

Boxplots with Tukey's quartiles are shown for the tack (left), midline (center), and handle (right) with the measured retinal thickness in micrometers along the array's long axis during postoperative months 1, 3, 6, and 12. The median value is indicated by the horizontal line in the box encompassing data points in the 25th to the 75th quartiles. The median values remained fairly unchanged at the tack and the handle, however steadily increased at midline from month 1 through month 12. The X-axis represents months after surgery, the Y-axis represents thickness in microns.

Figure 3. Maximal Macular Thicknesses Along the B-scan by Location through Month 12 after Argus II Implantation.

Boxplots with Tukey's quartiles are shown for the tack (left), midline (center), and handle (right) with the maximum retinal thickness along the B-Scan measured in micrometers at postoperative months 1, 3, 6, and 12. The median value is indicated by the horizontal line in the box encompassing data points in the 25th to the 75th quartiles. The X-axis represents months after surgery, the Y-axis represents thickness in microns.

Figure 4. Axial Electrode-Retina Gap Along Array's Long Axis by Location through Month 12 after Argus II Implantation.

Boxplots with Tukey's quartiles are shown for the tack (left), midline (center), and handle (right) with the electrode-retina distance (gap) measured in micrometers during postoperative months 1, 3, 6, and 12. The median value is indicated by the horizontal line in the box encompassing data points in the 25th to the 75th quartiles. Median gap was zero near the tack and the handle at all points, and steadily decreased at midline from month 1 through month 12. The X-axis represents months after surgery, the Y-axis represents thickness in microns.

Figure 5. The Maximal Electrode-Retina Gap Along the B-scan by Location through Month 12 after Argus II Implantation.

Boxplots with Tukey's quartiles are shown for the tack (left), midline (center), and handle (right) with the electrode-retina distance (gap) measured in micrometers during post-operative months 1, 3, 6, and 12. The median value is indicated by the horizontal line in the box encompassing data points in the 25th to the 75th quartiles. The median maximal gap was under 100 microns near the tack and the handle at month 1 and zero at most other time points. The median maximal gap at midline was 214 microns at month 1 and steadily decreased to 40 microns by month 12. The X-axis represents months after surgery, the Y-axis represents thickness in microns.

Figure 6. Representative Optical Coherence Tomography (OCT) Scans at Baseline and After Argus II Retinal Prosthesis Implantation.

Top Left. Baseline OCT scan shows intraretinal cyst and completely *adherent* hyperreflective preretinal membrane (arrow).

Top Center. Baseline OCT scan shows an example of a thick off-the-retina membrane (arrow) resembling either an epiretinal membrane or thick hyaloid.

Top Right. Baseline OCT scan shows macular concavity in a patient with one of the largest electrode-retina gaps (359 microns maximal gap at midline at month 1).

Middle Left. OCT scan shows low-lying off-the-retina membrane (arrow) commonly seen after Argus II implantation.

Middle Center. OCT scan shows a peculiar hyperreflective layer (asterisk *) adherent to the posterior surface of the array separate from the retina, which may represent either fibrosis or inflammatory material. Thickened retina is seen below the hyperreflective layer.

Middle Right. OCT scan at month 1 shows one of the largest maximal electrode-retina gaps (433 microns at midline) in the eye with a macular concavity shown in Top Right image.

Bottom Left. OCT scan shows a “snowplow” effect of the array pressing against the retina (arrow) and causing adjacent thickening.

Bottom Center. OCT example of boggy macular thickening under the array and hyperreflective layer (asterisk *) under the array. OCT quality is not sufficient to distinguish if cysts are present.

Bottom Right. OCT example of the array completely apposed against the retina. No retinal thickening is seen in this scan. Mild “snowplow” effect is visible (arrow).

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Table 1.

Baseline Demographics of Participants	
Number of participants	33
Number of sites	16
Gender - N, %	
Female	10 (30%)
Male	23 (70%)
Mean age ± SD at time of implantation, years	63±10
[Range]	[46–88]
Laterality of implant - N, %	
Right eye	19 (58%)
Left eye	14 (42%)
Mean Axial Length (mm) ± SD	23.2±1.0
[Range]	[21.8–25.9]

SD = Standard Deviation

Table 2.
Axial and Maximum Macular Thickness by Array Location through Month 12 after Argus II Implantation

VISIT	TACK			MIDLINE			HANDLE		
	Mean Axial Thickness Along Long Axis μm (SD)	Mean Maximal Thickness Along B-Scan μm (SD)	Mean Axial Thickness Along Long Axis μm (SD)	Mean Axial Thickness Along Long Axis μm (SD)	Mean Maximal Thickness Along B-Scan μm (SD)	Mean Axial Thickness Along Long Axis μm (SD)	Mean Maximal Thickness Along B-Scan μm (SD)	Mean Axial Thickness Along Long Axis μm (SD)	Mean Maximal Thickness Along B-Scan μm (SD)
Baseline ^a [n]		230.9 (59.8) [20]			236.5 (51.5) [23]		233.8 (46.4) [19]		
POM1 [n]	200.1 (73) [14]	227.5 (60.7) [16]	216.4 (96.2) [16]		269.3 (85.4) [16]	220.3 (60.7) [15]	266.1 (79.4) [16]		
POM3 [n]	216.1 (74) [16]	272.8 (88.8) [16]	265.5 (98.9) [25]		290.4 (89.2) [25]	249.6 (97.8) [18]	280.4 (97.5) [19]		
POM6 [n]	222 (71.7) [13]	254.4 (64.7) [13]	289.3 (124.7) [16]		337.5 (118) [16]	248.7 (102.5) [15]	302.3 (114.6) [15]		
POM12 [n]	233.3 (53.5) [9]	279.9 (35.3) [9]	355 (144) [14]		389.4 (134.4) [14]	266 (102.8) [14]	317.2 (96.2) [14]		
Slope ^b (SE)	0.95 (1.68)	3.60 (0.81)	7.79 (2.91)		6.02 (2.08)	0.25 (1.63)	1.93 (2.14)		
p-value	0.573	<0.001	0.007		0.004	0.881	0.368		

SD = standard deviation SE = standard error μm = micrometer

SD=standard deviation SE=standard error μm =micrometer

s POM = post-operative month

^aFor baseline maximal retinal thickness the maximal thickness along B-scan in the superior macula (i.e. near tack), through the fovea (i.e. near array midline) and inferior macula (i.e. near handle) were measured

^b($\mu\text{m}/\text{month}$) GEE model accounting for correlated measurements on the same subjects with visit months fitted as a linear covariate (excluding baseline) with identity link and correlation structure modeled as AR1 μm =micrometers

Table 3.

Mean Axial and Mean Maximal Electrode-Retina Gap by Array Location through Month 12 after Argus II Implantation

VISIT	TACK			MIDLINE			HANDLE		
	Mean Axial	Mean Max	Mean Axial	Mean Axial	Mean Max	Mean Axial	Mean Max	Mean Max	
	Gap Along Long Axis pm (SD)	Gap Along BScan pm (SD)	Gap Along Long Axis pm (SD)	Gap Along Long Axis pm (SD)	Gap Along BScan pm (SD)	Gap Along Long Axis pm (SD)	Gap Along BScan pm (SD)	Gap Along BScan pm (SD)	
POM1 [n]	73.7 (131.8) [15]	86.9 (107.8) [14]	167 (156.8) [16]	188.1 (163.6) [16]	66.1 (79.9) [15]	154.5 (152.1) [15]			
POM3 [n]	39.8 (85.8) [16]	59.1 (110) [16]	116.2 (140.9) [25]	149.8 (148.6) [25]	52.5 (84.9) [18]	88.8 (115.3) [19]			
POM6 [n]	28.2 (51.5) [13]	47.5 (79.2) [13]	72.6 (107.1) [16]	98.7 (114.8) [16]	49.9 (84.7) [15]	78.7 (110) [15]			
POM12 [n]	60.6 (119.4) [9]	76.0 (124.8) [9]	87.0 (150.7) [14]	116.5 (146.7) [14]	62.7 (80.6) [14]	91.8 (99.5) [14]			
Slope (SE)	-0.75 (0.87)	-0.22 (2.41)	-3.84 (2.41)	-4.84 (2.26)	-0.14 (2.12)	-2.92 (2.91)			
p-value ^a	0.393	0.927	0.111	0.032	0.948	0.315			

SD = standard deviation SE = standard error um= micrometers POM = post-operative month

^a (um/month) GEE model accounting for correlated measurements on the same subjects with visit months fitted as a linear covariate (excluding baseline) with identity link and correlation structure modeled as AR1

µm=micrometers

Table 4.
Number (Percent) of Eyes with Complete Electrode-Retina Touch (Zero Electrode-Retina Gap)

VISIT	TACK		MIDLINE		HANDLE	
	Along Axis N (%)	Maximum Gap N (%)	Along Axis N (%)	Maximum Gap N (%)	Along Axis N (%)	Maximum Gap N (%)
POM1	10 (67%)	7 (50%)	4 (25%)	3 (19%)	8 (53%)	3 (20%)
POM3	12 (75%)	11 (69%)	11 (44%)	8 (32%)	12 (67%)	10 (53%)
POM6	9 (69%)	8 (62%)	8 (50%)	5 (31%)	10 (67%)	8 (53%)
POM12	6 (67%)	6 (67%)	9 (64%)	7 (50%)	8 (57%)	6 (43%)
p-value ^a	0.334	0.854	0.006	0.020	0.953	0.577

POM = post-operative month

The number and frequency of eyes with no measurable gap on optical coherence tomography (OCT) imaging are reported at the three recorded array locations both in the long axis of the array and the maximal gap identified on the same B-scan. The midline, along the array of the axis, demonstrated a statistically significant increase in the frequency of zero electrode-retina gap over time after implantation of the array (p=0.006). The axial midline measurement approximates the foveal location.

^a A p-value for trend over time GEE logistic link AR1 correlation matrix, linear fit