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The functional performance of the Argus II retinal prosthesis

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Summary

Visual prostheses are devices to treat profound vision loss by stimulating secondary nerve cells anywhere along the visual pathway, typically with electrical pulses. The Argus® II implant, developed by Second Sight Medical Products (SSMP, Sylmar, CA, USA), targets the retina and features 60 electrodes that electrically stimulate the surviving retinal neurons. Of the approximately 20 research groups that are actively developing visual prostheses, SSMP has the longest track record. The Argus II was the first visual prosthesis to become commercially available: It received the CE mark in Europe in 2011 and FDA approval was granted in early 2013 for humanitarian use in the USA. Meanwhile, the Argus II safety/benefit study has been extended for research purposes, and is ongoing. In this review we will discuss the performance of the Argus II in restoring sight to the blind, and we will shed light on its expected developments in the coming years.

Keywords

Argus II; retinal prosthesis; visual prosthetics; epiretinal implant; *retinitis pigmentosa*; visual acuity; spatial resolution; low vision; vision rehabilitation; electrical stimulation of the retina

The Argus II retinal prosthesis

The Argus II retinal prosthesis aims to restore vision in patients with profound vision loss due to end-stage retinal degenerative diseases such as *retinitis pigmentosa*. The 60-electrode array is surgically implanted on the epiretinal side of the retina (Fig. 1). It elicits visual percepts by electrically stimulating surviving neurons. Visual input is provided by a glasses-mounted miniature camera and a video processor (Fig. 2).

The proof of concept of epiretinal prostheses was shown in the 1990s in acute experiments at Duke University and the Johns Hopkins Wilmer Eye Institute [1]. Testing of the first chronically implanted prototype, the Argus 16 with 4 × 4 electrodes, started in 2002 in a phase 1/phase 2 clinical trial involving 6 subjects (<http://www.clinicaltrials.gov/ct2/show/>

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NCT00279500) [2–6]. The next generation device, the Argus II, has a rectangular array of 6×10 round platinum-coated electrodes $200 \mu\text{m}$ in diameter, with center-to-center spacing of $\sim 575 \mu\text{m}$, and covers $11^\circ \times 19^\circ$ in the visual field ($\sim 22^\circ$ diagonally). The Argus II is being tested in an international, multicenter clinical trial (<http://clinicaltrials.gov/show/NCT00407602>) that started in 2007 and involved 30 subjects suffering from retinal degeneration (predominantly *retinitis pigmentosa*) [7]. It was extended past its original end-date for research purposes, as is customary for studies of novel devices, and is ongoing at the time of this writing. The study was a feasibility study, not a phase III clinical trial, and as such could not provide strong statistical conclusions regarding the efficacy of the Argus II. This is explicitly confirmed by the fact that the Argus II received FDA approval as a Humanitarian Use Device, on the basis of safety and probable benefit. The data provided in this review are based mainly on this selected number of subjects and may not be representative of the blind population as a whole. All subjects participating in the clinical trial received a fully operational take-home device and were encouraged to use their systems outside the clinical setting as often as they liked. In addition, several dozen commercially implanted patients in Europe and Saudi Arabia, implanted since CE approval in 2011, are using the implant on a daily basis. The Argus II has proven to be safe and stable during chronic implantation [8] and was the first retinal prosthesis to become commercially available. It received the CE mark in Europe in 2011, and FDA approval for humanitarian use in the USA was granted in early 2013. Its effectiveness will be discussed by critically comparing it to the alpha-IMS retinal implant. The alpha-IMS is the second visual prosthesis to be commercialized worldwide, and it received the European CE mark mid-2013.

The 1500-electrode alpha-IMS implant

The alpha-IMS device (Retina Implant AG, Reutlingen, Germany) has been tested in two clinical trials including a total of 47 patients. The 2nd of these, a multicenter international trial, is still ongoing [9–11]. It features 38×40 (~ 1500) square-shaped electrodes ($50 \times 50 \mu\text{m}$), measures $3 \times 3.1 \text{ mm}$, and covers a visual angle of $10^\circ \times 10^\circ$ (15° diagonally) [10]. Its subretinal location (Fig. 1) favors the stimulation of bipolar cells in a retina that has lost its photoreceptors due to degeneration. For diagnostic purposes, the first version of the alpha-IMS included a separate 4×4 direct-stimulation electrode array [9]. Light sensing is mediated by intraocular photodiodes, so it operates without an external camera. In contrast to approaches using an external camera such as the Argus II, intraocular light sensing has the advantage that normal eye movements can be used, instead of head scanning. In fact, large eye movements should be actively avoided by Argus II wearers, because of the perceived image displacements due to cortical feedback from the oculomotor system. Rehabilitation procedures, therefore, include training to keep a steady gaze, while scanning the environment by head movements. The experience is that Argus II implantees adopt this scanning behavior quite naturally, just as has been reported for sighted subjects in several prosthetic vision simulation studies [12]. A disadvantage of the alpha-IMS is the limited control over the stimulation parameters. Most importantly, the offset and gain can be adjusted jointly for all electrodes, but not for individual electrodes [10]. In contrast, the Argus II system allows for the adjustment of stimulation variables for each individual electrode.

Other retinal implant systems, such as the suprachoroidal implant from Bionic Vision Australia [13], the Boston implant [14, 15], EPIRET3 [16], and the Stanford retinal implant design [17] will not be discussed here, because quantitative data to critically compare their performance to the Argus II are not available at this time. Prostheses with more central targets, such as the optic nerve (e.g., [18, 19]), midbrain [20, 21], and visual cortex (e.g. [22–24]) are reviewed elsewhere [25–27].

Electrically stimulating a degenerated retina: ideal world versus reality

Ideally, each individual electrode in a retinal implant stimulates a localized retinal patch, thereby generating retinotopically organized and uniformly bright phosphenes. This situation is often used in simulation studies with sighted participants, in which pixelized ('phosphenized') images are displayed to normally-sighted subjects. Such idealized studies are helpful to characterize the minimal requirements for functional vision. Dagnelie et al. [25] predicted, through simulation studies, that a grid of 10×10 electrodes, spaced 0.4° in the visual field, and covering $4^\circ \times 4^\circ$ visual angle would allow for large-print reading at speeds of 10 - 15 min words/min. A comparable implant with 16×16 electrodes would be sufficient for slow paragraph reading of large print text. Reading speeds acceptable for sustained reading would necessitate a 25×25 electrode ($10^\circ \times 10^\circ$) device [28, 29]. Based on these simulation data, the alpha-IMS, with its 38×40 electrodes, should theoretically be able to sustain acceptable reading speeds, provided that each electrode produces a distinct phosphene. The reality proved different; only 4 out of 10 (40%) alpha-IMS subjects were reported to be able to perceive large-print letters (combining the data from two reports) [9, 10], while only 1 (10%) was reportedly capable of reading words in large print. The Argus II device, with just 6×10 electrodes, allowed approximately 50% of the 21 tested subjects to recognize large-print letters (41°) above chance level, while a subgroup of the four best performers were able to read short words [30]. Single-letter recognition could take anywhere between 6 seconds to 3.5 minutes in the Argus II trial. Although reading speeds were not formally reported in that alpha-IMS studies, qualitative evidence suggests that letter recognition could be performed in a few seconds [9].

Overall, based on these letter-based tasks, the performance of the Argus II and alpha-IMS can be considered similar, despite the large difference in electrode number and density. Moreover, some surprisingly complex tasks – such as recognizing the shape/outline of a large object – could be successfully, albeit slowly, performed by degrading the processed image to a single pixel [3]. Hence, the functionality of present-day implants is not determined by limitations in the number or density of the electrodes. Instead, factors such as the electrode-tissue interface [31, 32], severity of retinal degeneration and rewiring [33], cortical remodeling [34], and psychological factors such as the patient's preparedness for an intensive rehabilitation process [35] may be more important. Indeed, cochlear implants, which have been available for decades [36], were shown to perform almost equally well in terms of speech understanding when the number of channels was reduced from 20 to 7 [37]. As a consequence, cochlear implant engineering has mainly shifted its focus towards optimizing stimulation strategies, rather than maximizing electrode densities (e.g. [38, 39]). Although spatial resolution may be more important in retinal implants, we expect a similar trend to occur where much of the engineering efforts will go into improving image processing, such as the implementation of feature extraction paradigms where objects of interest such as edges [40] or obstacles [41] are overrepresented in the image to maximize the information contained in sparse stimuli. Optimizing the electrode-tissue interface and improved patient screening are two other aspects where much can be gained in the near future.

Single or dual electrode stimulation yield predictable percepts

Individual electrode thresholds in the Argus II can vary widely, possibly reflecting local variations in the distance of the electrode array to the retina and/or in the severity of retinal degeneration [6]. Taking individual thresholds into account, however, direct stimulation (i.e., without camera input) of one or two electrodes generally results in simple and predictable percepts. Acute studies in blind RP patients, using hand-held probes in the operating room, have shown that retinotopy is maintained with single-point stimuli, that

phosphenes separated by as little as 0.75° could be successfully discerned, and that 2/3 of the subjects could identify the direction of motion of an electrode moved across the retina [1].

More complex stimuli yield less predictable percepts

In general, simple stimuli using multiple electrodes, such as the presentation of horizontal and vertical lines, could be distinguished well by Argus-implanted subjects. However, more complex patterns like a 'U' shape proved to be more difficult for some subjects [3, 31]. Very similar results were reported by the alpha-IMS and EPIRET groups: Activation of single electrodes, or stimulation of columns or rows, resulted in predictable percepts [9, 16], whereas more complex shapes, such as letters, were more difficult to identify [9], or not recognized at all [42]. Apparently, spatial interaction plays an important role. Indeed, electrodes separated by as much as 800 μm center-to-center (390 μm edge-to-edge) were found to affect each other's responses, even when stimuli were temporally separated [43]. It was shown by others that letter recognition substantially improved when electrodes were stimulated sequentially instead of simultaneously [9, 42], indicating that summation effects (channel 'cross talk') should be minimized for effective shape representation. Even when using a 'temporal multiplexing' strategy, phosphene 'fading' due to retinal adaptation [7, 42–44] may still result in spatial interactions: Activation of one electrode may cause adaptation to occur at surrounding electrodes, thereby affecting their response even when stimuli are temporally separated [45].

In conclusion, the perceptual representation of multi-electrode stimuli differs from the sum of its individual components, even when stimuli are temporally separated. These complex spatiotemporal interactions necessitate the optimization of image processing strategies to minimize electrode interactions in the future. Even with the current state of technology, however, presenting 'visual braille' dots by direct simultaneous stimulation allowed an Argus II subject to read 4-letter braille words with an accuracy of 70% [46], showing that complex patterns can nonetheless be used to convey meaningful information.

Image processing

The Argus II represents the visual scene by encoding brightness via stimulus amplitude. Intensity coding was chosen, since it was shown that the dependence of phosphene brightness on stimulus level could be described by a simple saturating power function [1, 6] and as many as 10 intensity levels could be successfully identified by one patient [2], a finding supported by the alpha-IMS trial [9]. However, increasing stimulus amplitude not only affects brightness, but also increases the spread of excitation away from the electrode. Indeed, current level has a larger impact on phosphene size than it has on brightness [2, 47, 48]. In the alpha-IMS implant, a 50% phosphene size increase has been reported when increasing current level, and the authors conclude that stimulus level, rather than electrode size, determined phosphene size [42]. Hence, amplitude modulation may substantially decrease spatial resolution [32]. In contrast, pulse rate modulation has been shown to affect brightness while having little impact on phosphene size, and may be a more suitable parameter for brightness encoding [48].

Flicker fusion in Argus 16 subjects was reported to be approximately 40 Hz for single electrode stimulation [43]. Available pulse rates in the Argus II (3 – 60 Hz [49]) should generally be fast enough to sustain stable percepts. However, perceptual fading has been reported in some Argus II subjects [50, 51] and in alpha-IMS subjects. The alpha-IMS group has reported using relatively low stimulation rates of 1 to 20 bursts per second to prevent fading, which may result in 'blinking' percepts [9, 10], suggesting that a trade-off between flicker fusion and fading may be a consideration in retinal prosthesis stimulation.

Psychophysical tasks

Performance of simple, time-unconstrained tasks using camera input such as localizing relatively large, high-contrast shapes has been shown to improve in nearly all tested Argus II subjects (93 – 96%, dependent on the specific task and analysis), as compared to using any remaining native vision [7]. The performance of relatively simple tasks may improve over the course of several months because of learning effects [52]. The number of subjects that performed better with the Argus II switched on versus off dropped to approximately 50 – 60% in more complex tasks, such as maze tracing and detecting the direction of a moving bar [7, 49, 53]. The perception of complex and moving objects may be complicated because of spatiotemporal interactions ('cross-talk') between electrodes [9].

The alpha-IMS group reported similar findings; while most subjects (7/9) succeeded in perceiving and localizing a simple stimulus, detection of movement was accomplished by 5/9 subjects [10].

As stated above, the Argus II has been shown to allow for the recognition of large-print letters. Letters sized 41° in visual angle were identified above chance level in a grouped analysis including 21 subjects. In a subgroup of best performing subjects, four were able to read four-letter words [30]. For comparison, in the first report of the alpha-IMS study, 1 of 3 patients was able to recognize letters and read short words [9]. A subsequent report showed that 4 out of 9 patients were able to read letters [10].

Visual acuity

A common metric to express visual acuity (VA) is the minimum angle of resolution, and is commonly expressed in minutes of arc [54]. In this review, however, we will express resolution or VA in degrees ($^\circ$) rather than minutes of visual angle, because of the limited spatial resolution offered by present-day retinal implants.

The theoretical resolution achievable with Argus II is 4° (Fig. 3). In a grating VA task, only 23% of the Argus II subjects were able to resolve at least the coarsest grating tested (13°) [7], which approaches the visual field covered by the implant (20° across the diagonal). A contributing factor to the relatively poor performance may have been the number of activated electrodes; in another study where letter recognition was tested, approximately 60% of electrodes were activated across the 21 tested subjects. The six subjects capable of recognizing the smallest letters had, on average, 84% of their electrodes active [30]. Argus II electrodes are not used if they do not have a measurable subjective threshold up to the limit of the safe charge density for platinum electrodes (1.0 mC/cm^2) [30]. For comparison, the percentage of electrodes with measurable thresholds reported for the alpha-IMS implant was even smaller (43% of the 16 direct stimulation electrodes) [42]. The highest reported grating acuity in the Argus II clinical trial is 1.1° , well below the theoretical limit of 4° [7]. This apparent hyperacuity may be explained by effective scanning techniques, allowing subjects to temporally integrate percepts.

The theoretical resolution of the alpha-IMS is 0.5° [10]; approximately 8 times better than the Argus II. In the first report on alpha-IMS performance, 2 out of 3 patients were able to perceive gratings with reported acuities of 2° and 5° [9], i.e., no better than the best acuity reported in the Argus II study (1.1°). A later study reported that 6 out of 9 alpha-IMS patients could perform the task, with the best acuity reported as 0.3° , i.e., better than the theoretical alpha-IMS limit, and 4x better than the best acuity reported in the Argus II trial. Unfortunately, no detailed per-subject grating acuity data from the Argus II trial or the 2nd alpha-IMS study with 9 subjects have been made public. Complicating the comparison between the Argus II and alpha-IMS studies is the fact that the methods differed; for

example, the grating acuity task was performed using a four-alternative forced choice paradigm (4AFC) where time was limited to 5 seconds in the Argus II study, while it was a 2AFC task with unconstrained time in the alpha-IMS studies, likely making the task for the Argus II subjects more difficult. In addition, Argus II wearers rely on head scanning techniques, while alpha-IMS wearers can use normal eye movements, perhaps favoring better acuity scores in the latter.

Optotypes are also commonly used to determine VA [55]. Although not specifically designed to determine VA, a letter recognition study showed that the 6 best performing subjects in a group of 21 Argus II subjects could recognize letters ranging from 1.7° to 34° , of which two subjects had scores better than the theoretical resolution limit of the Argus II (1.7° and 2.1°) [30].

In the alpha-IMS trials, Landolt C-ring VAs could be determined in 2 out of 9 subjects, and were reported to be 1.6° and 0.45° , the latter being better than the best grating VA reported in the Argus II trial (1.1°), and approaching the theoretical 0.5° limit in the alpha-IMS [10].

We conclude that while simple stimuli can be perceived correctly by nearly all Argus II and alpha-IMS subjects, more complex stimuli are accompanied by decreased performance in both systems. Comparing the visual acuities between the Argus II and alpha-IMS studies is difficult because of differences in methodology. Therefore, the slightly better acuities reported in the alpha-IMS trials may be considered marginal and at least less substantial than would be expected based on the theoretical 8x better resolution of the alpha-IMS; the best reported acuity in the alpha-IMS study is 4x better than the best acuity in the Argus II trial.

Orientation and mobility

Orientation and mobility (O&M) tasks based on walking towards a high-contrast target and walking along a high-contrast line on the floor improved significantly when using the implant in a grouped analysis of Argus II subjects [7]. These findings show that, with sufficient practice, the Argus II is capable of increasing the mobility of people unable to navigate or orient themselves without a guide dog or white cane. Until now, no other retinal implant group has reported on O&M, but even in isolation the Argus II findings are encouraging [56]. Retinal implant technologies are just emerging, and the Argus II is currently marketed as a complementary device to the long cane and guide dog for complex tasks, such as orientation and mobility. Hopefully, retinal implants will eventually develop into stand-alone devices capable of helping people with pronounced vision loss to regain their independence, just as cochlear implants developed from lip-reading aids into fully functional devices capable of restoring speech understanding in as little as two decades [57]. Questionnaires assessing the quality of life have shown that 67% of the participating Argus II subjects (26 out of 30) experienced some positive effect of the Argus II system [56].

Five-year view

In the short term (< 1 year) SSMP's focus will be the improvement of the performance of the Argus II. Vision processing algorithms already include contrast enhancement and edge detection. To make optimal use of sparse information, feature-detection, such as face detection [58] or obstacle identification, may be implemented. A digital zoom function may be added to improve acuity for specific tasks [59]. The electrode-tissue interface might be addressed by improving the retinal tacking procedure, or through design changes to the implant.

Within 2 years, SSMP intends to investigate adding an eye tracker to the system to allow for more natural eye scanning techniques. Color coding [60] will be explored in this time frame as well.

Commercialization of the Argus II will be important in the coming years. After the recent FDA approval, the US market has opened up for sales, and efforts continue to increase the number of European countries where the Argus II will be available. At the time of this writing, 35 Argus II devices have been implanted commercially and the aim is to bring this number up to over 2000 implants within the next 5 years. A clinical trial of the Argus II as a treatment for AMD is scheduled in Europe within the next year. As of now, the Argus II is indicated specifically as a treatment for retinal degenerative diseases such as *retinitis pigmentosa*.

Over the next few years, the next-generation higher-acuity implant featuring 240 electrodes will be developed and tested in preparation for a new clinical trial. Plans exist to add peripheral electrodes to increase the visual field.

Within 5 years from now, SSMP intends to start a clinical trial with a cortical prosthesis based on the Argus II design to assess the clinical benefits and risks associated with this approach.

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List of abbreviations

CE	European Conformity
FDA	Food and drug administration
O&M	Orientation and mobility
SSMP	Second Sight Medical Products
VA	Visual acuity

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Key issues (8–10 bullet points summarizing the review)

- Performance in relatively simple visual tasks, e.g. object localization, improved in nearly 100% of the tested Argus II subjects
- More complex tasks, e.g. detection of motion, improved in approximately 50% of Argus II subjects.
- An orientation and mobility (O&M) task based on walking towards a high-contrast target, or walking along a high-contrast line on the floor improved significantly when using the implant in a grouped analysis of Argus II subjects.
- The differences between reported visual acuity of Argus II (60 electrodes) and alpha-IMS (1500 electrodes) wearers are small, despite the theoretical 8 times lower resolution of the Argus II device.
- Retinal implant functionality is likely limited by many factors including physical (e.g., channel interactions), physiological (e.g., retinal degeneration) and human factors (e.g., the patient's capability to comprehend prosthetic vision)
- Retinal implant functionality is limited by many factors including electrode-electrode interactions and a sub-optimal tissue-electrode interface. At present, hardware engineering factors, such as electrode size and electrode density, may be of lesser importance.
- Vision processing strategies, patient screening methods and optimizing the electrode-tissue interface are aspects of implant functionality that can be improved in the future.
- The Argus II device will be continuously improved, including the implementation of advanced vision processing strategies, zooming, eye scanning, and color coding.
- Within 5 years from now, SSMP hopes to implant more than 2000 Argus II devices worldwide.
- According to current plans, the next generation SSMP device will be a high-acuity retinal implant with 240 electrodes and a cortical 60-electrode implant.

Fig. 1. Schematic organization of the eye and the retina. (A) Schematic cross section through the human eye with an enlargement of the retina. (B) Different implant locations in the eye: Epiretinal (Argus II, EPIRET), subretinal (alpha-IMS), and suprachoroidal (Bionic Vision Australia). The epiretinal location favors ganglion cell stimulation, while subretinal implants favor the activation of bipolar cells. Reproduced with permission from Webvision [61]. Copyright © 2013 Webvision.

Fig. 2. External and implanted parts of the Argus II retinal prosthesis. (A) Photograph of the external parts of the Argus II prosthesis system (Second Sight Medical Products, Inc., Sylmar, CA) showing the glasses with the camera and external radiofrequency (RF) coil, and video-processing unit (VPU) with rechargeable battery. (B) Illustration of the implanted parts of the Argus II prosthesis system, including the 6×10 electrode array, electronics case, and subconjunctival RF coil. The RF link established between the external and implanted coil provides the implant with the necessary information for stimulation, as well as the necessary electrical energy. (C) Fundus photograph of an implanted Argus II array in the macular region. The array is secured to the retina with a retinal tack. The handle is used by the retinal surgeon to manipulate the array during surgery [7, 50, 62]. Pictures reproduced with permission from Second Sight Medical Products, Inc., Sylmar, CA.

Fig. 3.

Schematic representation of a part of the Argus II electrode array to show the theoretical grating visual acuity (VA) limit of the Argus II device. The electrodes have a diameter of 200 μm and center-to-center electrode spacing is 575 μm . The finest grating that can be represented on an electrode grid with these dimensions has a cycle of 1150 μm on the retina. Assuming that 1° covers 288 μm retinal surface [63], the maximum VA achievable with the Argus II is 4°. Note that the Argus II array has 6×10 electrodes and the entire electrode grid spans approximately 20° of the field of view along the diagonal.