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Standard ERG Equipment Can Be Used to Monitor Functionality of Retinal Implants

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Abstract— **Identifying whether or not a retinal implant has malfunctioned after implantation is crucial for safety and efficacy testing in preclinical animal studies and clinical testing in human volunteers. Technical failure can lead to charge injection to areas other than the retina leading to a misjudgment of safety considerations or psychophysical results. This study assessed the feasibility of using standard ERG recordings for the detection of failure of a subretinal implant in-situ using a porcine model. Corneally recorded potentials were compared before and after introduction of damage to the implant leading to failure to deliver charges to the retina. The recorded signal decreased by up to 173% following induced damage to the implant. This shows that standard ERG equipment can be used to monitor if a malfunction occurred in animal testing and can also be applicable in clinical trials.**

I. Introduction

RETINAL implants are being developed in various laboratories worldwide and require extensive psychophysical testing in clinical trials to evaluate the effectiveness of the implant in restoring vision. While some clinical trials are already underway in patients blinded by hereditary retinal dystrophies [1], [2], others are in pre-clinical testing for long-term safety and efficacy for clinical trials in planning [3]-[5]. Such studies are usually carried out as chronic experiments in animals sacrificing the animal after a certain period to assess changes in retinal tissue under stimulation. Monitoring the successful charge delivery to the retina is essential in those approaches. However, failures like shorted or damaged wires between a stimulator and electrodes implanted in the eye may not be detected readily.

This study analyzed whether or not standard electroretinography (ERG) recording equipment could be a tool to detect malfunction of an implant. Applying this technology early in animal testing has the advantage of easier transition into clinical trials in humans, as it is a widely used standard examination that can be performed in every eye hospital. Psychophysical testing in humans is confounded by a multitude of parameters, including the physical and mental state of the patient and the rate of spontaneous phosphenes reported by nearly all patients. These issues make reliable psychophysical data collection challenging. Some stimulators will continue to deliver charge to tissue along the wire path, even if a connection to a retinal electrode is broken. Impedance measurements using telemetry can provide a clue to such a failure but might not always be available and does not indicate the exact localization of wire or device damage. For those reasons malfunction of an implant may not be readily detected even in human psychophysical testing and must be monitored closely. ERG records very small electric potentials at the surface of the eye upon light stimulation. Currents injected into the retina by a retinal implant should therefore also be able to be recorded externally. We investigated the principle feasibility and suitability of this approach to detect an induced malfunction of a device that leads to currents being injected at another site other than the desired one. This study used a simplified approach to test the principal feasibility, employing post-mortem explanted pig eyes which were implanted with a subretinal implant [1], [6], [7]. Changes occurring in the signal were measured by standard ERG equipment during normal operation of the implant and after cutting the gold wires that carry power and signals close to the implantation site to simulate a potential damage with the bare polyimide foil that carries the wires remaining in the tissue. In contrast to standard ERG recording, the technique proposed here does not aim at recording retinal potentials, but merely voltage transients generated by the electrodes delivering current to the tissue.

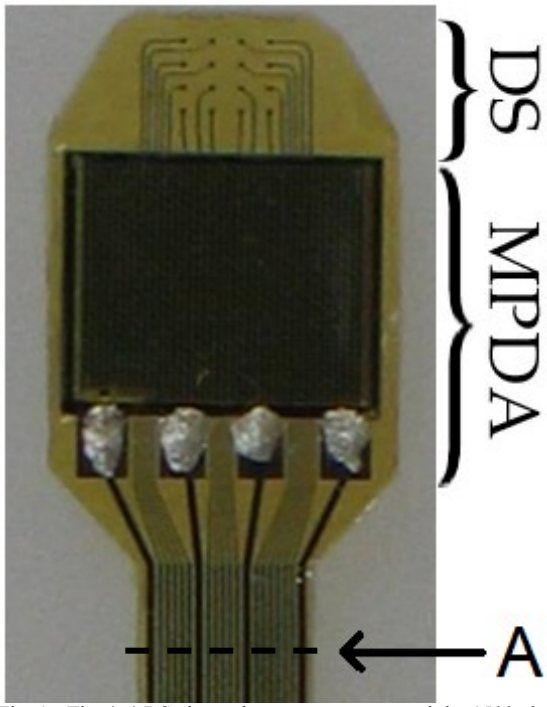

Fig. 1. The 4x4 DS electrodes are seen at top and the 1500 electrode microphotodiode array (MPDA), with dimensions of 3x3mm, is seen below. The activation signal was recorded from the DS array before and after making a cut through the polyimide foil at point A to simulate damage. (Image courtesy of Retina Implant AG)

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II. Materials and Methods

Three subretinal implants, as well as the hardware and software required for operation, were provided by Retinal Implant AG (Reutlingen, Germany). The implants consisted of a light-sensitive multi-photodiode array (MPDA) and a light-insensitive direct stimulation (DS) array (see Fig 1). The DS electrodes were controlled by a separate stimulation box with custom software, employing a constant voltage source, whereas the MPDA is stimulated by light; each of the 1500 microphotodiodes routes an externally applied voltage via an amplifier to its nearby electrode, the voltage amplitude depending on the strength of the light falling through the lens onto this particular spot [1]. This paper will focus only on the results from the DS array testing since it is most comparable to existing stimulation strategies being developed in other laboratories and for brevity.

The experiment was developed using an explanted porcine eye as a model for human eyes. Pig eyes were chosen because of their anatomical similarity to human eyes, including size and proportions [8]. Pig eyes also allowed for a similar medium to human eyes for conducting the signal. The pig eye was supplied by the slaughter-house located in Rottenburg, Germany. The eye was enucleated shortly after death and transferred to 0.9% NaCl solution kept at approximately 4 °C between testing for no longer than 3h in total. A scleral window was prepared near the posterior pole and the choroid carefully exposed, to allow for an insertion point for the retinal implants. For ease of surgical approach the implant was inserted suprachoroidally, not subretinally as done in the clinical study [1].

An Espion E2 Electrophysiology system (Diagnosys LLC, Lowell, MA) was used for signal recording from the eye. The Espion E2 system recorded the voltage from an ERG-jet electrode placed on the cornea at a sampling frequency of 5000 Hz. A reference needle-electrode was placed through the optic nerve. The pig eye was placed within a rubber isolating ring embedded in a custom holder. The eye was kept moist during recordings using 0.9% NaCl solution to maintain a steady contact between the eye tissue and electrodes. Each implant (n=3) was placed suprachoroidally in the prepared scleral window. The DS array was tested before and after cutting the polyimide foil containing the voltage supply for the chip and the wires for each DS electrode to simulate a mechanical failure (Figure 1).

The DS array consists of a 4x4 array of electrodes (area: 50 μm^2, made of Titanium-Nitride), which were driven with four different constant voltage signal forms, monophasic anodic, monophasic cathodic, biphasic anodic-first, and biphasic cathodic-first. The stimulation box is capable of independently producing outputs ranging from 0.1 to 3.0 V on each of the 16 electrodes. For this study the entire 4x4 array of electrodes was activated simultaneously with an equal voltage level varied from 0.1 to 3.0V and with a step size of 0.5V. Each signal form was tested by varying voltage as described while keeping stimulation frequency at 5 Hz and pulse duration at 5 ms. Twenty seconds of data were recorded at each voltage setting for each signal form, resulting in 100 spikes in each recording step and a total of 28 different configurations of voltage and signal form. This recording was first taken from each intact implant and then again after the polyimide foil was cut.

III. Results

The signals recorded from all three implants tested were averaged and the resulting voltage trains are shown in figures 2 and 3. Figure 2 shows a series of voltages ranging from 0.1 to 3.0V of a cathodic pulse. It can be seen that the recorded waveform scales with the stimulus setting, if the electrodes are passing current into the retina (solid blue line), but not if the lead wires are cut (dashed red line). This figure demonstrates further that a monophasic voltage train yields a biphasic current that is recorded by the ERG equipment. This is because the Helmholtz-double layers that build up during the voltage pulse discharge after the potential of the electrode is drawn back to ground-potential again. Figure 3 shows the recorded waveforms of the 4 different stimulation signal forms, all set to 2.0V. Note that the recorded waveforms showing the current injected in the tissue have 2 opposite phases when monophasic voltage pulses are used and 3 phases when biphasic voltage trains are used for stimulation. Also, a considerable difference in amplitudes between anodic and cathodic pulses can be seen, which is likely owed to non-linear properties of the electric interface of TiN electrodes in extracellular saline solution, resulting in higher impedances for anodic pulses. The dashed red line indicates the waveforms obtained when the lines to the electrodes were cut, resulting in an increase of impedance and current injection further away from the recording site.

The amplitude, measured from maximum amplitude peak to baseline, was calculated for each setting. The percent difference between signal amplitude before and after implant damage was calculated and the results are shown in Table 1. The increase after damage for an anodic signal form at 0.1V is due to the relatively small values generated by the anodic pulse at the low voltage setting of 0.1V.

Table 1. Percent Difference in Amplitude After Implant Damage

Voltage (V)	Anodic	Cathodic	Biphasic Anodic First	Biphasic Cathodic First
0.1	48.1%	-0.6%	1.2%	-4.9%
1.0	-41.4%	-150.1%	-149.9%	-128.8%
2.0	-69.0%	-169.4%	-158.4%	-162.5%
3.0	-161.4%	-173.3%	-157.5%	-163.0%

Table 1. Percent difference between intact implant and damaged implant signal amplitudes for each signalform at four different voltage settings measured from maximum amplitude to baseline.

IV. Discussion

ERG is a widely available clinical tool, which makes it convenient to use for retinal implant monitoring in clinical trials. ERG is a non-invasive procedure and has been applied widely in animal studies [9], for small animals [10], as well as for large animals [11]. Therefore, we recommend adding periodic ERG recordings to monitoring protocols to detect implant malfunctions in both chronic animal studies as well as clinical studies. Once the typical signal has been recorded and well established from frequent ERG monitoring, any deviation from the baseline will be an indication of a potential malfunction and corrective measures can be taken.

It should be noted that the actual voltages measured in this study follow stimulation settings in a qualitative way and should not be used as absolute measures. Voltages recorded here are dependent on relative electrode placement and individual anatomical features of the subject. The voltage measured from the cornea is not the actual voltage output of the implant, but rather the measured waveforms are correlated to the injected current and thus follow stimulation settings in a qualitative way. This is helpful as a surrogate marker in monitoring current output into the retina of implants when actual implant output is not easily accessible by other means. Clearly, in an intact electrode array, the amplitude is dependent on the strength of stimulation.

Although it seemed obvious that currents generated in the retina, whether it be the intrinsic signals of the retina or artificial stimulation, can be recorded using ERG techniques, it hasn't been tested before if this technique is suited to detect changes in the functionality of a retinal implant. Failures of those devices can be a break in the wires connecting the neuro-stimulator to electrodes close to the retina, cracks in encapsulation, short circuits due to mechanical forces e.g. during surgery, accidental electronic circuit failures in strong magnetic fields, corrosion of bonding points etc.. Such events lead to injection of currents at sites other than the retina, while the stimulator keeps generating identical stimulation pulses. If the change in impedance that is very likely associated with it is not detected, other means are required to detect such a mode of failure. This is particularly important in chronic animal studies testing safety of stimulation where actual delivery of charge to the retina has to be assured. Our results suggest that ERG recordings can provide a tool to detect such device failure. The reduction in recorded amplitudes is mainly owed to the fact that the cut wire has a far smaller surface in contact with conductive medium as compared to the electrodes. Therefore impedance will increase significantly, injected currents will decrease significantly. In turn the recorded voltage gradient as measured by ERG recordings will decrease. Another effect that explains the drop in recorded voltage is that the site of injection of currents changes to a location further away from the recording electrode on the cornea. This also contributes to an attenuation of the recorded signal. Many neurostimulators use constant current pulses rather than constant voltage

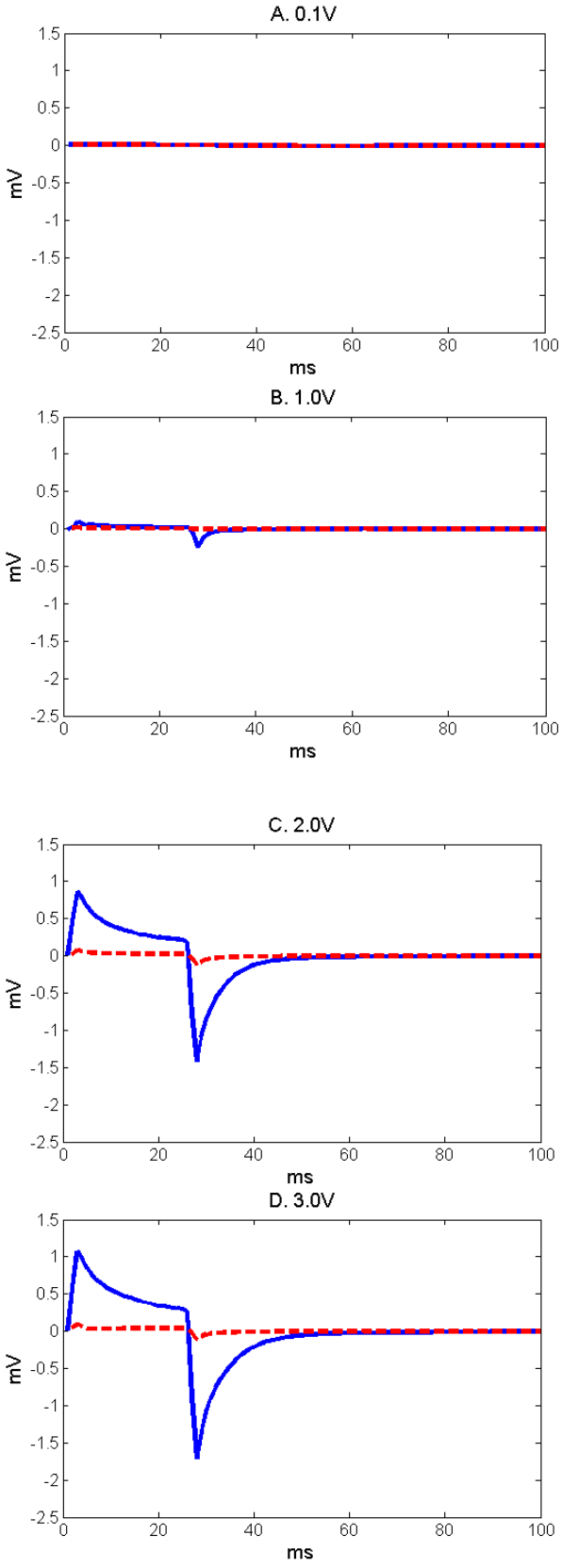

Fig. 2. The voltage recorded for the monophasic cathodic signal form before (blue solid line) and after (red dashed line) damage to the polyimide foil at a voltage setting from 0.1 to 3.0V.

pulses. In case of a damaged cable those devices will still inject the same amount of current in the tissue, but at a different site, namely at the site of breakage. It is likely that this can be picked up by ERG measurements due to its different localization in respect to recording electrode and different current distribution, though it was not specifically tested here.

V. Conclusions

This study provides evidence that standard ERG recording equipment is suitable for monitoring retinal implants after implantation to detect when a malfunction occurs. This is a broadly used technique that can be easily applied in animal and human testing in addition to other monitoring methods of implant function.

VI. Acknowledgments

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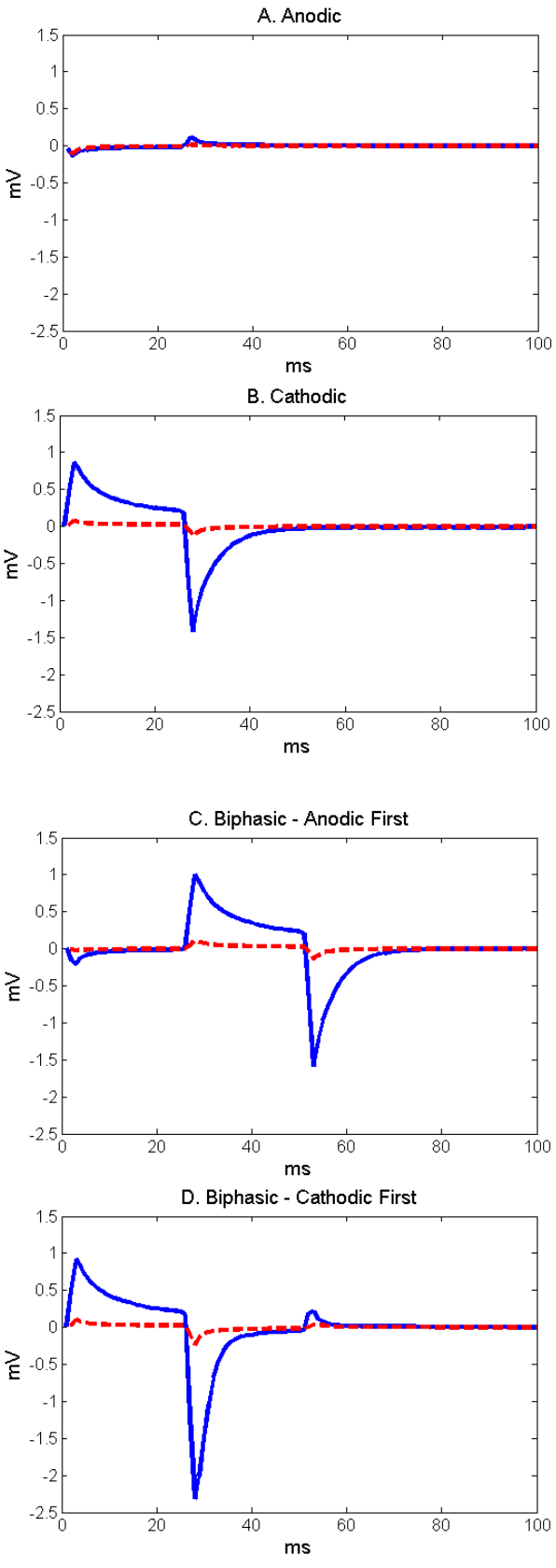

Fig. 3. The voltage recorded for the voltage setting of 2.0V before (blue solid line) and after (red dashed line) damage to the polyimide foil for each of the four possible signal forms.