Metabolic Long-Term Monitoring of Transcorneal Electrical Stimulation in Retinitis Pigmentosa

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**Keywords**
Retinal vessel oximetry · Inherited retinal diseases · OkuStim · Transcorneal electrical stimulation · Retinitis pigmentosa

**Abstract**

**Introduction:** Transcorneal electrical stimulation (TES) is a new therapeutical approach for retinitis pigmentosa (RP). With progression of RP, degeneration of photoreceptors results in lower oxygen consumption of the retina. Retinal oximetry (RO) is a noninvasive method to analyze oxygen saturation in retinal vessels and has shown promising short-term results as a therapy monitoring tool for TES. The aim of our study was to measure the long-term effects of TES on RO parameters over a period of 3 years (3Y).

**Methods:** A total of 18 eyes of 9 subjects (5♀ 4♂) suffering from RP were examined at baseline (BL), 6 months, and 3Y of TES (OkuStim\textsuperscript{®}) treatment. TES was performed for 30 min once a week at 200% of the individual phosphene threshold simultaneously on both eyes. The oxygen saturation was examined at BL and following TES therapy with the oxygen saturation tool of the Retinal Vessel Analyser (IMEDOS Systems UG, Jena, Germany). The global oxygen saturation parameters (in %), within 1.0–1.5 optic-disc diameters from the disc margin, in retinal arterioles (A-SO\textsubscript{2}) and venules (V SO\textsubscript{2}) were measured and their difference (A-V SO\textsubscript{2}) was calculated. In addition, we recorded the diameters in the main arterioles (D-A) and venules (D-V). ANOVA-based linear mixed-effects models were employed for statistical analysis using SPSS\textsuperscript{®}.

**Results:** After 3Y of TES treatment both the mean A-SO\textsubscript{2} (from 96.35 ± 12.76% to 100.89 ± 5.87%, \(p = 0.22\)) and V SO\textsubscript{2} (from 62.20 ± 11.55% to 64.55 ± 8.24%, \(p = 0.77\)) increased slightly. The A-V SO\textsubscript{2}, which corresponds to the oxygen consumption of the retina, presented also with a slight increment from 34.15 ± 9.68% at BL to 36.23 ± 7.71% without reaching statistical significance (\(p = 0.27\)). TES also did not appear to alter the vascular diameter parameters, D-A and D-V (\(p > 0.05\)).

**Conclusion:** Our long-term observations indicate that TES therapy in RP might lead to a slight increment in oxygen consumption of the retina. However, a larger cohort and longer duration may be needed to adequately power a follow-up study and to confirm this trend reflecting a possible benefit of TES for RP.

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Transcorneal electrical stimulation (TES) is a new therapy option for patients suffering from retinitis pigmentosa (RP) [1, 2]. RP is a heterogenous inherited retinal disease characterized by a rod-cone degeneration leading to progressive visual deterioration. TES seems to induce the release of neurotrophic factors which help the remaining retinal cells to survive [2–9]. The TES-pivotal trial and the corresponding follow-up study presenting 1-year data provided a more detailed explanation. However, the underlying mechanisms are not yet fully understood [1, 2].

It is known that changes of the retinal vasculature with neurovascular remodeling are a hallmark of RP [10–21]. Oxygen is an essential metabolite for retinal photoreceptors in order to maintain an intact visual function [22–24]. In RP, due to cellular apoptosis, a reduction of the retinal oxygen consumption with a consecutive increase in the retinal vessel oxygen saturation values was observed [10–21, 25]. By measuring the therapeutic effect on the retinal oxygen consumption, a recent pilot study presenting short-term effects after 6 months (6M) of TES found that retinal vessel oximetry (RO) might be superior to full-field electroretinography (ffERG) or visual field (VF) as a biomarker in evaluating the treatment of TES in RP patients with a short-lasting, noninvasive, contact-free, and patient-friendly measurement [25]. This study could show a significantly increased oxygen consumption of the remaining photoreceptors of the retina which might reflect a positive therapeutic response to TES [25]. However, so far, no long-term data are available for the usage of RO as a monitoring tool in the context of TES. Recent studies with patients suffering from neovascular age-related macular degeneration or diabetic macular edema under anti-VEGF therapy demonstrated that RO might be a reliable technique for evaluating the treatment effect by its oxygen metabolic response [23, 24]. Therefore, the aim of our study was to compare retinal vessel oxygen saturation parameters in RP patients undergoing TES therapy over a long-term period of up to 3 years (3Y) in order to find changes that would be attributed to the therapeutic intervention.

Materials and Methods

This prospective study was performed from January 2018 until May 2021 in a single tertiary care center (University of Basel, Department of Ophthalmology, Switzerland) on a total of 18 eyes from 9 subjects suffering from RP. Approval of the local authorities (Ethics Commission of Central and Northern Switzerland, EKNZ, Basel, Switzerland) was obtained with a positive vote for prospective observational investigation (trial number EKNZ BASEC 2020-00122).

The inclusion criteria for all study participants were as follows: Caucausian origin, refractive spherical equivalent error ≤6 diopters of myopia or hyperopia, no history of ocular surgery, implants as pacemakers, or any other ocular or systemic pathology (intraocular treatment as vitreoretinal surgery, diabetic retinopathy, retinal or choroidal neovascularization, exudative age-related macular degeneration, glaucoma, history of retinal detachment, diseases of the optic nerve, systemic diseases as diabetes mellitus, systemic hypertension, or neurological diseases) that might influence the RO measurements. To be included for TES, all RP patients had to meet criteria as follows: clinical and electrophysiological diagnosis of RP, absence of macular edema, a residual central VF ≥10° visual angle, no further contraindications to TES therapy. Exclusion criteria were as follows: fundus oximetry images of poor quality, unstable TES treatment performance, or expressed unwillingness to participate in the study. All research procedures were performed in accordance with institutional guidelines and the Declaration of Helsinki. Written informed consent was obtained before examination. All patients underwent a detailed ophthalmic examination at baseline (BL), 6M, and (3Y of TES treatment which included refraction, best-corrected visual acuity measured under standardized Early Treatment Diabetic Retinopathy Study (ETDRS) conditions slit-lamp examination, biomicroscopy, fundoscopy in mydriasis, fundus autofluorescence, VF testing with semi-automated kinetic perimetry (V4e, III4e, I4e, III3e isopters tested with Octopus 900®, Haag-Streit AG Bern, Switzerland), and ffERG (Diagnosys LLC Espion system; ISCEV standard [26]. Furthermore, if approved by the patient’s health insurance, also a molecular genetic assessment was included. In RP patients with extinguished ffERG at BL, electrophysiological testing was not repeated at the 6M and 3Y follow-up. All patients were recruited from the hospital’s hereditary retinal degeneration consultation hour and were diagnosed by 2 experienced fellowship-trained retina specialists (M.d.V.W. and H.P.N.S.). Tropiphen eye drops (tropicamide 0.5% and phenylephrine 1%, formula of our institutional pharmacy) were used to widen both pupils before RO measurements. Three drops were applied at 10-min intervals in each eye.

Transcorneal Electrical Stimulation

TES (OkuStim®, Retina Implant, Reutlingen, Germany) was performed according to the guidelines of the pivotal trial [1]. The OkuStim® system consists of 3 parts: a stimulation box, a special frame that is adjusted to the patient’s face, and electrodes that are placed in the frame to ensure good contact with the conjunctival tissue of the lower eyelid and the inferior bulbar conjunctiva for low impedance during TES-threshold measurement and stimulation. For a stable positioning in the frame, standard DTL-based electrodes are employed with an additional stirrup. On the ipsilateral side of the forehead, a ground-red dot electrode (3M Europe, Diegem, Belgium) is attached. Prior stimulation for each patient, an individual electrical phosphene threshold is determined by a single skilled operator in a darkened room on each eye individually in 3 independent measurements per eye (U.M.). These stimulation parameters are then programmed onto a patient’s USB stick, which is plugged into the OkuStim TES device. Stimulation...
is performed once a week for 30 min on both eyes at 20 Hz with current-balanced 5 ms-positive deflections followed by 5 ms-negative deflections at 200 percent of the electrical phosphene threshold over a period of 3Y. The patient could choose between a supervised TES stimulation in the hospital or a nonsupervised TES stimulation at home. In order to ensure a reliable and safe TES treatment, especially in the setting of a home stimulation, the patient and an additional relative of her/him need to be thoroughly instructed. If needed, the instruction is repeated until a safe handling can be ensured. The OkuStim box is programmed to halt stimulation automatically in case the impedance increases for security reasons. Before study inclusion, all patients’ TES stimulation parameters (duration, timing, impedance, and frequency of all stimulation sessions) were recorded and evaluated for consistency.

**RO Acquisition**

RO was performed at the BL visit before TES initiation, 6M, and 3Y after first stimulation. For RO, we used a spectrophotometric oximetry filter (IMEDOS Systems UG, Jena, Germany; Fundus camera FF450, Carl Zeiss Meditec AG, Jena, Germany). Fundus photos were captured using a camera system that included a DCC Digital Camera KY-F75 (JVC Inc., Yokohama, Japan) and a Zeiss fundus camera using a 50-degree camera angle. The system’s software (VISUALIS; IMEDOS Systems UG) distinguishes oxygenated hemoglobin from deoxygenated hemoglobin based on differential light imaging features at particular wavelengths, thus allowing the oxygen saturation level in the inspected retinal vessel to be measured. The acquisition of oximetry imaging is performed at 2 wavelengths: at the green channel (548 ± 10 nm) to capture the oxygen-insensitive image, and at the red channel (610 ± 10 nm) to capture the oxygen-sensitive image [13, 27]. Two concentric rings, 1 with a radius of 1.0 optic-disc diameters and the other with a radius of 1.5 optic-disc diameters, are formed in the peripapillary area using an optic disc-centered imaging procedure. The area of interest, represented by the region between these 2 circles, was where we took all measurements (as labeled in Fig. 1). Four test– retest fundus images for each eye were obtained [20, 21, 25, 28, 29]. Only 1 image with optimal illumination was chosen for further analysis, with red channel lighting 160 steps of the scale and green channel lighting >60 step of the scale. We selected manually for analyses all main arterioles and venules within the measurement area and evaluated the global mean oxygen saturation in retinal arterioles (A-SO₂) and venules (V SO₂) and calculated their difference, the A-V SO₂. In addition, the diameter of the corresponding retinal arterioles (D-A) and venules (D-V) were evaluated.

**Statistical Analysis**

Study endpoints were the following RO parameters: the mean arterial (A-SO₂; %) and venous (V SO₂; %) oxygen saturation as well as their difference (A-V SO₂; %). In addition, the mean diameters of the retinal arterioles (D-A; μm) and venules (D-V; μm) were measured. All RO parameters were recorded at BL before stimulation and following TES at 6M and 3Y follow-up.

Histograms and Shapiro-Wilk tests were performed to ensure a normal distribution for all parameters before further statistical evaluation. SPSS® (IBM SPSS Statistics, IBM Corp., Armonk, NY, USA, version 28.0.0.0) was used to build ANOVA-based linear mixed-effects models, which are suitable for repeated assessments since they allow for the consideration of the left and right eye dependency of the same participant. The eye, the refractive spherical equivalent, and the follow-up-effect were considered to predict the effect of TES on oximetry estimations at different follow-up visits (BL, 6M, and 3Y), where the eye, refraction, and the follow-up were treated as fixed factors and the subject as a random factor. The results are presented as mean and standard deviation for all parameters with the corresponding p values. p < 0.05 was defined as statistically significant. All pairwise comparisons with ANOVA were Bonferroni adjusted.

**Results**

Altogether, 18 eyes were enrolled in the study of 9 patients diagnosed with RP (5 ♀ 4 ♂; 9 right eyes and 9 left eyes, mean age 45.09 ± 11.13 years, range 33–67 years). Eight patients performed a nonsupervised TES stimulation at home after a thorough instruction, 1 patient received a supervised TES stimulation in the hospital. Throughout the time course of 3Y TES treatment, both the visual acuity (BCVA) and the VF did not show any significant change: at BL, logMAR BCVA was 0.23 ± 0.21, after 6M of TES treatment BCVA slightly changed to 0.35 ± 0.30 (p = 0.32) and to 0.20 ± 0.21 (p = 0.15) at the 3Y follow-up. VF (measured with the V4e isopter area with the Octopus 900®, Haag-Streit AG Bern, Switzerland),
was 4,979.51 ± 4,489.37 deg² at BL, improved slightly to 5,016.43 ± 4,664.10 deg² at 6M and decreased to 4,230.62 ± 3,911.31 deg² at the 3Y follow-up (\(p = 0.83\)). None of the RO parameters showed a statistically significant influence by spherical equivalent, age or gender (all \(p > 0.07\)). A subset of patients was screened for mutations in retinal disease genes and mutations in the following genes were found: 2 cases with USH2A, 3 cases with EYS, 1 case each with USH3A (CLRN1), RHO, and RP1.

| RO parameter        | Follow-up | p value over all follow-up visits (ANOVA) |
|---------------------|-----------|------------------------------------------|
|                     | BL        | 6M                                      | 3Y                                  |
| A-SO₂, % SO₂        | 96.35±12.76 | 100.72±5.53 | 100.89±5.87 | 0.2179 |
| A-V SO₂, % SO₂      | 34.15±8.68  | 38.93±9.67  | 36.23±7.71  | 0.2662 |
| V SO₂, % SO₂        | 62.20±11.55 | 62.79±12.06 | 64.66±8.24  | 0.7746 |
| D-A, μm             | 76.13±9.01  | 74.42±12.37 | 72.91±10.98 | 0.6754 |
| D-V, μm             | 96.41±17.37 | 91.53±17.10 | 91.03±11.54 | 0.5239 |

Oximetry Results

Comparison of Oxygen Saturation Values at BL, 6M, and 3Y after TES

In general, all oximetry parameters increased slightly throughout the TES timeline without reaching statistical significance: A-SO₂ was 96.35 ± 12.76% at BL, 100.72 ± 5.53% at 6M (\(p = 0.30\), when compared to BL, Table 1; Fig. 2), and 100.89 ± 5.87% at the 3Y follow-up (\(p = 0.27\), compared to BL). Also, the V SO₂ showed a slight increment in oxygen saturation levels and retinal vessel diameters.
from 62.20 ± 11.55% at BL to 62.79 ± 12.06% at 6M (p = 0.98, compared to BL) and 64.66 ± 8.24% at the 3Y follow-up (p = 0.77, compared to BL). Furthermore, the arteriovenular oxygen difference A-V SO₂ which showed significant changes in the pilot study did not present similar results in the long-term time course of TES: A-V SO₂ initially increased from 34.15 ± 8.68% at BL to 38.93 ± 9.67% at 6M (p = 0.2369, compared to BL). However, at the 3Y follow-up, the A-V SO₂ showed no further increment and remained slightly higher than at BL with 36.23 ± 7.71% (p = 0.7553, compared to BL). We found no significant differences in all pairwise comparisons between all follow-up visits (p > 0.05).

Retinal Vessel Diameter Results
Comparison of Retinal Vessel Diameter at BL, 6M, and 3Y after TES
As for the oxygen saturation, also the retinal vessel diameter results (D-A and D-V) throughout the time course of TES showed only slight changes; however, without reaching statistically significant results (Table 1; Fig. 2). Also, we found no significant difference in all pairwise comparisons between all follow-up visits.

Discussion/Conclusion
TES is a novel treatment approach for patients suffering from RP and currently the only evidence-based method to slow down disease progression [1, 2, 30, 31]. The pathophysiological background is not yet fully understood [1, 2]. However, studies in animals could confirm TES to induce a release of neurotrophic factors and thus change the microenvironment which improves the survival of the remaining retinal cells, and subsequently slows down the disease progression in RP [2–9]. Furthermore, due to its noninvasive nature and good safety profile with minimal side effects, this therapy option has become more and more popular among RP patients of both early and advanced stages of disease [1–3].

To date, therapy monitoring of TES has been evaluated with ffERG and VF measurements [1, 2]. However, both measurements have their limitations: as the ffERG is extinguished very early in the course of RP; it can often no longer be used for monitoring purposes [1, 2, 25]. Furthermore, as VF testing is a very time-consuming method and highly dependent on the cooperation of the patient it often produces very variable results which make a proper comparison of the findings very difficult.

In contrast to ffERG and VF testing, RO is a new, noninvasive, contact-free, short-lasting, and patient-friendly monitoring tool which has achieved a high acceptance in exploring the metabolic alterations of the retina in vascular and degenerative ophthalmic diseases [10–19]. More precisely, RO allows analyzing simultaneously, the retinal vessel oxygen saturation of the main retinal arterioles and venules as well as their corresponding diameters [32–35]. It has proven to be a valuable diagnostic tool especially for RP presenting with significant changes of the retinal oxygen metabolism: Both, the arteriolar and venous retinal oxygen saturation show an increase, while the arteriovenous difference which represents the retinal oxygen consumption, decreases [10–17]. In adult RP patients, these changes are accompanied by a severe vasoconstriction of the retinal arterioles, and venules as part of a neurovascular remodeling [10–17] while in children suffering from RP, these changes seem not to be as pronounced yet [18]. These findings can be explained pathophysiologically with the progression of retinal photoreceptor degeneration and the consecutive apoptosis in RP which reduces the retinal oxygen consumption and results in a hyperoxygenation of the extracellular space [25]. In addition, the blood-retinal barrier function is known to be impaired in RP [36–38] which results in a protein and oxygen invasion from the choriocapillaris and is thought to lead to further increase in extracellular oxygen accumulation [39]. This higher extracellular oxygen level induces further vasoconstriction and consequentially a reduced blood flow in retinal arteries with further alterations in retinal vascular hemodynamics [40]. As a consequence, a secondary neurovascular remodeling, such as proximal intraretinal pigment migration, inner retinal atrophy, neuronal, or glial migration occur as the atrophy advances [41]. These structural changes appear to be less dynamic than retinal vascular oxygen metabolism [21, 25]. All the above-discussed pathophysiological changes are also reflected in the RO measurements [10–17]. Therefore, by using RO several studies could show that the measurement of the retinal oxygen metabolism can be of diagnostic value [17–19, 21, 25].

Our pilot study including 43 RP eyes showed for the first time that RO might be useful for therapy monitoring in TES and found a significantly increased A-V SO₂ which represents the retinal oxygen consumption after 6M of treatment [25]. We assume that with the release of neurotrophic factors, TES improves the survival of photoreceptor cells which consecutively results in increased retinal oxygen consumption and increased arteriovenous oxygen difference resulting in increased retinal oxygen metabolism.
oxygen consumption [20, 25]. However, it was unclear, whether this effect would also hold true for long-term TES. Therefore, in this study, we compared retinal vessel oxygen saturation parameters in RP patients undergoing TES therapy over a period of up to 3Y to find changes that would be attributed to the therapeutic intervention. In general, the A-V SO₂ which had shown significant changes in the pilot study did not present similar results in long-term TES. The retinal oxygen consumption seems to increase throughout the TES timeline and remain on higher levels than what was measured at the BL visit; however, without reaching statistical significance. Nevertheless, our study could show that these higher levels of retinal oxygen consumption were also accompanied by relatively stable visual acuity and VF results over the period of 3Y TES treatment: both visual acuity and VF measurements did not show any significant deterioration. These findings further support the hypothesis of improved survival of the remaining retinal cells through TES-induced release of neurotrophic factors [2–9].

Our study has some limitations with a certain genetic and phenotypic heterogeneity of RP patients and a smaller sample size than what we reported in the pilot study. Unfortunately, due to the ongoing COVID-19 pandemic, a lot of patients avoided their follow-up visits in the hospital and could not be included in the present study. Therefore, we cannot exclude the possibility that the oximetry parameters would have reached statistical significance with a higher sample size. Further randomized, double-blinded, and controlled studies are needed to provide a clear evidence-based recommendation to use RO for TES therapy monitoring. In conclusion, our study could show that metabolic monitoring might be of potential diagnostic value in the context of TES. However, further studies are needed to verify its use in daily clinical practice.

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Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Study approval statement: This study protocol was reviewed and approved by the local IRB EKNZ in Basel, BASEC 2020-00122. Consent to participate statement: written informed consent was obtained from all individual participants included in this study.

Conflict of Interest Statement

Dr. Scholl is member of the Scientific Advisory Board of Apellis Switzerland GmbH, ARCTOS medical AG; Astellas Pharma Global Development, Inc./Astellas Institute for Regenerative Medicine; Biogen MA Inc.; Boehringer Ingelheim Pharma GmbH & Co; Gyroscope Therapeutics Ltd.; Janssen Research & Development, LLC (Johnson & Johnson); Novartis Pharma AG (CORE); Okuvison GmbH; Pharma Research & Early Development (pRED) of F. Hoffmann-La Roche Ltd; ReVision Therapeutics, Inc.; and Stargazer Pharmaceuticals, Inc. Dr. Scholl is paid consultant of Gerson Lehrman Group; Guidepoint Global, LLC; Tenpoint Therapeutics Limited; and Third Rock Ventures, LLC. Dr. Scholl is member of the Data Monitoring and Safety Board/Committee of Belite Bio and ReNeuron Group Plc/Ora Inc. and member of the Steering Committee of Novo Nordisk (FOCUS trial). Dr. Scholl is co-director of the Institute of Molecular and Clinical Ophthalm Basel (IOB) which is constituted as a non-profit foundation and receives funding from the University of Basel, the University Hospital Basel, Novartis, and the government of Basel-Stadt. These arrangements have been reviewed and approved by the University of Basel (Universitätsspital Basel, USB) in accordance with its conflict of interest policies. Dr. Hendrik Scholl is principal investigator of grants at the USB sponsored by the following entity: IVERICbio (Ophthotech Corporation); Kinarus AG; and Novartis Pharma AG. Grants at USB are negotiated and administered by the institution (USB) which receives them on its proper accounts. Prof. Scholl is the Editor-in-Chief of the journal. Individual investigators who participate in the sponsored project(s) are not directly compensated by the sponsor but may receive salary or other support from the institution to support their effort on the project(s).

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Author Contributions

Nesrin Meral and Olga Zabek contributed to conceptualization and drafting of the article. Maria della Volpe Waizel contributed to data preparation, interpretation, and revision of the draft article. All co-authors contributed to writing, provided intellectual input, and approved the final version of the article.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author.

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