(30)

Electrophysiological tests in evaluation of glaucoma and ocular hypertension treatment – up to date knowledge. A review

Testy elektrofizjologiczne w ocenie leczenia jaskry i nadciśnienia ocznego – aktualny stan wiedzy. Przegląd piśmiennictwa

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Streszczenie: Cel: opisanie na podstawie danych z literatury skuteczności testów elektrofizjologicznych (elektroretinogram stymulowany wzorcem, wieloogniskowy elektroretinogram i wieloogniskowe wzrokowe potencjały wywołane) w ocenie funkcji komórek zwojowych siatkówki w oczach z nadciśnieniem ocznym i jaskrą po obniżeniu ciśnienia wewnątrzgałkowego.
Materiał i metody: dane opublikowane w bazie PubMed w latach 1964–2012.
Wyniki: rezultaty badań opisane w kilku pracach sugerują, że za pomocą elektroretinogramu stymulowanego wzorcem typu stanu ustalonego można zarejestrować znaczącą poprawę funkcji komórek zwojowych siatkówki po leczeniu tymololem, acetazolamidem, beta-blokerami oraz analogami prostaglandyn. Tylko w jednym badaniu potwierdzono zmiany uwidocznione w wieloogniskowym elektroretinogramie, które powstały w następstwie obniżenia ciśnienia wewnątrzgałkowego po zabiegu trabekulektomii. Nie było istotnych statystycznie korelacji między zmianami zachodzącymi podczas obniżania ciśnienia wewnątrzgałkowego a zmianami uwidocznionymi w badaniu wieloogniskowych wzrokowych potencjałów wywołanych.
Wnioski: elektroretinogram stymulowany wzorcem typu stanu ustalonego jest testem najczęściej stosowanym w ocenie rezultatów leczenia nadciśnienia ocznego i jaskry.

Słowa kluczowe: jaskra, nadciśnienie oczne, elektroretinogram stymulowany wzorcem – PERG, wieloogniskowy elektroretinogram – mfERG, wieloogniskowe wzrokowe potencjały wywołane – mfVEP.

Summary: Purpose: On the basis of the literature data to assess the efficacy of the electrophysiological tests (pattern electroretinogram, multifocal electroretinogram and multifocal visual evoked potentials) in evaluation of retinal ganglion cells function in glaucomatous and ocular hypertension eyes, after intraocular pressure reduction.
Material and methods: Data published in the literature available at the Pub Med library between 1964–2012.
Results: Several results of studies suggest, that steady-state pattern electroretinogram reveals significant improvement of retinal ganglion cells' function after treatment with timolol, acatazolamide, beta-blockers and prostaglandin analogues. Multifocal electroretinograms' changes, after lowering the intraocular pressure by trabeculectomy, were confirmed in only one study. There were no statistically significant correlations between changes in intraocular pressure reduction and multifocal visual evoked potentials.
Conclusions: Steady state pattern electroretinogram is the most commonly used electrophysiological test in evaluating the results of glaucoma and ocular hypertension treatment.

Key words: glaucoma, ocular hypertension – OHT, pattern electroretinogram – PERG, multifocal electroretinogram – mfERG, multifocal visual evoked potentials – mfVEP.

Introduction

Glaucoma is described as an optic neuropathy, in which retinal ganglion cells (RGCs) degenerate and in consequence a progressive loss of vision is obtained. Nowadays researchers try not only to understand more about the pathophysiological mechanisms of this disease and to make early diagnosis, but also to prevent or slow down a nature cause of the disease. The prevention of glaucomatous damage development has the aim to lower intraocular pressure (IOP) as a major risk factor. All forms of treatment such as drugs, lasers and incisional surgeries try to achieve optimal values of IOP. However, the optimal IOP reduction varies and depends on the degree of visual field damage at diagnosis and on the rate of progression (1). There is no single safe level of IOP and it varies between patients and eyes. That is why the „target IOP" is the highest IOP that is expected to prevent further glaucomatous damage or slow disease progression to a minimum (1).

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Dietlein and associates (2) tried to evaluate the percentage of IOP, that should be lowered from its baseline value. They recommend, that the reduction should be from 20% to 50%, depending on the degree of already existing damage, the baseline IOP, the rate of progression and finally the patient's age. According to their review, topical monotherapy can lower the IOP between 15% to 30%, while the amount of IOP reduction observed after incisional glaucoma surgery varies from 50–90%. We still do not know, how much should be the IOP decreased to improve the RGC function.

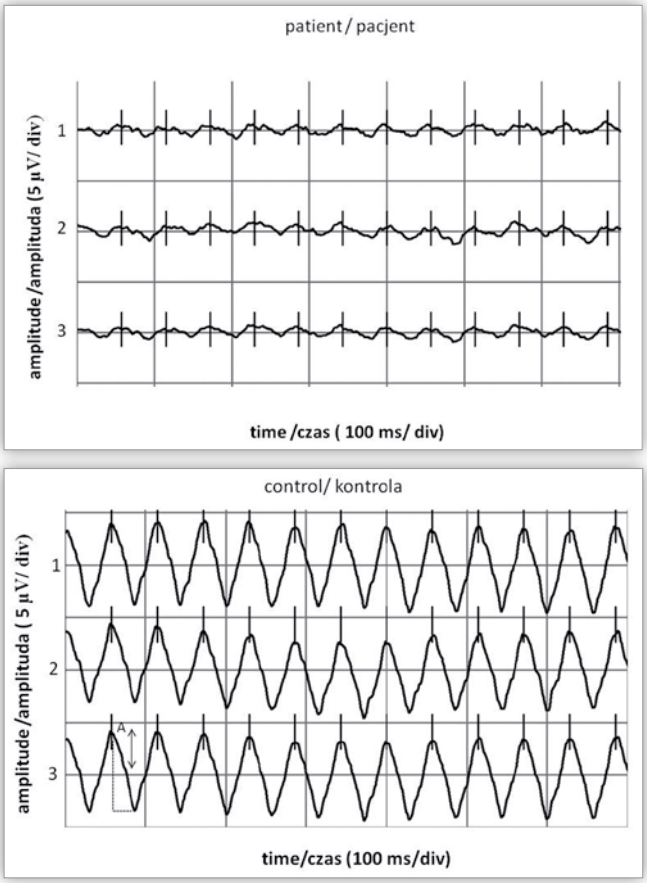
A golden standard in detecting glaucoma is standard automated perimetry (SAP), performed on Humphrey Visual Field Analyzer (24–2 threshold test). The common tests to describe an optic nerve, as well as the retinal nerve fiber layer thickness are: HRT II – Heidelberg Retina Tomography II, OCT – optical coherence tomography and GDx – nerve fiber analyzer. However it seems to be right to look as well for the functional changes of RGCs, which very often occur earlier than visual field (VF) changes (3, 4). The aim of this review is to evaluate the role of electrophysiological tests in estimating RGCs functional changes after treatment and what benefits may it bring to glaucoma patients.

Pattern electroretinogram – PERG

PERG – first described in 1964 (5) – is the most commonly used electrophysiological test in the clinical practice for evaluating the activity of RGCs. The inner retinal layers, mainly represented by RGCs, are responsible for generating the bioelectrical potential (6). Technically – it is a retinal biopotential response to a temporally modulated pattern, which is black and white check board or grating. According to International Society for Clinical Electrophysiology of Vision (ISCEV) standard for clinical pattern electroretinography – 2012 update (7), the stimulus is viewed with central fixation and covers approximately 15 central degrees of visual field (VF). The PERG waveform consists of a small initial negative component with a peak time of approximately 35 ms (N35), followed at approximately 50 ms by a larger positive component (P50), which is followed by a larger negative component at 90–100 ms (N95). The response from P50 represents in 70% RGCs and in 30% the cones from the macular region, while RGCs are in 100% responsible for the N95 response.

The most common PERG technique is a transient response. However for glaucoma patients the steady state PERG is the most often used, because many researchers' results suggest (8), that this type of PERG is more sensitive in detection of RGCs dysfunction in comparison with transient PERG. The difference between these two techniques depends on the frequency of the checkerboard reversal: in the transient response <4 rev/s and in the steady-state ≥ 8 rev/s are evoked. There are also two standardized PERG-glaucoma paradigms: "PERG Ratio" Paradigm (elaborated by Bach and the Freiburg group) (8) and the "PERGLA" Paradigm (by Porciatti and Ventura) (9). These both paradigms employ a Fourier analysis, but in the PERGLA paradigm skin electrodes instead of cornea (DTL) are used and the stimulus is grating instead of checkerboard. Although there are no clearly investigations comparing the above-mentioned methods, they do not differ in the essence and can be easily replaced (8). "PERGLA" Paradigm's repeatability is good and similar within – and between – trials, which shows that this method may be helpful in detection and monitoring RGCs' changes in glaucoma (10).

Figure 1 shows modified PERGLA (in electrophysiological laboratory in Szczecin) with reduced amplitude in glaucomatous eye in comparison with a normal response of a healthy eye.



1, 2 – separate sequential series of 200 signals/ 1, 2 – oddzielne sekwencje 200 sygnałów
3 – average response from 1 and 2/ 3 – uśredniona odpowiedź z 1 i 2
A – amplitude (half of the peak to trough amplitude)/ A – amplituda (połowa wartości międzyszczytowych)
parameters of stimulation/ parametry stymulacji:
frequency/ częstotliwość: 8,25 Hz
black and white reversing horizontal bar pattern/ czarno-biały odwracalny poziomy wzór
mean luminance/ średnia jasność: ca. 50 cd/m^2
contrast/ kontrast: 97%

Fig. 1. "PERGLA" (modified) – reduced amplitude in the eye with a glaucomatous neuropathy (above) in comparison with the eye of a healthy control.

Ryc. 1. Zmodyfikowany test PERGLA – obniżenie amplitudy w oku z neuropatią jaskrową (powyżej), w porównaniu ze zdrowym okiem z grupy kontrolnej.

One of the reports, where PERG was used in establishing the results of placebo and timolol treated eyes, was a study published by Nesher and associates (11). In this research they tried to determine whether long-term reduction of IOP leads to a corresponding protection of PERG. After minimum 6 years of timolol therapy (which reduced the IOP on average 19.6%), given to 21 patients with ocular hypertension (OHT), PERGs were studied. Although there were no significant differences in the mean PERG amplitude between the controls and placebo treated eyes, the controls and timolol treated eyes or the timolol-treated and placebo-treated eyes, another important interconnection was found. Statistically significant correlation was

the IOP difference between the group with the placebo-treated and timolol treated eyes and the corresponding PERG amplitude. These changes were found in 3 from 4 different check sizes (i. e. 0.25, 0.50, and 1.00 degree checks). Authors showed, that PERG amplitudes tended to be lower in eyes with higher IOP.

In another investigation Colotto and associates (12) tried to measure PERG changes in 48 treated OHT eyes. They assessed the relationship between PERG loses and IOP levels in the moderately elevated range (21–25 mmHg), after 8 months follow-up under timolol. The main conclusion was that in treated OHT, the greater and more frequently electroretinographic abnormalities appeared in eyes with elevated pressures, as compared to those with normalized ones (range:15–18 mmHg). This finding shows that the differences in PERG amplitudes may reflect different degrees of RGC dysfunction, which is associated with IOP levels. What is more, it is interesting to note, that PERG can not only document a retinal dysfunction associated with OHT, but it also reflects the protective functional effect associated with IOP normalization, in hypertensive eyes undergoing medical treatment.

Next application of PERG was documented in a pilot study by Ventura and associates (13). They compared PERG amplitude and/or phase of 49 eyes with either OHT or glaucoma (followed up in the previous 3 years), after topical treatment with acetazolamide, with a goal IOP reduction of 30%. They selected patients, who had previous baseline PERG measurements, so that the comparison could be possible. The PERG amplitude and/or phase improved after treatment more than 95% confidence intervals of the test-retest variability of the control group (untreated glaucoma). What interesting, the PERG improvement was in both: high and low-tension glaucoma eyes. Only eyes with severely impaired visual field showed little improvement in PERG. The above mentioned results lead to conclusion, that it is possible to at least partially restore the RGC function after IOP reduction, provided that the glaucomatous eye has scarcely early VF impairment.

In the study written by Salgarello and associates (14), PERG changes in a group of 27 treated, non-converting OHT patients were measured. During the medical treatment with beta-blockers and prostaglandin analogues, all patients had a controlled IOP (mean $\pm$ SD: 19.1 $\pm$ 1.4 mmHg). Mean PERG amplitude increased in comparison with baseline after 24 $\pm$ 6 months follow-up. What is interesting, HRT morphometry did not show significant changes and this provides evidence, that after IOP control, partial restoration of PERG abnormalities is possible. According to the authors, this effect may occur only when baseline PERG function is just slightly altered, not as much as in manifest glaucoma, where RGCs are more likely to be lost than dysfunctional. The same conclusions appeared in the investigation of Ventura and associates (15), where IOP lowering hindered a progressive loss of RGCs function, which was measured by PERG.

Multifocal electroretinogram – mfERG

The multifocal electroretinogram is a test of local retinal function (16). With this technique, many electrical responses from retina are recorded under light adapted conditions with a corneal electrode. This test allows a topographic map of local electroretinogram (ERG) activity, as well as the central retina, to be measured. Although the mfERG responses are dominated by bipolar and photoreceptor responses, Wittström and associates (17) analyzed studies by Chan and Brow (18, 19), where mfERG's responses in the first and second order kernel analysis were depressed in OHT and glaucoma eyes compared with normal eyes. Additionally, the macular response showed a large amplitude reduction compared with peripheral retinal responses. The above mentioned results may indicate, that the outer and inner retinal layers as well as the macular function are affected by glaucoma.

That is why Wittström and associates (17) used mfERG in order to better understand the IOP – lowering effects of retinal function in glaucoma patients. They enrolled eleven patients (11 eyes) with medically uncontrolled glaucoma, who underwent trabeculectomy. Clinical investigations, such as VF (tested with SAP), OCT, full-field ERG and mfERG were performed preoperatively as well as 2 and 6 months after surgery. What interesting, mfERG was the only test, which showed a significant difference between pre- and postoperative values. Its P1 amplitude improved significantly 6 months after surgery in area 1 and 2 ring and the implicit time of P1 in area 2 significantly decreased. These demonstrated changes may indicate, that a significant lowering of IOP improves the function of outer and mid layers of central retina.

The above mentioned publications' results confirm the role of electrophysiological tests in evaluation of glaucoma and ocular hypertension treatment. However, not all researchers described positive influence of IOP reduction on RGC function. For example Sehi and associates (20) tried to evaluate the impact of IOP reduction on RGC function in glaucoma suspect and glaucomatous eyes receiving latanoprost, using PERGLA. This prospective, placebo controlled, double masked, crossover trial, did not reveal significant diurnal variations on PERGLA amplitude, either at baseline or using latanoprost or placebo. There may be a few reasons of such results; one of them may be, that mean reduction of IOP after latanoprost, which according to authors was 20 $\pm$ 13%, was insufficient to improve the signal generated by RGCs. Additionally, some studies' results (13, 14) have demonstrated, that PERG amplitude is reduced in early glaucoma and the detection of further changes in the more advanced disease is more difficult, because the number of dysfunctional RGCs is in minor and structural changes are dominant. That is why we cannot expect RGC improvement. It is also possible, that the variability of PERGLA might limits its ability to detect reversal of RGC dysfunction.

In another investigation Jindal and associates (21) looked at improvement of multifocal visually evoked potentials (mfVEP) after lowering IOP. This electrophysiological test, introduced by Baseler and associates (22) is an objective method for topographical assessment of RGCs and their axons' function. It is a promising technique, in which many (typically 60) responses, each associated with a local region of the visual field (or retina), are recorded simultaneously (22, 23).

The above mentioned study 17 patients with elevated IOP were enrolled. IOP was reduced using a combination of topical (pilocarpine, latanoprost, brimonidine, timolol and/or dorzalamide), and oral medications (acetazolamide or methazolamide).

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The target IOP reduction was at least 30%. Unfortunately, this pilot study failed to confirm statistically significant correlations between the IOP reductions and changes in mfVEP measures, although most of the parameters demonstrated positive correlations. Probably the sample was too small and the study employed global indices of VF. Not unlikely, that focal changes of VF should have been compared with mfVEP results to find statistically significant correlations after treatment.

Conclusions

After analysis of the data from the literature, it is reasonable to say, that the steady state PERG has the highest value in estimating RGCs function after treatment of OHT or glaucoma patients. Larger group of patients and longer follow up are necessary to prove the efficacy of PERG and other electrophysiological tests in estimating the results of glaucoma and OHT treatment.

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