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PUPIL RESEARCH IN CLINICAL PRACTICE

Habilitation thesis

(Collection of Articles)

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Abstract

Examination of pupils in patients with disorders of the eye, the visual pathway or the central nervous system provides interesting information about the anatomy and pathophysiology of the pupil light reflex. Classically, the pupil light reflex pathway is considered to be a simple reflex arc consisting of the retinal ganglion cells, intercalated neurons in the midbrain, the oculomotor nerve and short ciliary nerves. However, with the discovery of intrinsically photosensitive retinal ganglion cells (ipRGCs), we have learned that the pupillomotor information delivered to the midbrain may originate not only in the outer retinal layer (activation of rods and cones) but also in the inner retinal layer (activation of ipRGCs), and pupillographic measurements in patients with various disorders of the visual pathway support the existence of two pupillomotor channels that drive the pupil light reaction – the subcortical (more primitive, luminance channel associated with the ipRGCs) and the suprageniculate (responds to shifts in structured stimuli, is driven by the rods and cones and receives input from the visual cortex and extrastriate areas). The pupil provides a valuable subject of research to experts in different fields. In ophthalmology, the examination of the pupil light reaction offers a unique objective method of testing the visual pathway function. This habilitation thesis is presented as a collection of published articles with a commentary that introduces into the topic and describes the current state of knowledge.

Contents

1 Introduction

Examination of pupils is an integral part of a medical examination. It offers an objective evaluation of the functioning of the central nervous system including the visual pathway and as such is of interest particularly to neurologists and ophthalmologists. Further, the pupils are an efferent structure of the sympathetic and parasympathetic nervous systems and as such can be subject to various pharmacological tests of the autonomic nervous system. When we are sleepy, the so-called "pupillary oscillations" on the pupillary edges can be observed and used to measure the level of sleepiness. This method has found use in occupational medicine, sleep medicine and psychology. Therefore, the pupil provides an interesting subject of research to experts in different fields.

In ophthalmology, the examination of the pupil light reaction offers a unique objective method of testing the visual pathway function. The pupil light reflex can be tested manually or with automated procedures. Researchers worldwide have developed many different devices to test different aspects of the pupil light reaction under specific conditions and in various diseases. Some of these solutions have been successfully adapted into practice and are produced commercially. Some are available only as prototypes and used mostly for research purposes.

Classically, the pupil light reflex pathway is considered a simple reflex arc consisting of the retinal ganglion cells, intercalated neurons in the midbrain, the oculomotor nerve and short ciliary nerves. However, pupil experts have always been aware of some contradictory clinical findings that were subject to debate and could not fully be explained by the widespread belief of the functioning of the pupil light reflex and as a result, the pupil light reflex is no longer considered a pure subcortical reflex arc. Moreover, the pupillary research has received new impetus since the discovery of the melanopsin containing retinal ganglion cells (intrinsically photosensitive retinal ganglion cells, ipRGCs) in 2002. Further development of this knowledge has brought new insights into the understanding of the pupillary behaviour.

As part of the research group in Tübingen, Germany I could be part of different projects dealing both with clinical applications and the pathophysiology of the pupil light reflex. The presented habilitation thesis summarizes my work in the field of pupil research.

2 Anatomy of the pupil light reflex

The neural pathway of the pupillary light reflex as first described by Wernicke [1] in the 1880s consists of four neurons (Fig. 1). Afferent fibers of the retinal ganglion cells travel in the optic nerve and undergo hemidecussation at the chiasm before entering the optic tract. In the posterior third of the optic tract, the pupillomotor fibers separate from the sensory fibers, branch medial via the brachium of the superior colliculus to the lateral geniculate nucleus and synapse in the ipsilateral pretectal nucleus in the dorsal midbrain. Intercalated neurons from each pretectal nucleus then project to both Edinger-Westphal nuclei and parasympathetic fibers from the Edinger Westphal nuclei innervate the iris pupillary sphincter muscle. According to this model, the suprageniculate visual pathway should have no influence on the pupillary light reflex. However, studies in patients with lesions of the retrogeniculate pathway have shown that the pupillary pathway is more complex than previously assumed and the retrogeniculate visual pathway and the visual cortex are also involved in the pupillary light reaction.

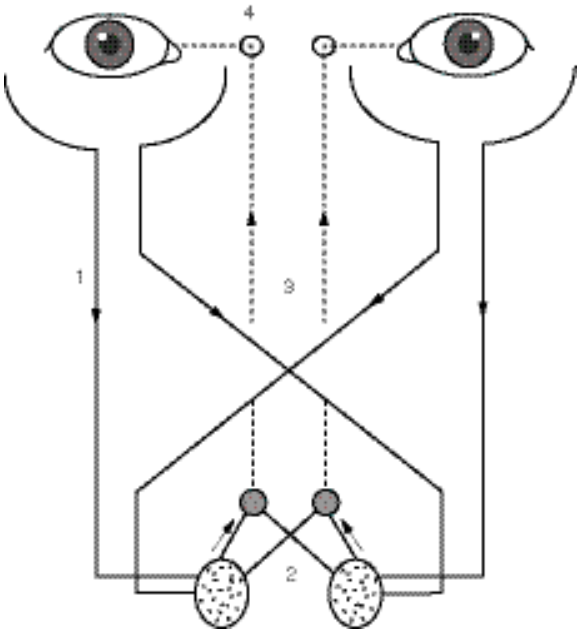

Fig. 1: The human pupillary pathway as first described by Wernicke consists of four neurons (excluding photoreceptors and bipolar cells in the retina): retinal ganglion cells (1), intercalated neurons in the midbrain (2), oculomotor nerve (3) and short ciliary nerves (4). The simplicity of this model can be no longer accepted. Reprinted from [1]

3 Examination of pupils

Examination of the pupils offers an objective evaluation of visual function as well as of the vegetative pathways to the eye. Essential information is gathered within a short time. This makes pupillary inspection a valuable part of routine ophthalmological, neurological and general medical examinations. Due to the proximity of pupillary pathways to various anatomic structures, pupillary dysfunction can be caused by a variety of disorders, some of which may be life-threatening. Due to differences in the course of pupillomotor and sensory fibers, pupillary tests can help in the localization of a visual pathway lesion. The ophthalmologist plays a key role in detecting pupillary disorders and in directing further investigations. Therefore, one should have a good knowledge of the diagnostic significance of pupillary function and dysfunction.

The problem of pupillary tests is the high interindividual variability of the pupil light reaction, which makes it almost impossible to decide without any other information if the pupil light reflex is normal or pathological. On the other hand, the difference of the pupil light reaction between both eyes, or between the corresponding parts of the visual field is much less variable and so comparative examination methods like the swinging-flashlight test or pupil perimetry are of great benefit.

There are several ways of how to examine the pupil light reaction. Some methods are based on the asymmetry in the afferent visual pathway, others on the examination of the visual field by means of measuring the pupil light reaction to focal light stimuli or on stimulation methods that are similar to multifocal electroretinography. Recently developed chromatic pupillography can identify pupil light response mediated by the rods, cones or the intrinsically photosensitive retinal ganglion cells containing melanopsin.

3.1 Relative afferent pupillary defect and swinging flashlight test

The most frequently evaluated pupillary parameter in clinical practice is the relative afferent pupillary defect (RAPD). It is typically related to lesions within the anterior visual pathway and is almost always present in unilateral or asymmetric bilateral diseases of the optic nerve, chiasm or the optic tract. It can be diagnosed by means of the swinging flashlight test and is characterized by diminished pupillary constriction on direct illumination with a normal consensual response to illumination of the contralateral eye.

Swinging flashlight test can be performed as follows: In a darkened room ask the patient to fixate an object in a few meters' distance. Shine with the ophthalmoscope in an angle of 45° from below and from the distance of 20 to 40 cm into the patient´s eyes. Move the light quickly from one eye to the other and observe the direct pupil light reaction of both pupils. Both pupils should be illuminated for the same time (ca. 2 seconds) and the switch between both eyes should be repeated at least five times. If a relative afferent pupillary defect is present on one side, then at the illumination of this eye both pupils will either enlarge without any previous contraction or this contraction will be smaller and shorter. RAPD can be quantified by means of neutral density filters and expressed in log units: A filter is placed between the light source and the "good eye". If there is still a RAPD defect visible, a filter with higher density is chosen until the difference in pupillary constriction between both eyes disappears or even the RAPD switches side. The density of the filter necessary to compensate the side difference is a measure for the RAPD.

The presence of RAPD allows valuable conclusions as to the cause of visual loss. No RAPD will be found if the visual loss is caused by media disturbance. Not even the densest unilateral cataract ever causes an RAPD. There are even many cases of cataracts and corneal opacities causing RAPD on the other side! This is because the test light is scattered directly onto the macula by the opaque media, while with clear media the eye is illuminated by the image of the test light in the retinal periphery (Ulbricht´s bowl effect). Unilateral or asymmetrical optic nerve disease, on the other hand, will always cause RAPD. With retinal diseases, RAPD varies but is never as clearly expressed as with optic nerve diseases. After an optic neuritis, the RAPD may persist, despite normalized visual acuity and field. Amblyopia may cause a mild RAPD, rarely exceeding 0.6 log units, mostly 0.3 or less. However, in the presence of a RAPD, the diagnosis of amblyopia should be made with caution [3].

Optic tract lesions, lateral geniculate lesions and, retrogeniculate lesions very close to the LGN produce contralateral RAPD in spite of symmetrical field defects. This finding could never be explained sufficiently with the conventional model of the pupillary pathways. Only recent research using modern imaging methods partially helped to solve the problem and will be discussed in paragraph 4.

3.1.2 Swinging flashlight test in glaucoma

Glaucoma is the second leading cause of blindness worldwide. It is defined as chronic, progressive optic neuropathy leading to typical changes of the optic nerve head and visual field. Until late in the course of the

disease the patient may not be aware of any visual impairment. With early diagnosis and treatment can the visual loss be stopped or at least slowed down. Therefore, to prevent blindness from glaucoma, population screening for glaucoma is necessary.

The major risk factor of the disease is high intraocular pressure. So, the most important examination method in glaucoma is the measurement of intraocular pressure. This method has high specificity; however, the sensitivity is quite low. In a substantial group of glaucoma patients, the intraocular pressure may be statistically normal. Perimetry also belongs to standard diagnostic methods in glaucoma, nevertheless is time-consuming and especially older patients may experience difficulties.

Even in developed countries, it is estimated that 50% of glaucoma sufferers remain undetected [4]. Since many cases of glaucoma go unidentified and untreated, attempts have been made to create effective screening for glaucoma. However, although we dispose of methods that help us diagnose glaucoma, screening methods have for the most part been ineffective and inaccurate in detecting the disease.

RAPD accompanies almost always a unilateral or a bilateral, asymmetric optic nerve lesion. Primary open-angle glaucoma affects usually both eyes, however, proceeds often asymmetrically and as such should result in RAPD. Therefore, the swinging-flashlight-test might be a suitable screening tool for glaucoma. Nevertheless, until recently, the prevalence of RAPD in glaucoma patients has not been evaluated in detail. We were one of the first groups to investigate the prevalence of RAPD in glaucoma patients.

In our paper "Relative afferent pupillary defect in glaucoma" [A] we report a retrospective study the aim of which was to estimate the frequency of RAPD in glaucoma and to find whether its occurrence relates to the severity of the visual field defect and its side asymmetry as detected by standard automated perimetry. Among patients with primary open angle glaucoma examined at the glaucoma unit of our university eye hospital patients were identified in whom a swinging-flashlight-test as part of their routine examination was carried out. The central 30° visual field was examined by means of static perimetry using the Tübinger Automatic Perimeter or the Octopus Perimeter. The visual field findings and their side difference were compared between patients with and without RAPD by means of the Wilcoxon rank-sum test.

In each patient, we calculated a visual field score as follows: (number of absolute defects + ½ number of relative defects) / number of all defects in the visual field. Therefore, a higher score indicates a more advanced

visual field loss. The asymmetry of the visual field was calculated as the absolute difference in the visual field score of both eyes.

After having taken into consideration the inclusion criteria, 100 glaucoma patients were included in the study, 34 of them had RAPD (34%). For the visual field analysis, only the data of 85 patients, who received the same perimetric strategy, were used. 25 of them had RAPD (29%). The calculated visual field scores in patients with RAPD were significantly higher than those in patients without RAPD ($p < 0.01$), that means their visual field loss was generally more advanced. Also, the side difference in the visual field of both eyes was significantly greater in patients with RAPD ($p < 0.01$). A receiver operating characteristics (ROC) curve showed that the side difference in visual field defect is a good predictor for RAPD with an area under the curve (AUC) of 0.81.

In our study, RAPD could be diagnosed in about one third of patients with primary open angle glaucoma which is in accordance with similar studies [5,6,7]. RAPD was found especially with more advanced visual field loss and with visual field defects of greater side asymmetry. On the other hand, its absence did not mean that there is no visual field defect at all.

We believe that the potential benefit or RAPD in glaucoma diagnostics is underestimated and the swinging-flashlight test not used enough in clinical practice. It is an easy and objective test available to all doctors, not only ophthalmologists, and as such a perfect complement in glaucoma suspects. It should not be considered as a substitute to perimetry, but rather as a supplement to it. The presence of RAPD indicates an advanced stage of the disease. The swinging-flashlight test can be particularly useful in patients who do not manage standard perimetry well. This may be important now that the population is getting older and the number of patients with dementia is increasing. The presence of RAPD can be used as a sign of progression and can be helpful in the interpretation of visual field findings.

3.2 Pupil perimetry (campimetry)

Visual field examination (perimetry) is an important method in ophthalmology and neurology. It enables us to localize lesions of the visual pathway and follow functional changes in time. Conventional perimetry is a subjective examination method and its results may be greatly influenced by the cooperation of the patient. Examination of the pupil light reflex (PLR), on the other hand, provides an objective assessment of the visual

pathway function. Though PLR shows great interindividual variability, its intraocular and interocular differences between various regions of the visual field are much less variable.

Objective assessment of the visual field is a method that is lacking in ophthalmology. It would be useful in patients who cannot master standard automated perimetry. This may be the case particularly with older people and with the increasing age of our population, this is certainly an emerging problem. Further, an objective visual field test can help unmask an attempt to simulate a visual field defect and as such be useful for expert evidence.

Pupil perimetry or campimetry is an objective visual field test that measures PLR to focal light stimuli projected onto the retina. Light stimuli are presented at various locations in the visual field like in standard perimetry. However, as the threshold for the pupil light response is higher than the differential light threshold in conventional perimetry, stimuli in pupil perimetry must be brighter or larger. Visual field defects in pupil perimetry can be recognized by a reduced or absent pupil light reaction within these areas. Studies dealing with clinical applications of pupil perimetry have shown that most diseases affecting the retina and the visual pathway caused pupil field scotomata which match the defects found in standard perimetry [8,9,10,11].

Most of my pupil research has been devoted to pupil perimetry (campimetry). I have used the prototype device developed in Tübingen both for clinical and experimental work. Though first considered by my colleagues at the eye clinic as a rather laboratory test, through my lectures and measurements, I have managed to make them aware of pupil perimetry and this method has become part of the ophthalmological examination especially in patients suspected of simulation. Apart from this, we have used pupil perimetry in several research projects that should either test the usability of this method in different ocular diseases or help explain the physiology and pathophysiology of the pupil light reflex.

In general, pupil perimetry can be performed either by means of a special pupillographic device or by a modified standard perimeter. However, most of these devices serve for research purposes and only a few machines are available commercially. In our laboratory, the pupillographic device consists of a computer, a 19-inch CRT screen for the stimulus presentation and a third monitor for a continuous monitoring of fixation by observation (Fig. 7.5). Stimuli are displayed on the computer screen at a distance of 20cm from the subject's eye. A small red spot is presented for fixation. Blinds around the device prevent stray light from the room disturbing the measurement. The pupil reaction is recorded by means of an infrared-sensitive video camera. The pupil edges can be determined by the contrast of the dark fundus and a very light iris infrared reflex.

During the test, the examiner can observe the quality of fixation, the stimulus sequence, as well as the continuous pupillographic curve. For the stimuli, white light is usually used and different stimulus intensities can be tested with a constant background luminance of 2.7cd/m^2. The stimulus is usually presented for 200ms every 2000ms.

In contrast to standard visual perimetry, pupil perimetry represents a method for objective visual field examination. As already said, it can be very useful particularly in patients suspected of stimulation or in patients who do not manage standard perimetry well enough.

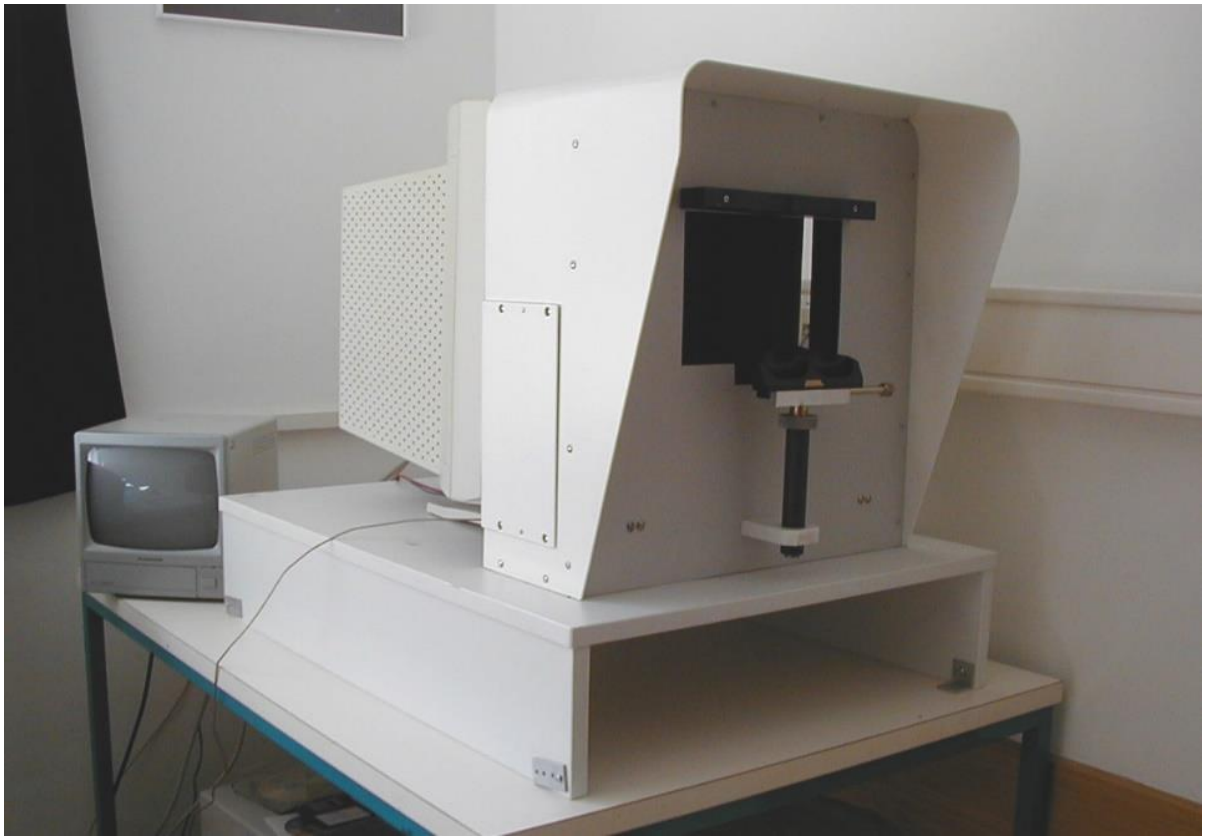

Fig. 2 Pupil perimetry (campimetry) in our pupil laboratory. The pupillographic device consists of a computer, a screen for the stimulus presentation and a third monitor for a continuous monitoring of fixation. The examination is carried out in darkness, separately for each eye

3.2.1 Pupil perimetry in patients with retinitis pigmentosa and functional visual field loss

Non-organic or functional visual loss is defined as loss of visual function where there is no lesion or organic basis to explain it. A patient exhibiting this type of visual dysfunction may have a psychiatric illness such as hysteria. But more often the patient perceives some secondary gain, such as disability pension. In children, it is often a behaviour expressed when there is significant stress in their lives, for example impending divorce or difficulties at school.

Disability diagnosis is a part of the social security system. Measurement of visual acuity, visual fields, and extra ocular movement are fundamental primary tests for disability determinations. However, disability assessment in ophthalmology may sometimes be difficult because the possibilities of an objective proof are limited and suitable examination methods are not widely available. Therefore, patients suspected of simulation should be preferably examined at centres where they have experience with the proceedings in such patients and dispose of methods needed for an objective evaluation of vision.

Functional visual loss can manifest as decreased visual acuity or visual field loss. Visual acuity as indicated by the patient can be verified by visual evoked potentials. However, in feigned visual field loss, it may be quite difficult to prove simulation as reliable objective test are lacking. Standard automated perimetry is a subjective test, the results of which fully depend on the patient´s response. To reveal feigned visual field loss, it is often necessary to use special tricky tests to catch out the malingerer.

The most common pattern of feigned visual field defect is concentric visual field loss, followed by hemianopic defects. In suspicion of simulated concentric visual field loss, kinetic perimetry may often be helpful. Repeated testing of a region with the same test stimulus should yield a result that lies at about the same eccentricity as the first presentation. Patients with non-organic abnormalities will frequently respond with ever-decreasing eccentricity on repeat testing using the same stimulus. When the responses are plotted, it yields a field with a spiralling isopter. Such spiral appearance is characteristic for non-physiologic visual field loss. Another proof of feigned concentric visual field loss is a non-expanding or "tunnel field". In this test, the isopters are plotted with the patient seated 1m and 2m from the screen. Even in patients with organic concentric visual field loss, the borders of the visual field should expand with increasing distance from the screen. If the isopter plotted at 2m will lie at the same distance from fixation as the isopter plotted at 1m, the patient is demonstrating a non-expanding field, which is very suspicious of simulation [12].

Electrophysiological tests can also help disguise functional visual loss. Electroretinography measures the electrical responses of various cell types in the retina, including the photoreceptors (rods and cones), inner retinal cells (bipolar and amacrine cells), and the ganglion cells. Depending on the parameters of the stimulus and adaptation level of the examined eye, full-field flash ERG reflects the activity of the rods or cones. However, unless 20% or more of the retina is affected with a diseased state the full-field ERGs are usually normal and as such not very suitable in feigned visual field loss.

Multifocal ERG (mfERG) uses an alternating stimulus with multiple hexagons and allows assessment of ERG activity in small areas of the retina. MfERG may be more useful in feigned visual field loss than the full-field ERG because it provides a topographic overview of the electrical activity of the retina and can be better compared with perimetry, especially in the central region. The pattern ERG (PERG), evoked by an alternating checkerboard stimulus, primarily reflects the activity of retinal ganglion cells and may be useful in assessing the function of these cells in diseases like glaucoma. The visual evoked potentials (VEP), is a measurement of the electrical signal recorded at the scalp over the occipital cortex in response to light stimulus. The VEP provides information primarily about the function of central visual function because such a large region of occipital cortex is devoted to macular projections. Thus, peripheral visual loss might be overlooked by VEP testing. A modality that may be more useful in feigned visual field loss is the multifocal VEP (mfVEP). It is designed to detect small abnormalities in optic nerve transmission and provide topographic correlation along the visual pathway. However, only limited studies to date of the anterior visual pathways correlate visual field abnormalities to the abnormalities confirmed by mfVEP [13,14].

As has already been said, to disclose non-organic visual field loss by objective methods may be a challenging issue in ophthalmology. If an expert opinion is required, for example in social court issues, objective methods are necessary. At first, an electroretinogram would be done of course, however, reduced ERG does not necessarily imply visual field loss and blinking or otherwise poor compliance might produce reduced ERG responses. It is, therefore, desirable to have an additional tool. Also, in the light of the emerging gene therapy in ophthalmology, an objective visual field test would be helpful.

Pupil perimetry or campimetry represents such an objective method of testing the visual field by examining the pupillary response to focal light stimuli projected onto the retina. It is therefore principally suited as a tool to distinguish organic from non-organic visual loss. Before applying pupil perimetry in cases with constricted visual fields it needs to be clarified that it is really possible to demonstrate organic constricted fields.

Retinitis pigmentosa (RP) is an inherited, degenerative eye disease that causes severe vision impairment due to the progressive degeneration of the rod photoreceptor cells in the retina. The progressive rod degeneration is later followed by abnormalities in the adjacent retinal pigment epithelium and the deterioration of cone photoreceptor cells. In the early stage of the disease patients first notice compromised peripheral and dim light vision due to the decline of the rod photoreceptors. As peripheral vision becomes increasingly compromised, patients experience progressive "tunnel vision" and eventual blindness. Visual field defects are usually located first in the mid-peripheral visual field and may progress to the far peripheral field, eventually extending into the central visual field as tunnel vision increases.

Patients with retinitis pigmentosa and concentric visual field loss are therefore ideal for a comparison with persons simulating such a visual field defect. We performed such a comparison in a study that was published in 2009 in Graefe´s Archive for Clinical and Experimental Ophthalmology under the title "Pupil campimetry in patients with retinitis pigmentosa and functional visual field loss" [B].

The aim of the study was to show in a small series of cases that pupil perimetry can demonstrate real concentric visual field loss in retinal degeneration and distinguish from feigned visual field loss and normal visual fields. By means of infrared-video-pupillography, light responses to perimetric stimuli were recorded. The stimulus pattern consisted of 41 stimuli presented in the central 30° visual field. Stimulus intensity was 140 cd/m2. Five healthy subjects, six patients with retinitis pigmentosa and two patients with suspected functional visual field loss were examined. In all groups, the pupil fields were compared to the standard visual fields obtained on the same day both by a subjective assessment of an experienced observer and statistical evaluation. To compare the RP group with the control group, the pupil responses at individual eccentricities were analysed using a two-tailed Wilcoxon rank-sum test. Due to the small number of patients with non-organic visual field loss, their results were not evaluated by descriptive statistics or the non-parametric test, but the actual pupil response was discussed in comparison to the other two groups.

Pupil perimetry in control subjects showed pupil light reaction at all tested locations in the visual field with the highest amplitude in the centre of the visual field and a decrease towards periphery (Fig. 3). In patients with retinitis pigmentosa whose visual field was constricted to the central 3 to 10°, the pupil reaction was present only within the preserved visual field (Fig. 4). Pupil perimetry in the two patients suspected of feigned concentric visual field loss showed a well evocable pupil reaction at all tested locations, with no evidence of any concentric constriction of the visual field in either eye.

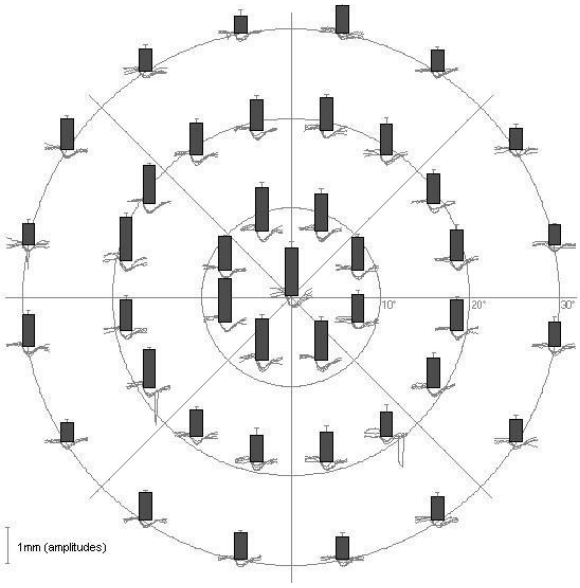

Fig. 3 Pupil field (30°) in a healthy person. At each tested location in the visual field, four pupillographic curves can be observed. The columns graphically represent the intensity of the pupil light reaction. The pupil light reaction is greatest in the centre of the visual field and decreases towards the periphery.

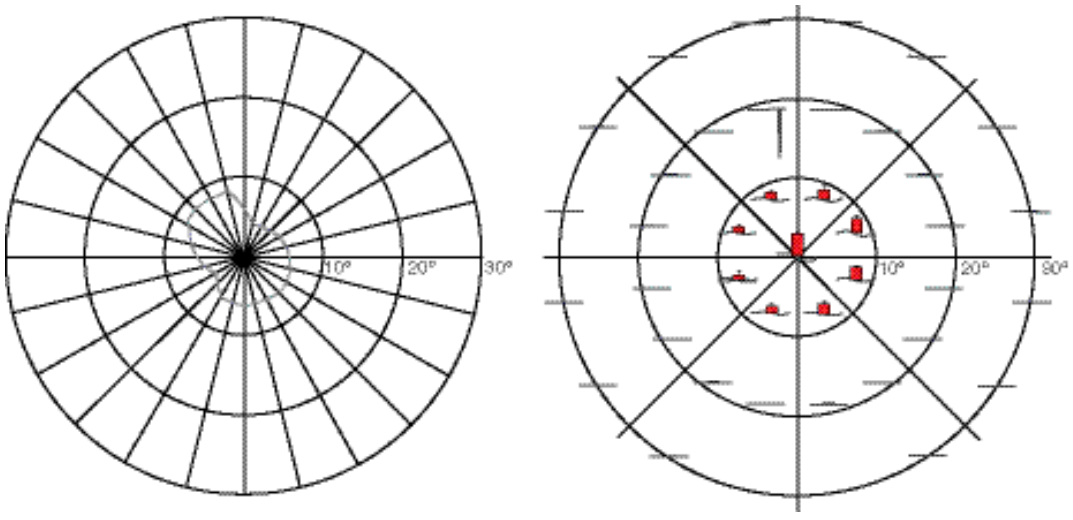

Fig.4 ***(left)*** *Schematic drawing of advanced concentric visual field loss in a patient with retinitis pigmentosa as detected by kinetic perimetry (Goldmann stimulus V4),* ***(right)*** *Corresponding pupil field with pupil light reaction present only within the preserved visual field*

Also, when compared by statistics, the pupil responses differed significantly between the control subjects and the RP patients in the centre of the visual field, as well as at the eccentricity of 10, 20 and 30 degrees. The pupil constriction amplitude of patients with feigned visual field loss resembled the results of the control subjects and differed completely from the results of RP patients.

Pupil perimetry could reproduce the visual field in retinitis pigmentosa very well. Pupil perimetry in patients with functional concentric visual field loss did not show a pattern like retinitis pigmentosa at all. On the contrary, it confirmed normal functions in allegedly blind areas of the visual field, thereby ruling out a severe retinal dystrophy. This study provided evidence that pupil perimetry is applicable in differential diagnoses of retinal dystrophy and functional concentric visual field loss.

Before our study was published, not much information existed about the pupillary visual field in retinitis pigmentosa. Since then, our paper has been cited by other studies dealing with the non-organic visual loss or retinitis pigmentosa in general.

To disclose non-organic hemifield defects it may sometimes be sufficient to perform a binocular perimetry test. Not to get uncovered, patients often close one eye during the examination, which can be recognized by the presence of blind spot on the printout. Electrophysiological methods in simulated hemifield loss have only limited value. Pupil perimetry, on the other hand, can be very helpful as shown by our group in the paper "How sensitive is pupil campimetry in hemifield loss?" published in Graefe´s Archive for Clinical and Experimental Ophthalmology in 2009. Surprisingly, visual field defects caused by retrogeniculate lesions could be reproduced by pupil perimetry even better than defects due to pregeniculate lesions of the visual pathway.

The ability of pupil perimetry to objectify hemifield defects justifies its use in the examination of patients with suspected functional visual loss. For clinical practice, it would certainly be desirable to know the sensitivity and specificity of pupil perimetry in feigned hemifield loss, however, this is not realistic as the number of patients with functional visual field loss shall never reach the limits needed for a satisfactory statistical analysis and so we can only draw conclusions from our clinical experience. That retrogeniculate lesion can be demonstrated by pupil perimetry is of importance for the diagnosis of feigned hemifield loss, because in this situation no other ophthalmological findings such as optic atrophy or relative afferent pupillary defect can be observed to disprove the presence of a hemifield defect.

According to our results, pupil perimetry can help reveal non-organic visual field loss and can be a good supplement to other examination methods used in these cases, where as many objective proofs as possible are welcome. The only disadvantage is that pupil perimetry is not widely available. In our laboratory, the patients were examined on a prototype device and unfortunately, we have not yet managed to start a commercial production of this equipment. In the past, researchers worldwide usually performed pupil perimetry by modifying standard perimetry, e.g. the Octopus perimeter. Of course, stimuli used in pupil perimetry must have different properties than the ones used in standard perimetry, but otherwise only an infrared video camera for the registering of pupil light reaction is necessary. Fortunately, a few devices have become available commercially during the last two years, for example, the NuCoria Visual Field Analyzer (NuCoria, Australia) or Pupilmetrix™ PLR60 (Applied Neurodiagnostics, Ltd, UK). However, there are not enough studies available yet that would show the sensitivity and specificity of these devices.

3.2.2 Pupil perimetry in glaucoma

Glaucoma is a progressive optic neuropathy which, if untreated, can lead to severe damage to the visual field. The disease is diagnosed by clinical examination of intraocular pressure, optic nerve head and visual field, although because of the high variability involved in visual field testing it can be difficult to identify people with early disease. For this reason, there has been a continuing search for an objective method of examining the eye for signs of glaucomatous damage. Apart from evaluating the prevalence of RAPD in glaucoma patients, we have also decided to examine if pupil perimetry can become a useful screening tool for glaucoma.

Glaucoma only seldom progresses symmetrically on both eyes. That is why a relative afferent pupillary defect is often present. Also, the damage to the visual field is often asymmetric not only between both eyes but also damage to the retinal nerve fibres is often asymmetric between the upper and lower retina [15,16,17]. Using these principles, Asman and Heijl [18] reported the development of the ‘Glaucoma Hemifield Test’ which uses standard perimetric results obtained from the Humphrey field analyser to empirically determine socalled ‘up-down’ differences in the probability maps to detect localized visual field loss. The method is based on the knowledge that early visual field defects (in glaucoma) are frequently restricted to either the upper or lower hemifield and that localized defects are manifested by asymmetries in the differential light sensitivities across the horizontal meridian.

Based on this knowledge we hypothesized that this asymmetric change, characteristic of glaucomatous retinal nerve fibre damage, may be detectable as asymmetries in relative sensitivity of the pupillary light reflex (PLR) in the upper and lower retinal hemifield when compared to healthy people. We designed a study, the aim of which was to find out if the pupillographic assessment of the visual field by means of pupil perimetry can identify glaucomatous visual field defects and as such be used for glaucoma screening purposes. The results were published in 2012 in Klinische Monatsblätter für Augenheilkunde under the title „Glaucoma screening by means of pupil campimetry" [C].

For the study, 20 patients with open angle glaucoma (study group) and a visual field defect in at least one eye were examined by means of standard automated and pupil perimetry. Their results of pupil perimetry were compared to 30 healthy subjects (control group). Based on the characteristic pattern of visual field changes in glaucoma patients we designed a special stimulus pattern for pupil perimetry. It consisted of 16 white-light-stimuli within the central 30° visual field and particularly between 10° and 20° above and below the fixation mark, that is in the so-called Bjerrum region, where the arcuate visual field defects mostly occur. Three stimulus intensities (16,4 cd/m^2; 27,1 cd/m^2 und 40,5 cd/m^2) were tested. The individual pupil light reaction (PLR) amplitudes at all examined locations in the visual field, their sums and partial sums were compared between both groups by the two-sided two-sample t-test. The diagnostic performance of the method in glaucoma diagnosis was evaluated by ROC-curves (receiver operating characteristics).

The average PLR at all locations in the visual field was reduced in glaucoma patients compared to healthy persons (Fig. 5). The sums of the PLR were reduced in glaucoma patients as well. Significant differences in the PLR were found especially in the central and paracentral visual field. The best AUC-values (area under the curve) were reached with the highest stimulus intensity, the highest AUC-value overall was 0,769. However, although the difference in PLR between glaucoma patients and the control group was significant, the reached AUC-values fell short of being ideal for screening purposes.

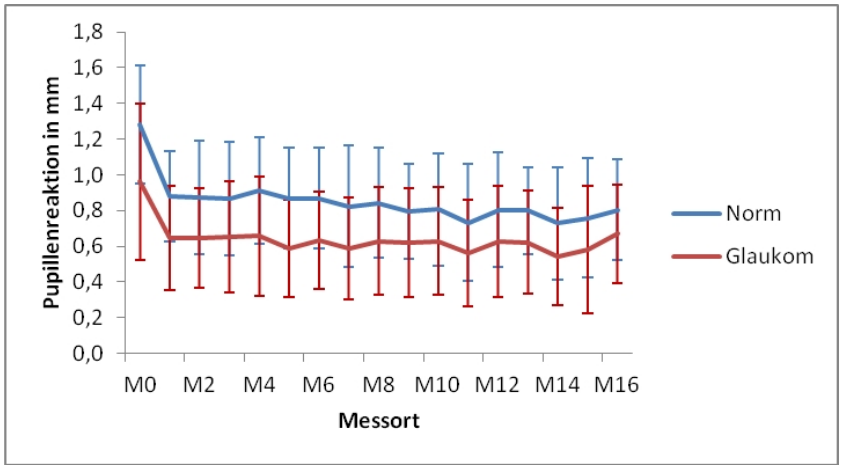

Fig. 5 Comparison of the average pupil light reaction in glaucoma patients and healthy subjects with its standard deviation at the tested locations in the visual field M0 to M 16 [C]

Nevertheless, our study brought several interesting findings. Surprisingly, the central pupil response was reduced by the same amount as in the Bjerrum region, which is rather unexpected when considering the classic course of glaucoma. A typical visual field defect in glaucoma is an arcuate defect respecting the course of nerve fibres on the retina and sparing the visual field centre. Damage to the centre of the visual field with a decrease in visual acuity is usually observed in advanced stages of the disease. Nevertheless, our study showed a significantly reduced PLR particularly in the centre of the visual field and the highest AUC values were reached for the central and paracentral visual fields. However, a similar result was obtained in recent perimetric studies with regionally condensed stimulus arrangements; in patients with moderate glaucoma, visual field defects in the paracentral region, particularly in the upper half field, were detected [19]. So, the central and paracentral visual field seems to be affected in glaucoma patients sooner than expected. This can cause significant problems with reading, driving, etc. and should not be underestimated in clinical practice.

The use of pupillography in glaucoma patients has been recently examined by other research groups as well. Kalaboukhova et al. evaluated the frequency of RAPD in glaucoma patients and healthy subjects by means of their special infrared pupillometry. Their test could detect glaucomatous optic neuropathy with a sensitivity of 86,7% at a specificity of 90%, which is, however, still too low for a screening method [20]. Similar to our study, Chen proposed that the asymmetric change, characteristic of glaucomatous retinal nerve fibre damage, may be detectable as asymmetries in relative sensitivity of the pupillary light reflex (PLR) in the upper and lower retinal hemifield. With his testing algorithm, the pupillary evaluation of retinal asymmetry in a test group of 40 glaucoma patients and 40 control patients agreed with perimetry in 70% of eyes tested [21]. Wride et al.

tested the same approach in 30 glaucoma patients and 30 healthy subjects with a commercially available device The Pupilmetrix™PLR60. The sensitivity of the method reached even 93,1% at a specificity of 76,7%. The overall agreement with the clinical diagnosis of glaucoma was 84,7% [22].

Apparently, changes in the pupil light reaction can be detected in glaucoma patients by various methods, however, up to now none of these methods has proved itself as a good screening method for glaucoma. With regard to the new discoveries in retinal physiology, the use of pupillometry in glaucoma patients has been evaluated by other pupillographic methods as well and will be presented further. I summarise the advances of pupillography in glaucoma in the article "Current state of pupil-based diagnostics for glaucomatous optic neuropathy" that was published in the journal "Ophthalmologe" in 2012 [D].

3.2.3 Pupillomotor receptive fields

The principle of pupil perimetry is similar to visual perimetry – white light stimuli of defined intensity are presented on a background of defined luminance at defined locations in the visual field. In pupil perimetry, the patient´s response to the stimulus is not signalled by pressing a button, but the pupil light reaction is registered by means of an infrared video camera. As such, pupil perimetry represents an objective method of visual field examination.

Most used in our practice is a stimulus pattern consisting of 41 stimuli located within the central 30°. The diameter of the individual stimuli is 4°. For all stimuli, white light is used, stimulus intensity is 140 cd/m^2 with a constant background luminance of 2.7 cd/m^2. Each stimulus is presented for 200 ms every 2000 ms. A small red spot is presented constantly as a fixation mark. The perimetry program presents each stimulus at each tested location four times. If the pupil size cannot be recorded four times without problems (e.g. of blinks), the stimulus is presented more often until four recordings of the pupil size are done for each stimulus. Afterwards, the average amplitude of the pupillary response in mm for each tested location in the visual field is calculated and graphically displayed from these four pupillary responses.

In visual perimetry, the raster comprises usually 60-80 test spots. In automated perimetry, the standard stimulus is Goldmann stimulus size III, which corresponds to the diameter of 0,43° and the duration of stimuli is usually about 100ms. So, the stimuli used in visual perimetry are much smaller than the ones used in pupil perimetry (4°) because when comparing both perimetric methods, methodological differences must be considered.

Pupillomotor threshold is higher than the visual threshold, and it varies considerably between individuals. Additionally, intraindividual variability exists. In most individuals, stimulus intensity has to exceed the visual threshold considerably to provide a stable and repeatable pupillary response. So, the stimuli used in pupil perimetry are much larger and brighter than stimuli used in visual perimetry to elicit a pupil light reaction. On the other hand, brighter stimuli increase stray light and this limits the maximal level of stimulus brightness because the local response is replaced by a stray-light response. In quite a few patients with visual field defects in conventional perimetry proven by objective morphologic findings, pupil perimetry fails to demonstrate a scotoma. If the stimulus is chosen too dim, it may remain below the pupillomotor threshold; if it is too bright, it will elicit a stray light response. It is virtually impossible to find for each individual and each retinal location a stimulus that elicits a local response without any additional stray light effect. Techniques that help to extract the local response from stray light "noise" tried to be adapted from electrophysiological recordings [23]. Although the results were promising, their incorporation into practice failed.

In view of the necessity of repeated measurements due to the variability of the PLR, the number of stimulus locations is limited. The test would otherwise be endless and unbearable for the patient. With our stimulus pattern, the test lasts about 5-6 minutes per one eye, depending on the cooperation of the patient. This is a reasonable time usually well tolerated by the patients.

The stimuli used in pupil perimetry are much larger the stimuli used in visual perimetry - 4° versus 0,43°. The size of stimuli in visual perimetry is derived from the size of the retinal receptive fields as known from psychophysiology. The receptive field of an individual sensory neuron is the particular region of the sensory space (e.g., the body surface, or the visual field) in which a stimulus will modify the firing of that neuron. Receptive fields have been identified for neurons of the auditory system, the somatosensory system, and the visual system. For example, the receptive field of a ganglion cell in the retina of the eye is composed of input from all of the photoreceptors which synapse with it, and a group of ganglion cells, in turn, forms the receptive field for a cell in the brain. This process is called convergence.

Hartline in 1940 introduced the concept of a receptive field to describe the spatial properties of retinal ganglion cells in frogs [24]. The classic center-surround receptive field organization of ganglion cells was discovered some years later in cats [25] and monkeys [26]. Their psychophysical equivalent, i.e. concentric areas of summation and inhibition found using subjective methods have been named perceptive fields [27].

The retinal receptive field is identified as the region of the retina where the action of light alters the firing of the neuron [24]. Each receptive field is arranged into a central disk, the "center", and a concentric ring, the "surround", each region responding oppositely to light. For example, light in the centre might increase the firing of a particular ganglion cell, whereas light in the surround would decrease the firing of that cell [25,26].

The properties of stimulus in visual automated threshold perimetry are based on longstanding experience and knowledge about retinal receptive fields. They are thought to be the basis of the relationship between the threshold luminance and size of stimulus as described by the Ricco [28] and Piper laws [29] on complete and partial summation. For smaller stimulus areas, Ricco´s law holds: the threshold luminance of the stimulus is indirectly proportional to the area of stimulus ($L \times A = C$, where L stands for the threshold stimulus luminance, A is the stimulus area and C a constant). This is due to the complete summation found within the center of the receptive field which produces a slope of 1 when log sensitivity (1/threshold) is plotted as a function of log area. As soon as the surrounding areas are covered by the stimulus and inhibitive interaction becomes involved, only a partial spatial summation occurs. This is defined by Piper´s law ($L \times \sqrt{A} = C$), in which sensitivity is proportional to the diameter of the stimulus: the slope of the line on logarithmic coordinates is less than 1. The critical area, defining the center of the receptive field is found at the intersection of these two lines of different slope. Scholtes et al. showed that in the range of the smallest diameters there was a straightforward agreement with Ricco´s law whereas large stimulus diameters curves follow more or less Piper´s law [30].

However, is there any physiological background that would substantiate the size of the stimuli used in pupil perimetry? Is there any pupillary analogy to the current retinal receptive fields? Do summation and inhibition occur in the pupillomotor system? This was supposed to be answered by our project on pupillomotor receptive fields. The aim of our study was to obtain information about pupillomotor summation areas, i.e. areas of the retina which, when stimulated, show evidence for spatial summation and possibly inhibition of the pupillary response. It was a novel and challenging project, but at the same time quite difficult because there was only very few and old information available in the literature. In the end, our study was published in Graefe´s Archive for Clinical and Experimental Ophthalmology in 2014 under the title “Investigation of summation mechanisms in the pupillomotor system” [E].

Computerized infrared (IR) pupil campimetry was performed in 30 normal subjects aged 18 to 32 years (10 males, 20 females, mean age 27.4 ± 3.1 SD). The subjects were recruited from the staff and students of the

University Eye Hospital in Tübingen. To gain information about the spatial characteristics of the pupillary response, we recorded the change in pupil diameter caused by stimuli of increasing size at four different retinal eccentricities, each with four different stimulus luminances. For each stimulus intensity, 12 stimuli were tested with diameters of 1°-10° in one deg steps, 12° and 15° in order of increasing size. We examined three different locations in the upper temporal visual field quadrant: 0°, 20° and 40° eccentricity, as well as at 20° in the lower nasal visual field quadrant (-20°), alternating between them to avoid adaptation.

The perimetry program presented each stimulus at each tested location four times. If the pupil size could not be recorded four times without artefacts (e.g. blinks), the stimulus was presented more often until four valid recordings of the pupil size were obtained for each stimulus. The pupillary response (i.e. the change in pupil diameter) was analysed for each pupil record.

In data analysis, the average of the pupillary response amplitudes of all subjects was calculated for each stimulus location and intensity. The logarithms of these averaged values were plotted against the logarithm of the area of the stimulus and a piecewise linear fit of the data was calculated (broken stick). The break and offset were determined.

When the average log amplitude of the pupil light reaction was plotted as a function of the log area of the stimulus, a bi-linear curve could be observed (Figs 1-3). The change in the pupil response to smaller and larger stimuli could be particularly observed at higher stimulus intensities (87 and 140 cd/m^2). The intersection points of the two linear responses are 2.01° in the fovea, 2.80° at 20° upper temporal retina, 2.85° at 20° lower nasal retina and 4.86° at 40° upper temporal retina. The gain of the two-phase stimulus-response curve for smaller stimuli was different from that for larger stimuli and resembled the relationship between threshold energy of light stimulus and stimulus diameter known from psychophysical experiments [25,26]. The two-phase response in pupil size indicates that with increasing spot diameter, the response profile of the summation area alters. We hypothesized that the break in this stimulus-response curve might give an estimation of the size of the pupillomotor summation area. When the stimulus becomes larger than the assumed summation area and invades an inhibitory surround, the stimulus response decreases.

Our results indicate that pupillomotor summation areas are larger than receptive fields of a retinal ganglion cell, their size increases with eccentricity in the visual field and the pupillomotor sensitivity of the retina decreases with distance from the fovea, in agreement with our knowledge about retinal receptive fields measured psychophysically [31].

There is no information about pupillomotor summation areas in the literature. Comparison of the pupillary and sensory threshold in relation to the area, duration, and localization of the stimulus at different levels of adaptation has been studied in the fovea and at 20 degrees nasal only by Alexandridis in the1970s [32]. His results show that threshold measurements of the pupillomotor response curve both in peripheral and central stimulation are in agreement with Ricco´s law up to a stimulus size of 30° diameter and that larger stimuli follow Piper´s law. With sensory threshold measurements, Ricco´s law holds only for smaller stimulus sizes, especially in the periphery. However, Alexandridis investigated summation effects of pupillomotor threshold but did not define any receptive fields.

In conclusion, the results of our study show that the pupillary light reaction is related to the size, intensity and retinal location of the stimulus. The relationship between size and pupil reaction can with caution be considered as biphasic and can be fit by two intersecting lines. These results are reminiscent of receptive field behaviour and suggest that pupillomotor summation areas might exist within the pupillary pathway. They show larger diameters than the receptive fields of the retinal ganglion cells but respect the summation rules valid for the retinal receptive fields. If this is so, stimuli used in pupil perimetry should really be larger than the stimuli used in standard visual perimetry to counteract this difference.

3.3 **Multifocal pupillography**

As already mentioned, there is a strong demand for objective perimetry both in ophthalmology and neurology. Not only to disprove malingering or simulation but also to examine patients who cannot master conventional perimetry well. Multifocal pupillography is a promising new method of objective visual field evaluation that could become part of clinical practice in ophthalmology quite easily as electrophysiological equipment is available at almost every university eye center.

In 2012 and 2014 I applied for a grant project the aim of which was to test multifocal pupillography in the diagnosis of ocular disorders, particularly in patients with a pre- or retrogeniculate lesions of the visual pathway. Results of the patients´ group should have been compared to a group of healthy subjects. For the purposes of the project, a special infrared camera should have been attached to the equipment currently available at the electrophysiological laboratory of our department of ophthalmology in Brno. Unfortunately, the project was never allocated support. Nevertheless, although I did not get the possibility to do the research

on multifocal pupillography, I think it should be listed in my enumeration of currently available pupillographic techniques.

Multifocal techniques (multifocal electroretinography - ERG, pattern ERG and multifocal visual evoked potentials - VEP) offer an objective evaluation of the function of the retina and the visual pathway. They are based on the principal of multifocal stimulus presentation. These procedures enable a simultaneous scanning of the electric activity from many regions of the retina. Stimuli are presented in the form of checkerboard stimuli, in which individual areas periodically change its contrast. However, except for mfVEP, the information is limited to retinal function. In optic nerve diseases and lesions of the higher visual pathway mfERG stays normal. Moreover, these methods require a time-consuming fixation of electrodes and in mfERG artificial mydriasis is necessary too. Multifocal pupillography (objective evaluation of the visual pathway function by multifocal stimulation) is based on the idea, that the computer registers changes in pupil diameter instead of electrical retinal activity. The examination by means of multifocal pupillography is short, non-contact, does not require artificial mydriasis and is very little influenced by factors like lens opacity or refractive error.

Multifocal pupillography is a method studied especially by the team of Ted Maddess in Australia. They tested multifocal pupillography in various diseases including glaucoma [33,34], diabetic retinopathy [35] or age-related macular degeneration [36]. Most of their studies dealing with multifocal pupillography investigated the diagnostic accuracy of multifocal pupillography in glaucoma. Their studies showed that the pupil light reaction in patients with glaucoma as detected by multifocal pupillography is smaller and its latency longer than in healthy persons and the sensitivity and specificity of multifocal pupillography is similar to methods currently used in glaucoma screening [33]. Recently it has been shown that multifocal pupillographic objective perimetry may potentially be a useful method in monitoring progression of age-related macular degeneration (AMD) and in assessing changes in retinal function after therapeutic interventions in early AMD [37]. Wilhelm from our research team showed in a few patients with optic neuropathy that objective perimetry by means of multifocal pupillography can reproduce a visual field defect detected by standard perimetry [23].

Multifocal pupillography seems to be a promising method for objective evaluation of the retinal function. The results of studies on multifocal pupillography are very interesting and encourage further development of this method. However, the experience with multifocal pupillography in lesions of the visual pathway is still missing. I hope I will have an opportunity to work with this method in the future and contribute to the clinical introduction of this method.

3.4 **Pupillographic sleepiness test**

In 1963, Lowenstein and co-workers described a phenomenon they named "fatigue waves "[38]: slow rhythmic changes of the pupillary diameter that occurred in complete darkness in subjects who were obviously sleepy. Later, in her famous monograph, Irene Loewenfeld wrote [39]: "Fatigue waves are involuntary and unconscious, so that they cannot be produced deliberately; and best of all, running records can be obtained without touching the subject. These show the slightest fluctuations from one moment to the next, from day to day, from week to week, and over longer periods." When this was published, in 1993, sleep medicine and sleep disorders, especially hypersomnia, attracted new attention [40].

Pupillary oscillations in the dark are stronger when the subject is tired than when he is alert. The response of the pupil in the sleepy state is determined by the noradrenergic pathway from the locus coeruleus to the Edinger–Westphal nucleus and is directly related to the overall activity in the alertness-promoting locus coeruleus [41,42,43,44]. Measurement of the pupillary oscillations, therefore, gives a measure of central nervous system activity and sleepiness, which is reproducible and not prone to subject bias and motivation [45].

Assessment of sleepiness is usually based on subjective gradings by the patient (e.g. Stanford Sleepiness Scale, or on rather time-consuming and costly tests such as the multiple sleep latency test [40]. Only a few authors applied pupillographic tests in sleep medicine between 1963 and 1993. The reasons for this rather limited use of pupillography were mainly technical problems especially due to the long duration of the test. Assessment of sleepiness requires examination times of at least 10 minutes. As video pupillography became available, the possibility of image processing by personal computers was the appropriate tool to cope with the special demands of long-term pupillography.

The pupillographic sleepiness test (PST) is an objective method for measuring pupillary oscillations. The method has now been used for 15 years in sleep medicine, sleep research and clinical pharmacology, and has been tested both in the laboratory [40,45, 46,47] and in field studies [48,49]. Normal values for the outcome parameter, the pupillary unrest index (PUI), have been determined for adults [50] with no effect of gender or age. The pupillographic measures correlate significantly with the sleep latency of the multiple sleep latency test, a method that is internationally well known and widely used, as well as with sleepiness-related frequency bands in the waking electroencephalography (EEG) [51]. Unlike many other methods applied routinely in sleep laboratories, the use of the PST is not restricted to the clinical setting. It does not require highly

specialized equipment or personnel and is not time-consuming. Its validity to assess sleepiness has been previously investigated, and the correlation with subjective sleepiness, duration of night sleep, sleep latency in the multiple sleep latency test, as well as the relationship of sleepiness-related spontaneous oscillations of the pupil to the waking EEG in patients or sleep-deprived normal subjects is known [45,46,47].

In many studies, the pupillographic sleepiness test proved to be a fast and relatively simple method to measure sleepiness. It can be used in diagnosis, to determine whether a patient really suffers from daytime sleepiness or in therapy, to assess whether therapy is successful or not. An example of a relatively common sleep disorder is the sleep apnea syndrome affecting mostly men after the age of forty. Estimates of disease prevalence are in the range of 3% to 7% [52], with certain subgroups of the population bearing a higher risk. However, this is probably an underestimate, because many sufferers remain undiagnosed. Obstructive sleep apnea is being increasingly recognized as an important cause of medical morbidity and mortality. If left untreated, it leads to excessive daytime sleepiness, cognitive dysfunction, impaired work performance, and decrements in health-related quality of life. Observational and experimental evidence suggests that obstructive sleep apnea may contribute to the development of systemic hypertension, cardiovascular disease, and abnormalities in glucose metabolism. Sleep apnea is also considered as a risk factor for low tension glaucoma and floppy eyelid syndrome. The treatment of sleep apnea syndrome consists in many cases of nasal continuous positive air pressure (nCPAP).

The pupillographic sleepiness test can be applied in traffic medicine, to advise a patient about his ability to drive a car. A mobile version of PST was used in several on-road studies, especially with professional truck drivers [53]. From the occupational medicine point of view, PST can give an objective opinion on the patient´s ability to go back to work. This approach has been used in studies involving people working night shifts and exhibited to stress like the medical doctors [48,49]. PST examination has also been included in psychological studies. A large study on daytime sleepiness and its relation to the sleep behaviour was performed in school children [54].

Although I have not performed a study with PST, I have personal experience with this method from our laboratory and PST certainly belongs to the list of pupillographic examination methods. PST, as produced by AMTech (Figs. 6 and 7), was developed by our pupil research group – professors Barbara Wilhelm and Helmut Wilhelm, engineering support was provided by Holger Lüdtke.

Fig. 6 PSTxsIII Pupillographic Sleepiness Test (AMTech, Germany). Recording the spontaneous and involuntary pupil movement in darkness is the simplest method to measure and evaluate sleepiness objectively. The sleepiness waves are monitored by means of a IR-videocamera with built-in IR-illumination. The subject is bespectacled with a pair of goggles which are opaque for visible light and transparent for infrared light. Thereby the measurement is performed in darkness and only a crimson and dim fixation target is seen. The Pupillographic Sleepiness Test is an easy to operate, non-invasive and fast tool to obtain an objective assessment of the central nervous activation and drug related vigilance. Areas of application are sleep medicine, occupational medicine and pharmacology (www.amtech.de).

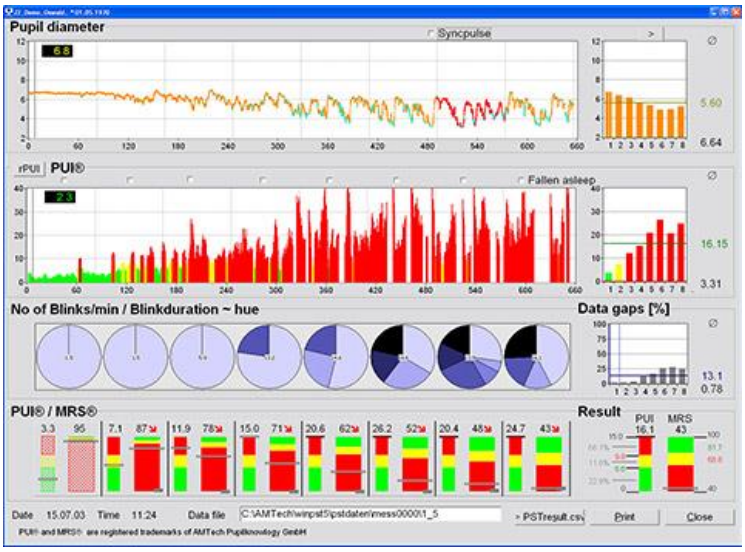

Fig. 7 The pupillographic curve shows extreme undulations of a sleepy person's pupil. The protocol gives information about the pupil diameter and the PUI over time, the horizontal and vertical eye position, the rate and duration of blinking and the data quality (www.amtech.de)

3.5 Pharmacological testing in pupillary disorders

Pupillary disorders can be produced by different conditions. It may be a pure ocular pathology like acute angle closure glaucoma or anterior uveitis that cause moderate mydriasis and pupilloplegia. Pseudoexfoliation syndrome is often accompanied by insufficient mydriasis due to damage of the dilator muscle. Lesions of the visual pathway can produce a relative afferent pupillary defect. And eventually, dysfunction of the autonomous nerve systems can also result in pupillary disorders by affecting the function of both pupillary muscles – pupillary sphincter and dilator muscles.

One of the best known pupillary symptoms is anisocoria. Anisocoria means a different size of both pupils. In some cases, it may be a sign of damage to the central nervous system, in other cases, its presence may not be alarming. The differential diagnosis of anisocoria may seem complicated and the patients often travel back and forth between a neurologist and ophthalmologist. Indeed, the diagnosis of anisocoria may sometimes be difficult and may require additional examinations. However, if certain rules are followed during the diagnostic process, the diagnosis should usually be established.

If the difference between both pupils is less than 1mm and the pupil light reaction is otherwise normal, then the anisocoria can be labelled as physiological. If the anisocoria is accompanied by ptosis and the so-called pupil dilation lag, Horner syndrome should be suspected. If the anisocoria is accompanied by disturbed pupil light reaction, motility disorders, and diplopia, it may be due to an oculomotor palsy. In case anisocoria is accompanied by disturbed pupil light reaction and a normal near reflex, then one can suspect a tonic pupil. Other causes of anisocoria include damage to the midbrain or the iris itself. Sometimes, it may be necessary to search for possible botanical or pharmacological effect on the size of the pupils.

To prove some of the above mentioned diagnoses, a pharmacological pupillary test may be necessary. The two most common situations in which a pharmacological test is required in clinical practice include the Horner syndrome and the tonic pupil. In the tonic pupil, the affected pupil is larger than the other one, does not react to light, but near reaction is preserved. On the slit lamp, under high magnification, worm-like movements of the pupillary edges can be observed. Tonic pupil is caused by unilateral parasympathetic lesion and affects mostly middle aged women. The tonic pupil may often cause diagnostic problems. Though it is a relatively common condition, it does not always look quite typical. The question of whether it is the tonic pupil, is best resolved by administering 0,1% pilocarpine to both eyes and evaluating the response of the involved pupil

relative to the opposite pupil after 30 minutes. Unlike the other eye, tonic pupil reacts to pilocarpine 0,1% with constriction due to cholinergic denervation [55].

Horner syndrome is classically described as the triad of miosis, upper lid ptosis with mild elevation of the lower lid and, depending on the site of the lesion, anhidrosis of the ipsilateral side of the face and/or body. Horner syndrome occurs as a result of disruption to the ipsilateral sympathetic innervation to the eye and face. Usually, a dilation lag is present as well. The long and complicated course of the oculosympathetic pathway predisposes it to a wide variety of pathologic processes, ranging from harmless vascular headaches to life-threatening conditions, such as carotid artery dissection, jugular vein thrombosis, or malignancy. Depending on the cause of Horner syndrome, early recognition and intervention can be lifesaving.

Sometimes, it may be difficult to distinguish physiologic anisocoria from Horner syndrome. This distinction can be difficult because Horner syndrome may have subtle clinical manifestations. Ptosis may be absent. Anisocoria may be absent. At best, each finding is minimal. And each finding can be generated by other causes. Especially in acute onset, the diagnosis of Horner syndrome can be postulated without a pharmacological proof. In other cases, for confirmation of Horner syndrome, we often depend on topical pharmacological testing. But what kind? I have pursued this topic in my article "Pharmacological Tests for Horner Syndrome" that was published in 2016 in Czech and Slovak Ophthalmology [F].

Cocaine is an indirect sympathomimetic agent, which works by blocking the re-uptake of noradrenaline from the synaptic space. In the normal eye, this should produce an increase in pupil diameter, while in Horner syndrome, the pupil will fail to dilate [55]. However, testing with cocaine has limitations. First, the normal control pupil may not dilate due to the relatively weak dilating effect of cocaine. Second, there is the risk of a false-positive result if the affected pupil is incapable of dilating for another reason. Third, cocaine is a controlled substance, which is often difficult to obtain. Cocaine testing in Horner syndrome has lost its luster as the gold standard for diagnosing oculosympathetic paresis in recent years owing mainly to the increased difficulty in maintaining its easy availability and it is slowly being replaced by other substances.

Apraclonidine is an adrenergic drug with a weak agonist action on α-1 receptors and a strong agonist action on α-2 receptors. In Horner syndrome, there is an upregulation of α-1 receptors in response to the loss of sympathetic innervation, which results in supersensitivity of the affected pupil such that it dilates in response to apraclonidine. In contrast, a normal pupil will either show no change in size or constrict because of α-2

activity. The current criterion for the diagnosis of Horner syndrome is a reversal of anisocoria after bilateral administration of topical apraclonidine.

Apraclonidine testing for the diagnosis of Horner syndrome is rapidly becoming the new standard for pharmacologic testing in Horner syndrome. In several studies, apraclonidine showed to be comparable with cocaine in detecting denervation supersensitivity in Horner syndrome [56,57]. As for cocaine, apraclonidine is useful for diagnosing Horner syndrome, but not for localization of the site of the lesion. However, this substance, produced commercially as a glaucoma medication (Iopidine®), is not available in the Czech Republic. Is there any other option?

In my article, I present a patient, who was examined at our department due to anisocoria that has been present for more than one year. Besides the anisocoria, the patient had no other pathological symptoms. The pupil on the right eye was larger than on the left eye by more than 1mm. Photoreaction was present in both eyes with a dilation deficit on the left eye. There was also a slight ptosis on the left. The anterior and posterior eye segment was normal, only the iris of the left eye was slightly decoloured. The ophthalmological finding was pointing to Horner syndrome on the left side. The cause of the syndrome was not found until then. This is not unusual as the cause of Horner syndrome remains unknown in up to one-third of patients.

When I wanted to perform the cocaine test, I found that nowadays it is very complicated for an ophthalmologist to obtain cocaine, as it is no longer used as an anaesthetic drug and it is a controlled substance. My attempt to order a single bottle of apraclonidine from abroad was not successful either. Also, other substances like hydroxyamphetamine or pholedrine are not available anymore in the pharmacy. Therefore, based on literature search, I decided to conduct an experiment with phenylephrine 1%. Phenylephrine 10% is currently used as a mydriatic agent (Neosynephrine-POS®) and so available to all ophthalmologists.

Because of the principle of denervation sensitivity, Horner syndrome produced by a lesion interrupting the postganglionic fibres should dilate the pupil when 1% phenylephrine is placed in the conjunctival sac [57]. I measured the pupillary diameter before and one hour after the administration of 1% phenylephrine to both eyes. Before instillation of the drops, the pupils measured 5mm (right eye) and 3mm (left eye). After one hour, the anisocoria was almost reversed, with pupils measuring 5mm (right eye) and 5 mm (left eye), and the ptosis has partially resolved. The result of the test pointed to a postganglionic sympathetic lesion on the left.

To confirm my experiment, I performed this test also with cocaine one month after the first test. The administration of 5% cocaine caused dilation of the control pupil, the size of the pupil affected by Horner syndrome did not change. The test confirmed the diagnosis of Horner syndrome on the left.

The usability of phenylephrine for a pharmacological test in Horner syndrome has been tested by other studies as well. Ramsay reported denervation supersensitivity to 1% phenylephrine in 71% of tested patients with Horner syndrome [58]. In another study with 14 patients diagnosed as having isolated postganglionic Horner syndrome, the sensitivity of 1% phenylephrine was 81% and the specificity 100% [59].

According to some studies, denervation supersensitivity needs 1-2 weeks to develop [60]. Because the 1% phenylephrine test is primarily based on denervation supersensitivity, a false-negative result may occur in very recently acquired Horner syndrome [61,62,63]. On the other hand, cases were published in which denervation sensitivity developed very fast, even within a few hours [56]. To resolve this controversy, a study with many patients would be necessary, however, this is rather difficult in Horner syndrome.

Based on my experiment and the results of other studies, the use of 1% phenylephrine for a pharmacological test in Horner syndrome is possible and currently represents the best available option in our country. However, topical cocaine (2,5%) should be further used in small children under the age of one year, because other α1-sympathomimetic agents may cause severe autonomic side effects in that age group [63].

4 Pupil light reflex in new light

The anatomy of the human pupil light reflex (PLR) pathway is a matter of debate. The neural pathway of the PLR was first described by Wernicke in the 1880s [1]. Afferent fibres from the retina travel in the optic nerve and undergo hemidecussation at the chiasm before entering the optic tract. Fibres emerging in the nasal retinal halves cross over to the contralateral optic tract, fibres from the temporal half of the retina proceed ipsilateral. In the posterior third of the optic tract, the fibres branch medial to the lateral geniculate nucleus (LGN) and synapse in the ipsilateral pretectal nucleus. Intercalated neurons from each pretectal nucleus then project to both Edinger-Westphal nuclei and parasympathetic fibres from the Edinger-Westphal nuclei innervate the iris pupillary sphincter muscle. However, clinical observations of pupillary behaviour in patients with different lesions of the visual pathway have repeatedly challenged this classical view of the PLR pathway.

Relative afferent pupillary defect (RAPD) is typically related to lesions within the anterior visual pathways and is almost always present in unilateral or asymmetric bilateral disease of the optic nerve, chiasm or the optic tract. However, studies in patients with lesions of the retrogeniculate pathways have shown that pupillary disorders (RAPD and pupillary hemihypokinesia) are possible even with lesions not involving the classical reflex arc [65,67,67].

So, the pupillary pathway seems to be more complex than previously assumed. The pupil is not controlled only subcortically, and the retrogeniculate visual pathway and the visual cortex are also involved in the pupillary light reaction. This hypothesis is supported by the recent discovery of retinal ganglion cells containing melanopsin which are intrinsically photosensitive and apart from other functions serve the pupil light reflex [68,69,70,71]. Clear anatomic evidence is still lacking but pupillographic measurements in patients with various disorders of the visual pathway support the existence of two pupillomotor channels that drive the pupil light reaction – the subcortical (more primitive, luminance channel associated with the intrinsically photosensitive retinal ganglion cells) and the suprageniculate (responds to shifts in structured stimuli, is driven by the rods and cones and receives input from the visual cortex and extrastriate areas).

I have summarized this topic in my article "Afferent pupillary disorders in postchiasmal lesions of the visual pathways" in Klinische Monatsblätter für Augenheilkunde in 2009 [G] and recently in the chapter "Pupillary disorders in homonymous visual field defects" in the book on Homonymous visual field defects that I have edited for the Springer International Publishing. This book was published in May 2017 [H].

4.1 **RAPD in optic tract lesions**

Optic tract lesions are characterized by homonymous visual field defects, asymmetric bilateral optic disc atrophy (more pronounced contralateral to the lesion) and contralateral RAPD (Fig. 8). The closer the lesion is located to the chiasm the more incongruent the visual field defects are. Visual acuity is usually not affected. The suggested causes for this contralateral RAPD in an optic tract lesion are a greater nasal photoreceptor density, a ratio of crossed to uncrossed fibers in the chiasm of 53:47 and a temporal visual field 61% to 71% larger than the nasal field [72]. A tract lesion disrupts fibers from the contralateral nasal retina and the ipsilateral temporal retina, thus disproportionally diminishing input from the contralateral eye and producing a corresponding RAPD. However, the magnitude of RAPD in patients with an optic tract lesion can range from 0.3 logE to 1.0 logE and this can, probably, be completely explained neither by the rather small asymmetry of crossed to uncrossed fibers nor the difference between temporal and nasal hemifield [73].

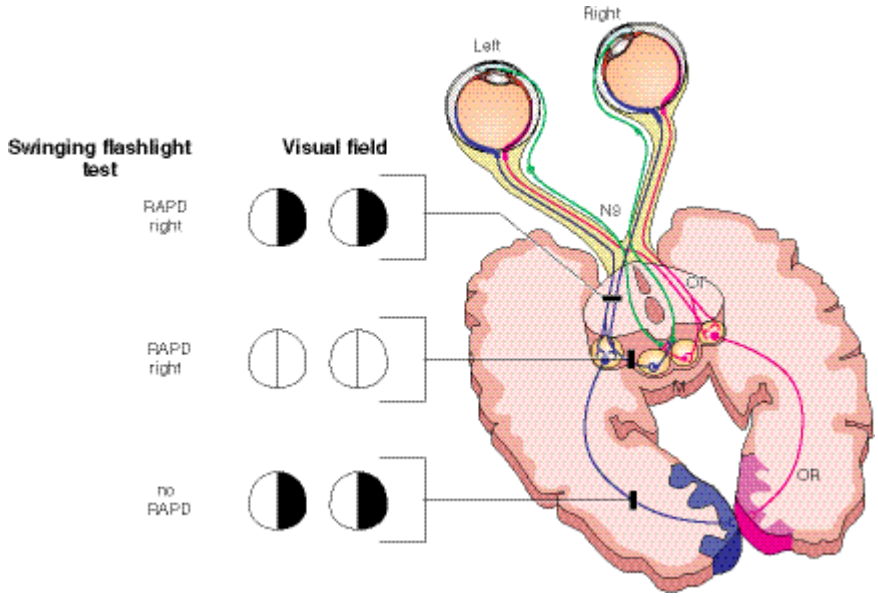

Fig. 8 *Schematic representation of different findings according to the course of the pupil light reflex pathway (OT – optic tract, M – midbrain, N3 – oculomotor nerve, OR – optic radiation). Lesions of the optic tract result in homonymous hemianopia with contralateral RAPD. Lesions of the brachium of the superior colliculus cause contralateral RAPD but no visual field defect. In supragenicular lesions with sufficient distance from lateral geniculate body homonymous hemianopia without RAPD develops [H].*

Patients with an optic tract lesion represent a unique model for studies of the hemifield organization of the afferent pupillomotor system. A complete tract lesion enables the comparison of the pupil light reaction from temporal and nasal retina without the disturbing influence of stray light because only the intact retinal half can participate in the pupil light reaction. Because of stray light such an estimation of the nerve fiber distribution in the pupillary pathway is not precisely possible in a healthy eye with both retinal halves functioning. By means of pupillography it could be shown that in the case of separate light stimulation of either of the retinal halves in optic tract lesions, the pupil light reaction was always greater in the preserved temporal visual field ipsilateral to the site of the tract lesion, compared to the functional contralateral nasal visual field. So, RAPD in optic tract lesions probably reflects the difference in light sensitivity of the intact temporal and nasal visual field [74].

4.2 RAPD without visual field loss

Prior to the termination of retinal ganglion cell axons in LGN, the pupillomotor fibers branch off and travel via the brachium of the superior colliculus to the ipsilateral pretectal nucleus, where they synapse with the next neuron of the pupillomotor pathway. This small region between the optic tract and pretectal area is called pretectal afferent pupillary pathway and is located inside the dorsal midbrain in the brachium of the superior colliculus. A pathology in this area will cause a contralateral RAPD without any visual impairment – that means no decrease in visual acuity, no visual field loss and no optic atrophy (Fig. 7). If the lesion was located more proximally (e.g. in optic tract), a visual field defect would be present and on the other hand, if the lesion was more distally (e.g. in Edinger Westphal nucleus), an anisocoria would be observed.

There are several reports [75,76,77] in the literature dating back to 1920s that describe patients with a unilateral RAPD without any visual impairment. Most of the patients had a pathology in the dorsal midbrain and all authors considered the cause lesion of the pretectal afferent pupillary pathway in dorsal midbrain. Recently, it has been shown by means of pupil perimetry that the pupil field in these patients looked exactly like the visual field in an optic tract lesion [67]. So, the RAPD without visual loss is simply a variant of the RAPD in an optic tract lesion, in which the site of the lesion is moved towards dorsal midbrain and leaves the visual function intact.

4.3 RAPD in suprageniculate lesions with homonymous visual field defect

Detection of a RAPD in acute homonymous hemianopias has been commonly used in differentiating infrageniculate from suprageniculate lesions, since neither optic atrophy nor a RAPD should occur in acquired affections of the optic radiation or the visual cortex. However, there are exceptions.

For instance, RAPD was described in patients with congenital occipital hemianopia [78]. The suggested mechanism was transsynaptic optic tract atrophy after intrauterine or perinatal damage to the suprageniculate visual pathway, which presumably affected also the afferent pupillary fibers to the pretectal area of the midbrain. This explanation sounds plausible and in accordance with what was written above.

Further, there are numerous studies, reporting disturbances of the PLR in patients with acquired HVFDs due to lesions not involving the optic tract, that are no more compatible with the traditional model of the pupillary pathway: either the presence of pupillary "hemiakinesia" or "hemihypokinesia" in the blind part of the visual field [65,79-86] or RAPD contralateral to the brain lesion, as a response to full-field light stimulation [87,88]. Results of these studies provide evidence that the pupil light reaction is not a pure subcortical pathway.

Further progress in understanding the underlying anatomic pupillary pathway could be achieved thanks to advances in neuroimaging. Modern methods of analysis enable us to define any lesion very precisely. Like this, clinically relevant RAPD, as a response to full-field light stimulation, could be limited to suprageniculate lesions that were found closer than 10mm to the LGN or involving it, but sparing the optic tract. In lesions located more than 18 mm from the LGN, RAPD did not occur [88]. It was concluded that RAPD was probably not caused by a lesion of the visual pathway itself but by a lesion of the intercalated neurons between the visual pathway and the pupillomotor centers in the pretectal area of the midbrain, comparable to the lesions that cause RAPD without visual field loss. Further, using a new strategy of lesion analysis by combining subtraction techniques with the stereotaxic probabilistic cytoarchitectonic map it was found, that a region in the early course of the optic radiation in the temporal white matter, close to the LGN, seems to be associated with the presence of RAPD. This finding is consistent with the hypothesis that the connection between visual pathway and pretectal area in the dorsal midbrain is probably closely related to the LGN and its involvement in suprageniculate homonymous hemianopias can lead to RAPD. So, there seems to be more input from suprageniculate neurons and the occipital cortex but the exact anatomy of this connection is still unclear. It may be that the critical area in the early course of the optic radiation near LGN is the site of integration of cortical signals in relation to the PLR into the pupillomotor pathway. Another explanation could be that some

afferent pupillomotor fibers of infrageniculate origin bypass the LGN and then travel through this critical area to the mesencephalon.

In summary, the classical view of the pupillary pathway in postchiasmal lesions of the visual pathway is basically true. Infra- and suprageniculate lesions can still be distinguished by the presence of RAPD. However, it must be kept in mind that RAPD can develop also in lesions in the surroundings of the pretectal area. And the situation is even more complicated in the case of pupillary hemihypokinesia that is to be discussed.

4.4 **Pupillary hemihypokinesia**

According to the classic idea of the pupillary pathway, infrageniculate lesions should present with a hypokinesia, suprageniculate lesions should not. However, many studies [6579-86] in patients with retrogeniculate damage and homonymous visual field defects have provided evidence for impairment of pupil responses to small localized stimuli registered by pupillography. Early clinical reports dating back to the 1940s were later reproduced by other groups using modern pupillometric techniques in patients well documented by magnetic resonance imaging or computed tomography and currently, there is no doubt that the retrogeniculate visual pathway or even visual cortex is involved in the pupillary light reaction. In patients with retrogeniculate damage, the so-called pupillary hemihypokinesia can be observed which differs from RAPD.

Pupillary hemihypokinesia (or akinesia) means a reduced or absent pupil light reaction to perimetric stimuli in the blind part of the visual field and was observed in all kinds of postchiasmal lesions (Fig. 7.9). The first pupillometric measurements in patients with suprageniculate lesions were performed already by Harms in 1949 [79] and have challenged the Wernicke´s description of the pupil light reflex. Harms found reduced pupil light reaction in war veterans with occipital lobe injuries. At that time, his results were called into question and the findings ascribed to the transsynaptic degeneration or to an overlooked pregeniculate damage. Harm´s findings were eventually reproduced many times, later also with the help of modern pupillographic equipment and sophisticated imaging methods. Still, even today we can only speculate about the underlying cause of this phenomenon.

In my research, I have performed pupil perimetry in patients with pregeniculate and retrogeniculate lesions of the visual pathway. The aim of my measurements was (1) to show that pupil perimetry can reproduce visual field defects found in standard perimetry and (2) to collect evidence of cortical influence on the pupil light

reflex. My observations were summarized in the article "How sensitive is pupil campimetry in hemifield loss?" published in 2009 in Graefe´s Archive for Clinical and Experimental Ophthalmology [I]. The purpose of the study was to demonstrate the ability of pupil perimetry to reproduce visual field defects caused by pre- and retrogeniculate lesions of the visual pathway. We wanted to address the understanding of the pupil reflex pathways, particularly the involvement of retrogeniculate structures but also show how far is pupil perimetry suited to disprove feigned hemifield defects.

For this study, 8 patients with a pregeniculate lesion (Group 1) and 8 patients with a retrogeniculate lesion of the visual pathway (Group 2) were selected from the patients of our neuro-ophthalmological department in Tübingen. All pregeniculate lesions were caused by tumours of the anterior visual pathway. Retrogeniculate lesions, on the other hand, were mostly due to occipital ischemia. Patients in both groups showed a visual field defect respecting the vertical midline. In all patients, the site and cause of lesion of the visual pathway were confirmed by magnetic resonance imaging or computed tomography.

Both groups were examined by means of infrared-video-pupillography, light responses to perimetric stimuli were recorded. The stimulus pattern consisted of 41 test spots of 4° diameter and 140 cd/m^2 luminance distributed in the central (30°) visual field. Background luminance was 2.7 cd/m^2. The pupil field loss of one randomly selected eye of each patient was assessed by three skilled visual field interpreters blinded to the patients´ data. The observers were asked to draw the pattern of the estimated field defect. The spatial concordance of the visual field and the pupil field as entered by the observers was assessed by the K-Train method. In this method, developed by Schiefer et al. [89], quality of the perimetric examination is quantitatively assessed by the ratio of intersection area and union area of the observer´s result and the real visual field defect. This sub-score reaches a maximum in the case of perfect coincidence, and goes down to zero if the two isopter sets do not have anything in common. Finally, to compare the results in both groups statistically, the ratios in the two cohorts were averaged and compared using the Wilcoxon rank-sum test.

The concordance between pupil and conventional perimetry was better in the group of patients with retrogeniculate lesions. Ratios of the intersection area and the union area in this group were significantly higher compared to the group with pregeniculate lesion of the visual pathway ($p<0.05$). So, in contrary to the state of knowledge, pupil perimetry could demonstrate retrogeniculate visual pathway lesions better than the pregeniculate lesions (Figs. 9 and 10). This is in contradiction to the classical view of the pupillary pathways where a retrogeniculate lesion actually should not influence pupillary function, whereas pregeniculate lesions should show pupillary scotomata.

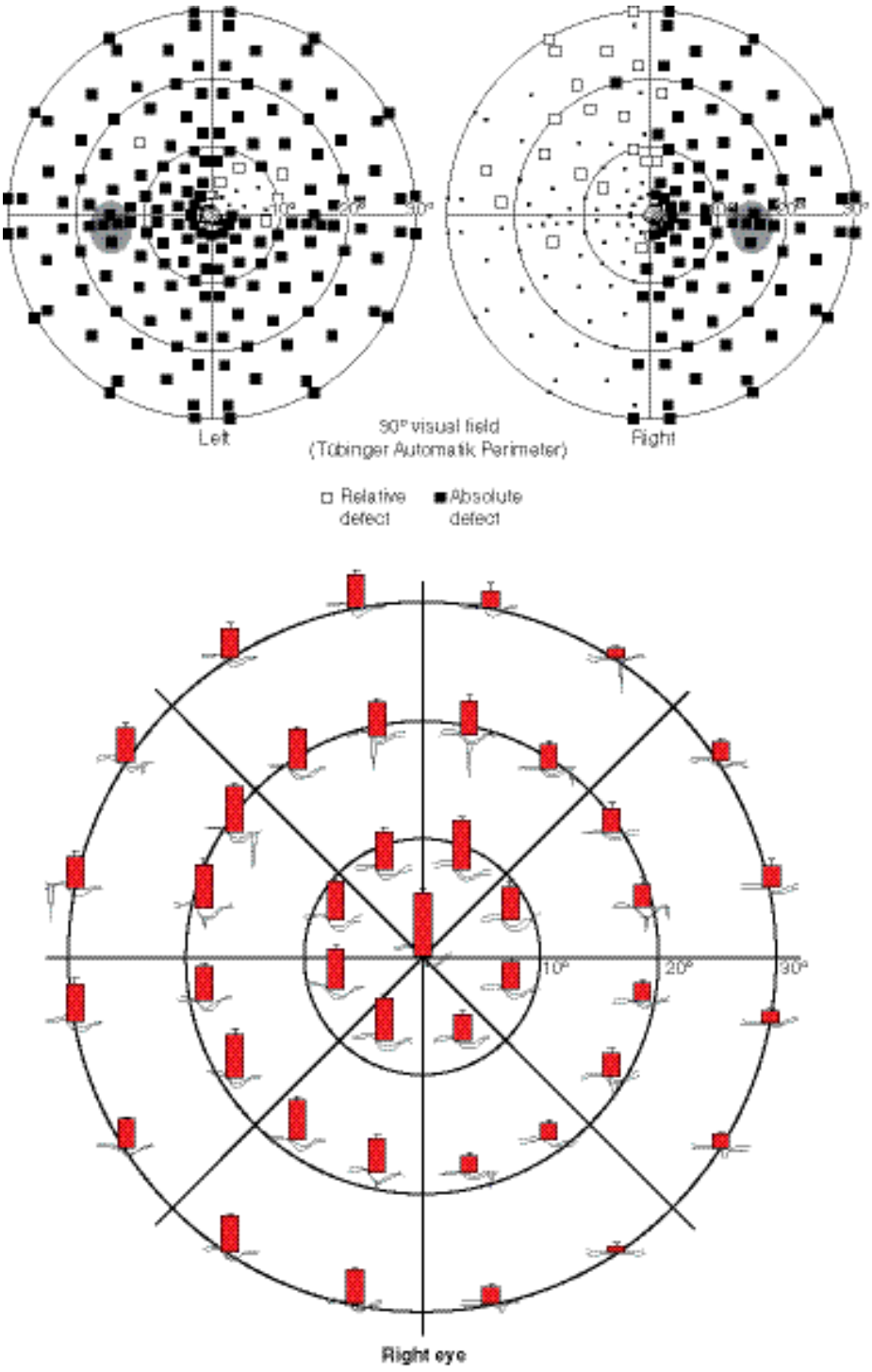

Fig. 9 ***(top)*** *Visual field in a patient with pituitary adenoma affecting the entire visual field of the left eye and the temporal hemifield of the right eye.* ***(bottom)*** *Pupil field of the right eye showing a corresponding pupil field defect in the temporal hemifield [H]*

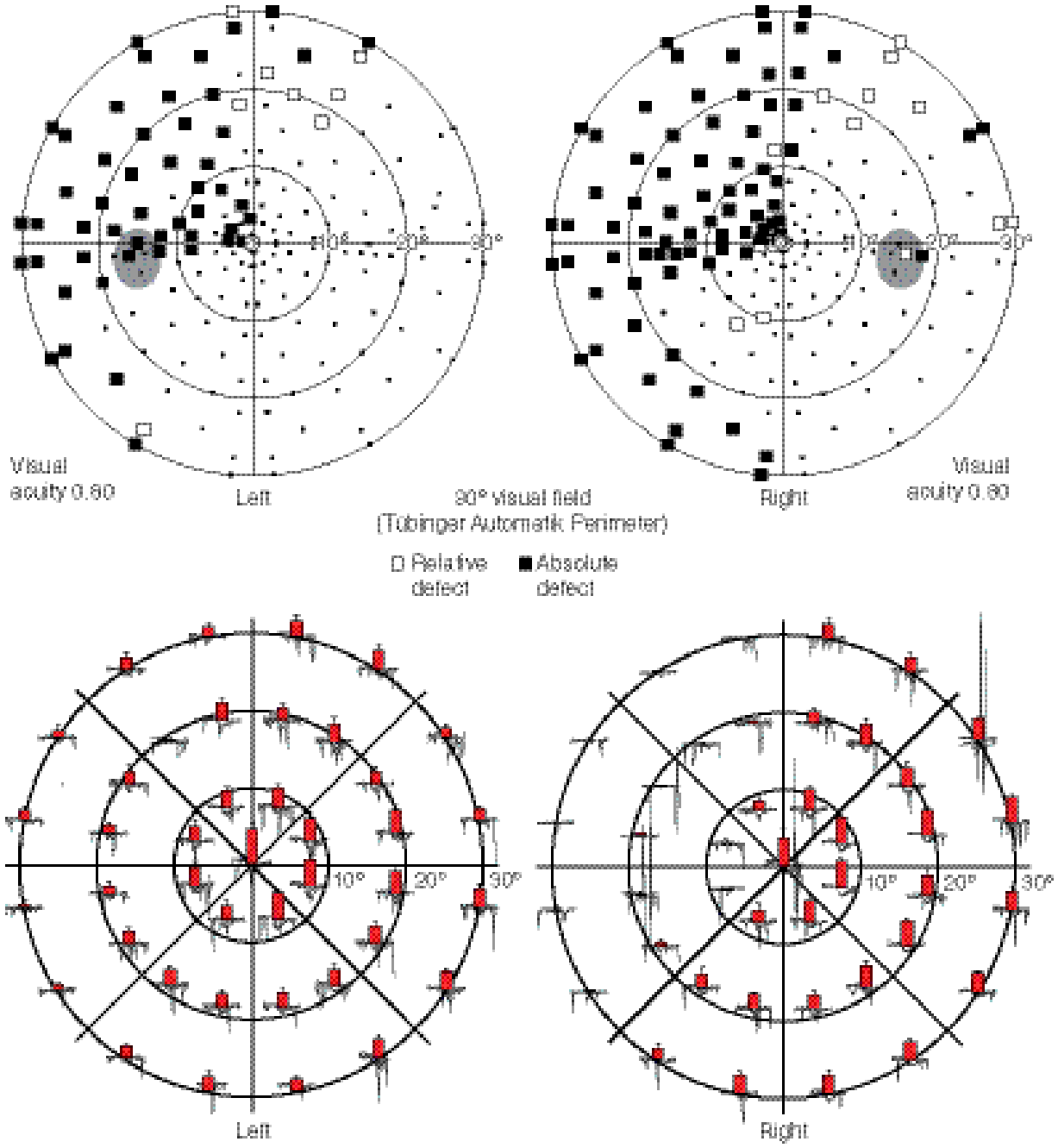

Fig. 10 ***(top)*** *Visual field in a patient with superior left homonymous quadrantanopia due to an ischemia.* ***(bottom)*** *Pupil field of the same patient showing a reduced or absent pupil light reaction in the affected portion of the visual field [H].*

The findings, for example, can be explained by the view, that in pre- and retrogeniculate lesions different components of the light response may be involved to a different extent. The steady-state component of the pupillary light response regulates the resting pupil diameter depending on the ambient light level; it is characterized by a large spatial summation and a wide dynamic range. This component is represented basically by the subcortical pupillary pathway. The transient component of the pupil light response is responsible for the constriction of the pupil in response to brisk light stimuli. In the presence of this component, the steady-state signal is largely discarded. The transient component reflects merely novel changes in luminance contrast; it is characterised by a "limited spatial summation, band-pass temporal response characteristics, and high contrast gain" [90,91]. It is obvious that the stimulus characteristics of pupil perimetry predominantly address this transient component. There is strong evidence that - after cortical processing of specific stimulus characteristics - projections from the extrastriate visual cortex contribute considerably to the transient pupil response component.

Indeed, pupillographic measurements with specific stimuli (isoluminant pattern stimuli, chromatic stimuli or moving stimuli) in patients with a retrogeniculate lesion indicate the possible existence of two separate pupillomotor channels: the PLR in the blind hemifield was reduced but not absent. However, all the other specific, "higher" pupil responses to stimulus attributes, like stimulus color, structure, or motion, were completely lost. On the other hand, studies in patients with Parinaud´s syndrome [92] demonstrated that there was a small, residual PLR and preserved reactions to pattern and colour stimuli as well as preserved pupillary sleepiness-related oscillations. Again, the existence of a cortical input to the pupillary pathway was suggested, since the retinal afferent input to the pretectal nuclei had been apparently damaged.

Hence, it is considered that two or more distinct channels could serve the PLR: a more primitive "luminance channel," which connects the retina directly with the pretectal area and responds to diffuse light, and "pattern channel," which is mediated supragenicularely and responds to shifts in structured stimuli, like isoluminant grating, motion, and isoluminant color stimuli. The PLR is primarily mediated by the luminance channel and to a smaller extent by the "weaker," supragenicularte pattern channel (Fig. 11). It seems that the intrinsically photosensitive retinal ganglion cells operate merely on the subcortical level, whilst the cortical pathway may rely more on ganglion cells that carry predominantly cone inputs. Additionally, it needs to be considered that a pupillary constriction could also be evoked by temporarily cancelling the inhibition of the Edinger Westphal nucleus by the central sympathetic inhibiting system. This might provide a second pathway for pupillary constriction.

In conclusion, pupillary findings in patients with pregeniculate lesions of the visual pathway are consistent with the assumed subcortical course of the pupil light reflex arc. However, the evidence of pupillary hemihypokinesia in patients with homonymous visual field defects due to retrogeniculate lesions of the visual pathway supports the hypothesis that the afferent pupillary system is not purely a subcortical reflex arc but consists of two pathways: one of these via intrinsically photosensitive retinal ganglion cells (ipRGCs) directly reaching the dorsal midbrain, the other running through the normal RGCs via the visual cortex although the exact anatomy of this pathway is still unclear. The subcortical pathway accounts for changes in pupil diameter to stimuli of high intensity, whereas the cortical part responds particularly to higher stimulus attributes like colour, structure or motion. Future research will certainly provide further understanding of the problem.

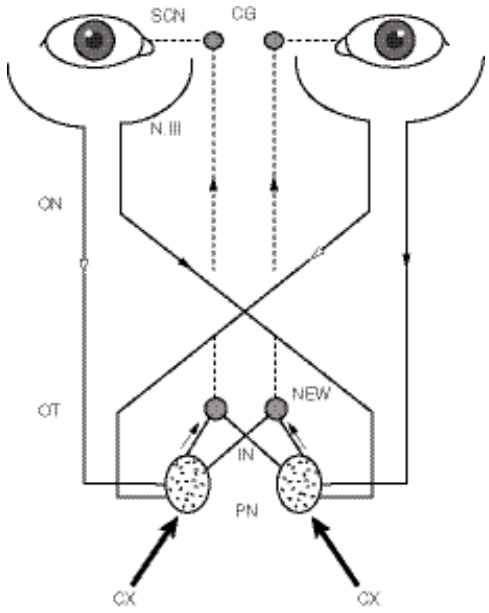

Fig. 11 Schematic drawing of the current view of the pupillary light reflex pathway. Afferent pupillomotor fibers travel in the optic nerve and undergo hemidecussation at the chiasm before entering the optic tract. In the posterior third of the optic tract, the pupillomotor fibers branch medial via the brachium of the superior colliculus to the lateral geniculate nucleus (LGN) and synapse in the ipsilateral pretectal nucleus (PN) in the dorsal midbrain. Intercalated neurons from each pretectal nucleus then project to both Edinger-Westphal nuclei. Parasympathetic fibers from the Edinger-Westphal nuclei (NEW) travel with the oculomotor nerve to the ciliary ganglion (CG) and via the short ciliary nerves (SCN) innervate the iris pupillary sphincter muscle. However, there seems to be more input from suprageniculate neurons and the visual cortex (CX), although the exact anatomy of this connection is still unclear. It may be that stimuli with different attributes are processed at a different level – subcortically or by suprageniculate neurons and the visual cortex. The proposed site of integration of cortical signals to the pupillary response should be located in the early course of the optic radiation near the LGN [88].

5 Intrinsically photosensitive retinal ganglion cells

In 2002, the pupil research was given new impetus by the discovery of intrinsically photosensitive retinal ganglion cells containing melanopsin (ipRGCs). The cells were identified by the group of Rob Lucas, a neurobiologist from the University of Manchester. Rob Lucas was invited to the Pupil Colloquium in Crete in 2003, where I was also presenting the results of my research. I remember what a disarray his presentation caused at that time and it was clear to everybody that a new era was coming. And indeed, since then many different studies on ipRGCs have been performed worldwide both in the fields of chronobiology and pupil research. I have summarized the current knowledge on ipRGCs in a paper that was published in Czech and Slovak Ophthalmology in 2016 [J].

The ipRGCs were first identified in chronobiological experiments in mice. The work by Lucas et al. demonstrated that transgenic mice lacking both rod and cone photoreceptors retain a pupillary light reflex that does not rely on local iris photoreceptors. These data, combined with their previous reports that rodless and coneless mice show circadian and pineal response to light, suggested that multiple non-image forming light responses use non-rod, non-cone ocular photoreceptors in mice. An action spectrum of the PLR demonstrated that this response is driven by a single opsin/vitamin A-based photopigment with a peak sensitivity around 479nm. These data represented the first functional characterization of a non-rod, non-cone photoreceptive system in the mammalian central nervous system [92]. Their further experiments showed that the photopigment is consistent with melanopsin [93].

The remarkable feature of melanopsin is that it functions as a photopigment and confers intrinsic photosensitivity to cells that express it [94]. In 2002, Berson et al. unequivocally demonstrated that melanopsin-expressing retinal ganglion cells are capable of depolarization to light stimulation in the absence of any synaptic input from rods and cones. In other words, these ganglion cells can function as independent photoreceptors [95]. This concept represents a breakthrough in our understanding of retinal circuitry and the process of photoreception and phototransduction that has previously held steadfast for more than 100 years. This select subset of retinal ganglion cells has a dual source of input: transsynaptic input conveyed from photoreceptor-mediated phototransduction and intrinsic activation via melanopsin mediated phototransduction. Either input alone or a summed input from both systems can generate cell discharge.

The existence of a parallel nonrod, noncone photoreceptive pathway in vertebrate eyes helped to explain many contradictory findings. Ophthalmologists recognized for long that certain clinical observations in patients with profound visual loss from photoreceptor disease could not be adequately explained by the traditional model of photoreception. Phenomena such as excessive light sensitivity, normal circadian rhythm, relative reservation of the pupil light reflex in outer retinal disorders, and paradoxical pupillary constrictions in darkness were difficult to reconcile with the traditional view that rods and cones were the only photosensitive cells of the eye [96,97].

Circadian biologists struggled with another seeming contradiction. Mice lacking functional rods and cones maintained a normal day/night cycle and their diurnal oscillation could be phase-shifted with light entrainment [98,99,99] Yet, mice lacking eyes did not demonstrate a circadian rhythm, indicating that the eyes were necessary for circadian entrainment, but rods and cones were not [100]. The discovery of melanopsin and a subset of intrinsically photosensitive retinal ganglion cells containing this photopigment has provided an anatomic basis for explaining these clinical puzzles and has prompted a new look at the connections between the retina and the brain.

So, the mammalian eye has two different sensory systems that respond to different qualities of light. The classic photoreceptor system (rods and cones) serves the familiar function of image formation which, by way of connections and processing by recipient neurons in the retina and visual cortex, provides for conscious visual perception. In contrast, the newly recognized melanopsin photoreceptive system functions in irradiance detection, much like a light meter. Irradiance detection is a measure of environmental brightness and occurs at a subconscious level. Irradiance detection serves to set the circadian clock. IpRGCs project to the brain centres for circadian rhythm (the suprachiasmatic nucleus and the intergeniculate division of the lateral geniculate nucleus) and sleep (ventrolateral preoptic nucleus).

In addition to their role in circadian entrainment, the melanopsin-expressing retinal ganglion cells mediate the pupil light reflex. Apart from the central projections mentioned above, the melanopsin-expressing retinal ganglion cells also project to the olivary pretectal nucleus of the dorsal midbrain, forming the afferent limb of the pupil light reflex [68]. This direct connection to the main pupil integrating centre by intrinsically photosensitive cells explains why people blind from photoreceptor disease can still have an intact pupil light reflex and normal circadian rhythm. It seems that rods, cones, and ipRGCs are complementary in driving the circadian rhythm and the pupil light reaction. For example, rods regulate the circadian rhythm in low light

intensities, whereas ipRGCs get involved with higher light intensity. It can be assumed that such a complementary behaviour applies also for the pupil light reflex.

With the discovery of ipRGCs, we have learned that the pupillomotor information delivered to the midbrain may originate not only in the outer retinal layer (activation of rods and cones) but also in the inner retinal layer (activation of ipRGCs). To determine the contribution of the individual photoreceptors to the pupil light reflex is more difficult in humans than in mice, where transgenic models can be generated. A certain help, however, can be provided by pupillography.

Fig. 12 depicts a typical pupil response to a 10csecond bright light in a normal human subject. Note that there are two components forming the response waveform during the constriction phase. When the light stimulus is turned ON, there is a rapid-onset, high-velocity pupil constriction until it reaches a minimum pupil size (maximal constriction amplitude). This early transient response is quickly followed by pupillary redilation, or escape, to a more sustained state of partial pupil constriction (sometimes also called the postillumination pupil response or PIPR) that continues for the remainder of the light stimulus. There is evidence, that the transient and sustained components of the pupil light reflex in humans can be explained by the proportional light input from the rod and cone photoreceptors and intrinsic retinal ganglion cell photoactivation. The data from pupil recordings in primates and humans support the hypothesis that the early transient pupil constriction under photopic conditions represents predominantly cone-driven response and that the sustained pupil constriction represents a summation of the adapted cone response and the steady-state intrinsic retinal ganglion cell activation. This assumption is supported by the electrophysiologic behaviour of the melanopsin-expressing ganglion cells. The individual components of the pupil light reaction can be subtracted by the so-called chromatic pupillography [94].

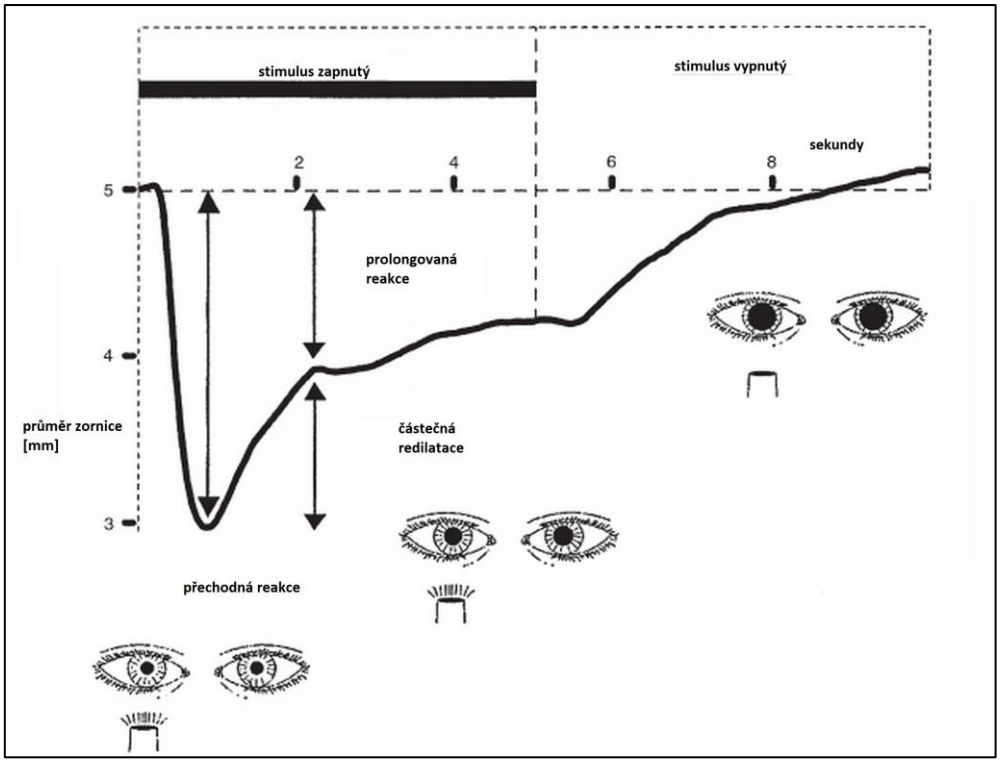

Fig. 12 An example of a pupillographic recording to a 5 second bright white light in a normal human subject. There are two components forming the response waveform during the constriction phase. When the light is turned ON, the transient phase is characterized by a short-latency, high-velocity maximal change in pupil size. Thereafter, the pupil partly redilates, or escapes, to a state of partial pupil constriction that represents the sustained phase of the pupil light reflex (modified from reference 71)

5.1 Chromatic pupillography

Melanopsin-expressing retinal ganglion cells constitute only about 0,2% of all retinal ganglion cells, which is about 3000 ipRGCs per eye. Five subtypes of ipRGCs have been morphologically and functionally characterized so far. They all have large bodies and large dendritic fields. They can be stimulated either by their own intrinsic, melanopsin-mediated response to light, by the rods and cones via synaptic connections with bipolar cells, or can be activated by both ways. The intrinsic activation of ipRGCs requires brighter and longer stimuli (100cd/m2) than the activation of rods and cones [102].

With time it became evident that the PLR is driven by rod-, cone- and ganglion cell-mediated activity. The absorption maximum of melanopsin in rodents has been defined as being around 479 nm and so the spectral

sensitivity of the ipRGCs differs from that of rods (497 nm) and cones (S-cones have an absorption maximum around 420 nm, M-cones around 534 nm, and the L-cones have an absorption maximum of 563 nm) [103]. White light, which is mostly used in pupillography, includes a wide range of wavelengths, so that the pupil light reaction is a summation of responses from all photosensitive cells in the retina.

However, as the receptor cells have different absorption maxima and sensitivities, selective activation of each receptor system separately by stimuli of different wavelengths and different intensities is possible. By using different narrow-band-width (coloured) light stimuli presented under dark and light adaptation, the PLR can be weighted to favour rod, cone or melanopsin activation in humans. That said, there is a renewed interest in the PLR as a means to assess retinal function noninvasively and this paradigm has developed into a method called chromatic pupillography.

While the rods and cones are found in the outer retinal layers, retinal ganglion cells are located in the inner retinal layers. So, the use of chromatic stimuli to elicit different pupillary responses may serve as an objective clinical pupillary test to assess the function of either of these retinal layers and as such help in the detection of retinal diseases and in assessing new therapeutic approaches particularly in hereditary retinal diseases like retinitis pigmentosa. Since its introduction, many protocols for the characterization of ipRGCs function have been developed and tested not only in healthy subjects but also in glaucoma [104,105], optic nerve diseases [106,107] or retinal dystrophies.

Most experiments with chromatic pupillography have been performed in patients with retinitis pigmentosa as they present a unique model of a photoreceptors´ disease. In patients with retinitis pigmentosa, their rod-weighted and cone-weighted pupil responses are reduced compared with normal controls [107,108,109]. In advanced stages of the disease, the pupil light reaction may be even more sensitive than standard electroretinography for detecting residual levels of photoreceptor activity [110]. Interestingly, the melanopsin-mediated pupil response is preserved in some patients with retinitis pigmentosa, whereas in others it is abnormally low [107,109,110]. The reasons for this differential response of inner retinal function are not yet elucidated. In some patients, completely blind from end-stage outer retinal degeneration, a slow PLR can still be clinically observed. This pupil response is derived mainly from inner retinal (melanopsin-mediated) phototransduction [94] and explains why patients blind from the rod and cone degeneration can retain a circadian rhythm [111,112].

The research group in Tübingen followed the news on the intrinsically photosensitive retinal ganglion cells since the beginning. My colleagues developed their own version of chromatic pupillometry, currently manufactured as the Compact Integrated Pupillograph (CIP, producer AMTech, Germany). With this instrument, I, together with my colleague from Japan, measured pupillary responses to chromatic stimuli first in healthy subjects and later compared the results to patients with retrogeniculate lesion of the visual pathway. Our measurements in healthy people were summarized in the article "Pupillary response to chromatic stimuli", that was published in the journal of Czech and Slovak Neurology and Neurosurgery in 2014 [K].

The aim of this study was to compare chromatic pupillary responses in a group of healthy subjects and determine if this method can be used for assessing outer and inner retinal function. The study group consisted of 17 healthy subjects. Subjects were tested with the Compact Integrated Pupillograph (CIP) – the chromatic pupillometer at our pupil laboratory in Tübingen. The measurements were performed in a darkened room. During the examination, one eye was illuminated by the coloured light stimulus and the pupil light reaction was registered in the other eye by an infrared video camera. Each stimulus was presented five times and the mean pupil contraction amplitude was calculated. In each subject, only the right eye was included in the study. For the study, we have developed our own protocol and the parameters of the stimulus were as follows: intensity 28 lx, duration 4 secs, and color blue (420±20 nm) and red (605±20 nm). The examined pupil parameters were baseline pupil diameter, maximal constriction time, relative amplitude at maximal constriction, at 3 secs after stimulus onset, at stimulus offset, at 3 secs after stimulus offset and at 7 secs after stimulus offset. Pupil response parameters to red and blue light were evaluated by paired t-test.

Red light has the longest wavelength (650nm) and activates mostly the cones. Blue light corresponds to a wavelength of about 450 nm. At low intensities, blue light activates the rods, with increasing intensity also the intrinsically photosensitive retinal ganglion cells and partially the cones become involved. According to the current knowledge, the intrinsic activation of the melanopsin-expressing retinal ganglion cells is invoked mostly by light stimuli of short wavelength (about 482nm), high intensity (100cd/m^2) and long duration (13s) [5].

In our study, except for the baseline pupil diameter (p=0,148), there was a significant difference in all pupil response parameters to red and blue light (p=0.001). With blue light, the relative amplitude was significantly greater and the time to maximal pupil constriction significantly longer compared to red light for all tested time points. Blue light evoked the „sustained" pupil contraction, while the red light rather the „transient" contraction (Fig. 13).

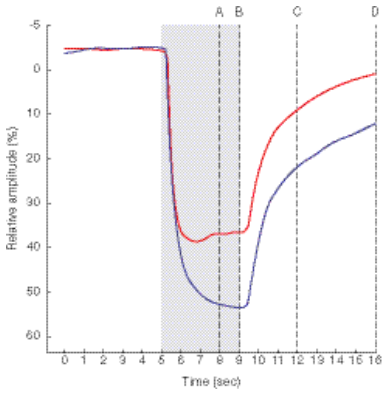

Fig. 13 The relative pupil light response amplitude to red and blue light stimulus in healthy subjects. With blue light, the relative amplitude is significantly greater and the time to maximal pupil constriction significantly longer compared to red light for all tested time points (indicated by the vertical lines A-D). Blue light evokes the „sustained" pupil contraction (driven by ipRGCs), while the red light rather the „transient" contraction (driven by rods and cones) [K].

It can be assumed, that greater relative pupillary amplitude in response to blue light is caused by the additional activation of the ipRGCs. Longer latency of pupillary constriction to blue stimulus supports the current evidence on the behaviour of the melanopsin-expressing retinal ganglion cells as published by Dacey et al., who studied the electrophysiological properties of a single in vitro retinal ganglion cell containing melanopsin. His in vitro recordings in macaque and human retinas showed that ipRGCs display a typical transient increase in firing rate at stimulus onset and a unique sustained firing that continues after light offset [102]. On the contrary, a cone-driven response to red light exhibits a rapid-onset, maximal burst of cell firing that attenuates and ceases during the light stimulus, that is, a transient cell response.

The electrophysiological properties of retinal photoreceptors correspond to the two components forming the response waveform during the pupil constriction phase. When the light stimulus is turned ON, there is a rapid-onset, high-velocity pupil constriction until it reaches a minimum pupil size (maximal constriction amplitude). This early transient response is quickly followed by pupillary redilation, or escape, to a more sustained state of partial pupil constriction that continues for the remainder of the light stimulus. The "transient" and "sustained" can be explained by a different contribution of the rods, cones, and ipRGCs to the pupil light reaction.

With our examination protocol, it was possible to unmask differences in pupil response to red and blue light in healthy subjects and to confirm the contribution of the melanopsin retinal ganglion cells to the pupil light

reflex preferably with blue light. Chromatic pupillography appears as a sensitive method for an objective evaluation of the function of the outer and inner retina. This can be useful in the evaluation of the progression of the disease or the effect of treatment, particularly in patients with retinal degeneration who are nowadays the target group of many experimental studies.

5.1.1 Chromatic pupillography in patients with homonymous hemianopia

The pupil light reflex is considered to be a simple subcortical reflex. However, as already said, many studies proved that patients with homonymous hemianopia due to a retrogeniculate lesion of the visual pathway showed pupillary hemihypokinesia, i.e. reduced or absent pupil light reflex to perimetric stimuli in the blind part of the visual field.

Factors believed to cause pupillary hemihypokinesia are the existence of another unknown pupillary pathway or retrograde trans-synaptic degeneration in occipital lesions. We now know that a small subset of retinal ganglion cells express (RGCs) the photopigment melanopsin and are intrinsically photosensitive. These intrinsically photosensitive retinal ganglion cells (ipRGCs) help to synchronize circadian rhythms and contribute to the pupil light reflex. Our hypothesis is that the afferent pupillary system consists of two pathways: one of these via the intrinsically photosensitive retinal ganglion cells directly reaching the dorsal midbrain, the other running through the normal RGCs via the visual cortex. If this was true, based on the results of our previous study, the pupillary response parameters for stimuli optimized for the ipRGCs should not be influenced in lesions of the postgeniculate visual pathways, whereas the response to stimuli that are not addressing the ipRGCs should be reduced. The purpose of our next study was to test the hypothesis of two separate pupillomotoric pathways. The paper with the results of this study has been preliminarily accepted to an impacted journal and hopefully will be published soon.

For the purpose of this study, 12 patients (59.1±18.8 years) with homonymous hemianopia due to postgeniculate lesions of the visual pathway and 20 healthy controls (58.6±12.9 years) were examined using chromatic pupillography. In all patients, the site and cause of lesion of the visual pathway were confirmed by magnetic resonance imaging and/or computed tomography. All patients had a homonymous visual field defect, varying from a complete homonymous hemianopia to homonymous paracentral scotomas. All patients showed normal optic discs without atrophy. One eye lacking the temporal visual field due to hemianopia and one randomly selected eye from normal controls were used for evaluation.

The parameters of the stimuli were the same as in the previous study on chromatic pupillography, that is the intensity was 28 lux of corneal illumination, stimulus duration was 4.0 secs, and colours were blue (420±20 nm) and red (605±20 nm). The examined parameters were baseline pupil diameter, latency, relative amplitude at maximal constriction, measured also at 3 secs after stimulus onset, at stimulus offset, at 3 secs after stimulus offset, and at 7 secs after stimulus offset.

In the control group, the short-wavelength response showed a transient pupil constriction after stimulus onset and a pronounced pupillary capture, then a sustained, post-stimulus pupil constriction following stimulus offset. The red response also showed the transient pupil constriction but of smaller amplitude when compared to blue light after stimulus onset, and no pupillary capture but a fast pupil redilation after stimulus offset. This is in accordance with the results of our previous study.

The statistical analysis of the differences between both groups showed that the pupil response parameters to long wavelength (red light), that is the relative amplitude at maximal constriction ($p=0.004$), at 3secs after stimulus onset ($p=0.004$) and at stimulus offset ($p=0.001$) of hemianopia patients were significantly smaller than those of healthy controls. Regarding the blue response, there were no significant differences between the two groups.

Because we did not see a difference between healthy controls and patients for the blue stimulus, the hypothesis that the ipRCSs' pupillary pathway does not run via the postgeniculate visual pathways seems to be confirmed. The ipRGCs might send axons directly to the olivary pretectal nucleus, the midbrain region associated with the pupil light reflex, and others to the suprachiasmatic nucleus and intergeniculate leaflet.

In contrast, the red response via other RGCs pathway was significantly reduced in hemianopia patients for the parameters after stimulus onset compared to the normal controls, but not after stimulus offset. As expected, there was no sustained pupil constriction for the red-light stimulus. Although the detailed anatomy of the pathway from visual cortex to the pretectal nuclei in humans is still unknown, interesting studies have been done on cortical input to the pupil light reflex.

Wilhelm BJ et al. [113] assessed the pupil responses as well as spontaneous pupillary oscillations in patients with damage to the dorsal midbrain (Parinaud's syndrome) and demonstrated that there was a small, residual pupil light reflex and preserved pupil colour and grating responses as well as preserved sleepiness related pupillary oscillations. By comparison, Keenleyside MS et al. [114] observed that in patients with

homonymous hemianopia the pupil light reflex in the blind hemifield was reduced but not absent. However, all pupil responses to stimulus attributes like stimulus color, structure, or motion which are regarded to be driven by cortical inputs were completely lost.

There are several possibilities how to explain this phenomenon. First, pupillary hemihypokinesia may not be caused by a lesion in the visual cortex itself, but by a lesion of the intercalated neurons travelling between the visual cortex and the pupillomotor nucleus in the pretectal area of the midbrain [67]. Second, the retrograde trans-synaptic degeneration from occipital lesions may have an effect on pupillary hemihypokinesia. For a long period of time, there was the view that retrograde trans-synaptic degeneration of RGCs does not occur in humans after acquired damage to the occipital lobe [115]. However, there are contradictory papers more recently using magnetic resonance imaging [116], and optical coherence tomography [117-119], revealing optic tract atrophy, peripapillary retinal nerve fibre layer thinning, retinal nerve fibre layer loss and ganglion cell complex thinning. Moreover, Jindahra P et al. reported that retinal changes can be detected as early as 3.6 months following damage to the occipital lobe [120]. These findings support the assumption that retrograde trans-synaptic degeneration may have an effect on pupillary hemihypokinesia. On the other hand, Yoshitomi T et al [121] found pupillary hemihypokinesia only five days after a stroke which would be far too early for a retrograde trans-synaptic degeneration to develop. Based on our findings, retrograde trans-synaptic degeneration is either a less relevant mechanism for the pupil pathway and/or it may spare projections travelling from ipRGCs.

We are aware that there are limitations of our study: The blue stimulus was probably too bright driving the pupil to mechanical limits. Also, the patient group may have been too inhomogeneous comprising both small and large visual field defects. However, our results support the hypothesis of two separate pupillary pathways and should be further investigated.

5.1.2 Chromatic pupillography in glaucoma

It is evident from studies that glaucoma selectively damages certain types of retinal ganglion cells earlier than others. This finding has led to the development of new perimetric techniques like blue-on-yellow perimetry, frequency doubling technology perimetry, motion automated perimetry or high pass resolution perimetry. In standard achromatic perimetry, early visual field defects in glaucoma may be missed due to the overlap of receptive fields of different retinal ganglion cells. Specific stimuli and conditions used in new perimetric

methods enable us to test only a certain group of retinal ganglion cells (parvocellular, koniocellular or magnocellular cells) and like this detect early visual field loss in glaucoma earlier than standard achromatic perimetry [122]. However, with time it has also been shown that these methods have high variability, are rather too difficult to be used in daily clinical practice and in fact, no superiority to standard achromatic perimetry could be shown [123]. Except for FDT perimetry, most of these methods are currently used only for research purposes.

Nevertheless, the concept of selective damage to certain types retinal ganglion cells in glaucoma is generally accepted and has been shown both in vitro and vivo. Interestingly, changes have been found not only on the retina but also in the lateral geniculate body of monkeys [124]. Now, how vulnerable are the intrinsically photosensitive retinal ganglion cells to glaucoma damage?

Kankipati et al. found that the postillumination pupil response (PIPR) was significantly reduced in glaucoma patients compared to healthy controls and correlated with the amount of visual field damage [105]. In a study by Feigl et al. it was observed that ipRGC function was reduced in advanced glaucoma patients compared with patients with early glaucoma and healthy subjects [125]. The fact that the PIPR was not reduced in early glaucoma is consistent with in vitro ocular hypertension experiments in rats that show that ipRGCs have a high cellular resistance to injury-induced damage [126]. Studies in patients with toxic neuropathy or hereditary mitochondrial neuropathy indicate a robustness of ipRGCs to injury as well and a neuroprotective role of pituitary adenylate cyclase-activating polypeptide has been discussed [127]. Melatonin has also been suggested to be neuroprotective in glaucoma because of its antioxidant and antinitridergic properties [128].

Monitoring glaucoma progression is as important as an early diagnosis and requires precise assessment of functional loss and structural change relative to baseline measurements. The gold standard for monitoring functional loss is standard automated perimetry, and statistical programs are available to assist the ophthalmologist in the difficult task of assessing progression. While imaging techniques are likely to be useful earlier in the course of disease, the monitoring and prognostication for advanced glaucoma are far more challenging. Visual sensitivity is more variable, testing requires larger stimuli, and statistical programs to assess progression of advanced stages are not available. The "macula split" as demonstrated by the size V target on the macula program of the Humphrey field analyzer can be used as a crude measure to assess the prognosis of vision and the probability of a wipe-out after surgery. So, the determination of ipRGC function using the blue PIPR may have potential to monitor or determine progression in the later stages of the disease, where other methods are lacking.

6 Conclusion

Current examination methods of visual function are mostly subjective methods. In fact, only electrophysiology and pupillography represent objective tests of ocular function. Pupillary tests have been traditionally used in neuro-ophthalmological conditions, however during the last years, these tests have become more popular also in other fields of ophthalmology like glaucoma. With the development of retinal prostheses for restoration of sight to patients blinded by retinal degeneration that are being developed by a number of companies and research groups worldwide, pupillography is used with advantage as an objective tool to assess the gained vision. Further, examination of pupils may be useful in sleep medicine, psychology, biology or pharmacology.

Some pupillary test can be performed manually, others need special equipment. Such equipment is mostly not commercially available and so is the pupil research usually confined to few centres worldwide that have long experience in this area. I was lucky to be part of the pupil research group in Tübingen. I could participate in very interesting and novel projects the results of which are very interesting and sometimes quite revolutionary. I learned how to conduct scientific work, process and present my results. I met many inspiring people and keep in touch with them. I learned a lot about neuro-ophthalmology and try to retain and improve my knowledge as much as possible. I hope my habilitation thesis gives a good overview of how I have contributed to the pupil research.

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8 Collection of articles

(arranged in order of appearance in text)

A. Skorkovská K, Wilhelm H, Lüdtke H, Wilhelm B. Relative afferent pupillary defect in glaucoma. Klinische Monatsblätter für Augenheilkunde 2011;228(11):979-983

B. Skorkovská K, Lüdtke H, Wilhelm H, Wilhelm B. Pupil campimetry in patients with retinitis pigmentosa and functional visual field loss. Graefe's Archive for Clinical and Experimental Ophthalmology 2009;247(6):847-853

C. Skorkovská K, Kelbsch C, Blumenstock G, Wilhelm H, Wilhelm B. Glaucoma screening by means of pupil campimetry. Klinische Monatsblätter für Augenheilkunde 2012;229(11):1097-1102

D. Skorkovská K, Schiefer U, Wilhelm B, Wilhelm H. Current state of pupil-based diagnostics for glaucomatous optic neuropathy. Ophthalmologe 2012;109(4):351-357

E. Skorkovská K, Wilhelm H, Lüdtke H, Wilhelm B, Kurtenbach A. Investigation of summation mechanisms in the pupillomotor system. Graefe's Archive for Clinical and Experimental Ophthalmology 2014;252(7):1155-1160

F. Skorkovská K. Farmakologické testy u Hornerova syndromu - kazuistika. Cesk Slov Oftalmol 2016;72(2):39-43

G. Skorkovská K, Wilhelm H. Afferent pupillary disorders in postchiasmal lesions of the visual pathways. Klinische Monatsblätter für Augenheilkunde 2009;226:886-890

H. Skorkovská K, Wilhelm H, Wilhelm B. Pupillary disorders in homonymous visual field defects. In: Skorkovská, K. (editor). Homonymous visual field defects. Springer International Publishing, 2017. p. 107-119. ISBN 978-3-319-52282-1

I. Skorkovská K, Wilhelm H, Lüdtke H, Wilhelm B. How sensitive is pupil campimetry in hemifield loss? Graefe's Archive for Clinical and Experimental Ophthalmology 2009;247(7):947-953

J. Skorkovská K, Skorkovská Š. Vnitřně fotosenzitivní gangliové buňky sítnice. Cesk Slov Oftalmol 2015;71(3):144-9

K. Skorkovská K, Maeda F, Kelbsch C, Peters T, Wilhelm B, Wilhelm, H. Pupillary response to chromatic stimuli. Cesk Slov Neurol N 2014;77(3):334-338

A. Skorkovská K, Wilhelm H, Lüdtke H, Wilhelm B.

Relative afferent pupillary defect in glaucoma.

Klinische Monatsblätter für Augenheilkunde 2011;228(11):979-983

Relativer afferenter Pupillendefekt bei Glaukom

Relative Afferent Pupillary Defect in Glaucoma

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- pupil
- relative afferent pupillary defect
- visual field
- perimetry

Zusammenfassung

Hintergrund: Ziel der Studie war festzustellen, wie häufig ein relativer afferenter Pupillendefekt (RAPD) bei Glaukompatienten ist und ob sein Auftreten mit dem Ausmaß von Gesichtsfelddefekten und ihrer Seitendifferenz bei schwellennah-überschwelliger Rasterperimetrie abhängt.

Patienten und Methoden: Es wurden retrospektiv Patienten mit Offenwinkelglaukom aus der Glaukomsprechstunde der Universitätsaugenklinik Tübingen herausgesucht, bei denen die Pupillen im Rahmen einer Standarduntersuchung mit dem Swinging-Flashlight-Test untersucht wurden. Das zentrale 30°-Gesichtsfeld wurde mittels statischer Rasterperimetrie mit dem Tübinger Automatik-Perimeter oder dem Octopus-Perimeter untersucht. Die Gesichtsfeldbefunde und ihre Seitendifferenz wurden zwischen Patienten mit und ohne RAPD mit dem Wilcoxon-Rangsummentest verglichen.

Ergebnisse: Nach der Berücksichtigung von Ausschlusskriterien wurden 100 Patienten mit primärem Offenwinkelglaukom in die Studie aufgenommen, 34 davon wiesen einen RAPD (34%) auf. Für die Gesichtsfeldanalyse konnten die Daten von 85 Patienten verwendet werden, da bei diesen eine identische perimetrische Strategie verwendet wurde. 25 Patienten davon hatten einen RAPD (29%). Die berechneten Gesichtsfelddefektmaße waren bei Patienten mit RAPD signifikant größer als bei Patienten ohne RAPD, ihre Gesichtsfeldbefunde also insgesamt fortgeschrittener. Auch die Seitendifferenz zwischen Gesichtsfeldern beider Augen war bei Patienten mit RAPD signifikant größer ($p < 0{,}01$). Eine ROC(Receiver Operating Characteristics)-Kurve stellte dar, dass die Seitendifferenz im Gesichtsfeldbefund mit einer AUC (area under curve) von 0,81 ein guter Prädiktor für den RAPD ist.

Schlussfolgerung: Der RAPD tritt ungefähr bei einem Drittel der Patienten mit Offenwinkelglaukom auf. Er kann besonders bei fortgeschrittenen Gesichtsfeldbefunden und Gesichtsfeldbefunden mit größerer Seitendifferenz gefunden werden. Sein Fehlen schließt ein Glaukom nicht aus.

Abstract

Background: The aim of this retrospective study was to estimate the frequency of relative afferent pupillary defect (RAPD) in glaucoma and whether its occurrence relates to the severity of the visual field defect and its side asymmetry as detected by standard automated perimetry.

Patients and Methods: Among patients with primary open angle glaucoma examined at the glaucoma unit of our university eye hospital patients were identified in whom a swinging-flashlight test as part of their routine examination was carried out. The central 30° visual field was examined by means of static perimetry using the Tübinger Automatic Perimeter or the Octopus Perimeter. The visual field findings and their side difference were compared between patients with and without RAPD by means of the Wilcoxon rank-sum test.

Results: After having taken into consideration the inclusion criteria, 100 glaucoma patients were included in the study, 34 of them had an RAPD (34%). For the visual field analysis only the data of 85 patients, who received the same perimetric strategy, were used. 25 of them had an RAPD (29%). The calculated visual field scores in patients with RAPD were significantly higher than those in patients without RAPD ($p < 0.01$), that means their visual field loss was generally more advanced. Also the side difference in visual field of both eyes was significantly greater in patients with RAPD ($p < 0.01$). A receiver operating characteristics (ROC) curve showed that the side difference in visual field defect is a good predictor for RAPD with an area under curve (AUC) of 0.81.

Conclusion: RAPD can be diagnosed in about one third of patients with primary open angle glaucoma. It can be found especially with more advanced visual field defects and visual field defects with greater side asymmetry. Its absence does not

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kom auf. Er findet sich vorwiegend bei stärker ausgeprägten Gesichtsfeldausfällen und Gesichtsfeldausfällen mit einer großen interokularen Differenz. Wir raten, den Swinging-Flashlight-Test in die Glaukomdiagnostik einzuschließen.

mean that there is no visual field defect at all. We advise to include the swinging-flashlight test in glaucoma diagnostics.

Einleitung

Das Glaukom ist die zweithäufigste Ursache von Blindheit weltweit. In 2020 wird es 79,6 Millionen Glaukompatienten geben, davon 74% Patienten mit Offenwinkelglaukom, welches bei 5,9 Millionen Personen eine beidseitige Blindheit verursachen wird [1]. Eine der wichtigsten Aufgaben ist es, zu erkennen, ob ein Gesichtsfeldausfall droht und deshalb die Therapie intensiviert werden muss.

Ein relativer afferenter Pupillendefekt (RAPD) ist ein wichtiges klinisches Zeichen, das typischerweise Läsionen der vorderen Sehbahn anzeigt. Ein RAPD begleitet fast immer eine einseitige oder bilaterale asymmetrische Sehnervschädigung. Das primäre Offenwinkelglaukom betrifft zwar meistens beide Augen, verläuft aber oft asymmetrisch und eine glaukomatöse Optikusneuropathie kann deswegen einen RAPD zur Folge haben.

Das Ziel unserer retrospektiven Studie war festzustellen, wie häufig ein RAPD bei Glaukompatienten ist und ob sein Auftreten mit dem Ausmaß von Gesichtsfelddefekten und ihrer Seitendifferenz abhängt.

Methode

Es wurden retrospektiv die Akten von Patienten der Glaukomsprechstunde der Universitätsaugenklinik in Tübingen zwischen den Jahren 2006 – 2009 durchgeschaut. In die Studie wurden Patienten mit bilateralem primärem Offenwinkelglaukom aufgenommen, bei denen die Pupillen von einem neuroophthalmologisch erfahrenen Oberarzt untersucht worden waren. Die Ausschlusskriterien waren wie folgt: Engwinkelglaukom, sekundäres Offenwinkelglaukom wie Pigmentdispersionsglaukom oder Pseudoexfoliationsglaukom, Netzhauterkrankung, andere Sehnerverkrankung als Glaukom, Strabismus, Amblyopie, fortgeschrittene einseitige Katarakt, Zustand nach einem intraokularen chirurgischen Eingriff (außer einer erfolgreichen Katarakt-Extraktion oder Trabekulektomie), die Anwendung von Miotika oder anderen Medikamenten, die die Pupillomotorik beeinflussen, nicht verwertbare Perimetrie mit mehr als einem Drittel falsch positiver Antworten.

Die Patienten hatten am Untersuchungstag eine Routineuntersuchung erhalten (Visusprüfung, Spaltlampenmikroskopie, Fundusbeurteilung und Perimetrie). Der Swinging-Flashlight-Test wird bei uns folgendermaßen durchgeführt: In einem möglichst dunklen Raum wird der Patient aufgefordert, ein Objekt in einigen Metern Abstand zu fixieren. Das Licht eines Ophthalmoskops wird in einem Winkel von 45° aus 20 bis 40 cm von unten auf die Augen gerichtet. Dann bewegt man mehrfach das Licht rasch von einem Auge zum anderen und beobachtet dabei die direkten Lichtreaktionen beider Pupillen. Beide Pupillen müssen bei diesem Test gleich lang (ca. 2 s) beleuchtet werden. Der Wechsel zwischen beiden Augen wird mindestens 5-mal wiederholt. Liegt ein RAPD an einem Auge vor, dann erweitern sich bei Belichtung dieses Auges entweder beide Pupillen ohne vorausgehende Kontraktion, oder diese Kontraktion wird abnormal gering und kurz ausfallen. Mittels Graufiltern lässt sich der relative afferente Pupillendefekt quantifizieren [2].

Nach dem Ergebnis des Swinging-Flashlight-Tests wurden Patienten in 2 Gruppen aufgeteilt. In Gruppe 1 war ein relativer afferenter Pupillendefekt vorhanden, in Gruppe 2 gab es keinen RAPD. Zwar lässt sich mittels Graufiltern der relative afferente Pupillendefekt quantifizieren, jedoch wurde diese Untersuchung nur bei wenigen Patienten vorgenommen.

Die Gesichtsfelduntersuchung fand bei allen Patienten in dieser Studie am selben Tag wie die Pupillenbeurteilung statt. Das zentrale 30°-Gesichtsfeld wurde mittels statischer Rasterperimetrie mit dem Tübinger Automatik-Perimeter oder dem Octopus-101-Perimeter untersucht. Verwendet wurde ein Programm mit 192 Testpunkten, maximale Stimulusleuchtdichte 1000 cd/m^2, Hintergrund 10 cd/m^2. Die Antwortkontrolle erfolgte mittels insgesamt mindestens 10 vorgetäuschter Punktdarbietungen, die Fixationskontrolle durch weitere 10 Darbietungen knapp überschwelliger Prüfpunkte im Zentrum.

Bei der Perimetrie kam in der überwiegenden Zahl der Fälle eine schwellennah-überschwellige Methode zum Einsatz [3]. Im Fall schwellenbestimmender Perimetrie wurde bei diesen Patienten nur der RAPD ausgewertet und der Gesichtsfeldbefund nicht in die Korrelationsberechnungen eingeschlossen. Dies traf in 15 Fällen zu.

Aus der Anzahl der absoluten und relativen Ausfälle und der gesamten Prüfpunkte wurde für jedes Auge ein Gesichtsfeldscore (eigentlich ein Gesichtsfeldausfall-Score) wie folgt berechnet:

(Anzahl absoluter Defekte + ½ Anzahl relativer Defekte)/Anzahl der Prüfpunkte im Gesichtsfeld

Ein höherer Score bedeutet also ein schlechteres Gesichtsfeld. Eine ähnliche Methode zur Quantifizierung des Gesichtsfeldausfalls haben Wilhelm et al. für das Tübinger Automatik-Perimeter (TAP) benutzt [4].

Aus den Gesichtsfeldscores beider Augen wurde für jeden Patienten die Seitendifferenz, die absolute Differenz der Gesichtsfeldscores, berechnet. Sowohl die Gesichtsfeldscores als auch ihre Seitendifferenz wurde zwischen den Gruppen mit dem Wilcoxon-Rangsummentest verglichen.

Ergebnisse

Es wurden Daten von 110 Glaukompatienten gesammelt, bei denen im Rahmen einer Routineuntersuchung in der Glaukomsprechstunde die Pupillen untersucht wurden. Nach der Beurteilung von Ausschlusskriterien blieben 100 Glaukompatienten, davon 34 mit RAPD (34%). Bei 15 Patienten wurde eine für die Studienauswertung ungeeignete perimetrische Strategie eingesetzt. Für die Gesichtsfeldanalyse wurden also schließlich die Daten von 85 Patienten mit primärem Offenwinkelglaukom verwendet.

In Gruppe 1 (Glaukompatienten mit RAPD) wurden 25 Patienten eingeschlossen (29%), davon waren 9 Frauen und 16 Männer. Das Medianalter der Patienten betrug 69 Jahre. In Gruppe 2 (Glaukompatienten ohne RAPD) waren es 60 Patienten

Tab. 1 Visus (BCVA), Gesichtsfeldscores mit ihrer Seitendifferenz und das Alter der Patienten mit RAPD (Gruppe 1).

	Median	25% Perzentil	75% Perzentil	Minimum	Maximum
Alter	69	60	76	43	85
GF score rechts	0,223	0,070	0,458	0,010	0,846
GF score links	0,229	0,065	0,469	0,018	0,839
GF score Differenz	0,188	0,100	0,406	0,011	0,724
BCVA rechts	0,90	0,80	1,00	0,20	1,30
BCVA links	0,90	0,60	1,00	0,10	1,30

Tab. 2 Visus (BCVA), Gesichtsfeldscores mit ihrer Seitendifferenz und das Alter der Patienten ohne RAPD (Gruppe 2).

	Median	25% Perzentil	75% Perzentil	Minimum	Maximum
Alter	65	56	72	34	84
GF score rechts	0,043	0,024	0,166	0,010	0,607
GF score links	0,046	0,026	0,178	0,010	0,544
GF score Differenz	0,046	0,005	0,114	0,000	0,323
BCVA rechts	1,00	0,90	1,00	0,70	1,25
BCVA links	1,00	0,90	1,00	0,50	1,25

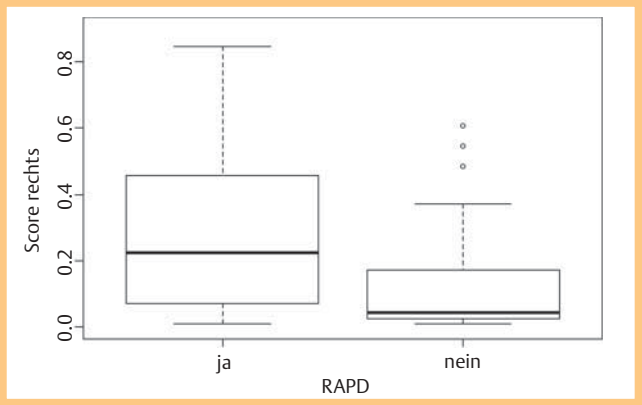

Abb. 1 Gesichtsfeldscores vom rechten Auge in beiden Gruppen (Box-Plot-Diagramm).

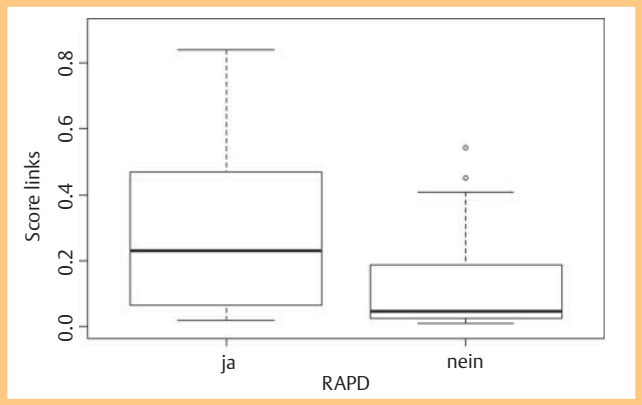

Abb. 2 Gesichtsfeldscores vom linken Auge in beiden Gruppen (Box-Plot-Diagramm).

(71%), 31 Frauen und 29 Männer, mit einem Medianalter von 65 Jahren. Der Median, das 25. und 75. Perzentil, das Minimum und Maximum der besten korrigierten Sehschärfe, der Gesichtsfeldscores beider Augen und ihrer Seitendifferenz sind für beide Gruppen in ▶ **Tab. 1, 2** zusammengefasst.

In Gruppe 1 waren die Gesichtsfeldscores signifikant größer als in Gruppe 2 ($p < 0{,}01$), die Gesichtsfeldbefunde also insgesamt fortgeschrittener (▶ **Abb. 1, 2**). Auch der interokulare Unterschied im Gesichtsfeldscore beider Augen (Seitendifferenz) war in Gruppe 1 größer als in Gruppe 2. Der Unterschied in der Seitendifferenz zwischen beiden Gruppen war statistisch signifikant ($p < 0{,}01$, ▶ **Abb. 3**).

Um festzustellen, ab welchem Gesichtsfeldunterschied ein RAPD mit größerer Wahrscheinlichkeit zu erwarten ist, wurde als Grenzwert der Median der Gesichtsfelddifferenzen aller Patienten genommen. Dieser liegt für beide Gruppen zusammen bei 0,063. In Gruppe 1 war die Gesichtsfelddifferenz bei 19 (76%) Patienten größer und bei 6 (24%) Patienten kleiner als der Median. In Gruppe 2 war die Gesichtsfelddifferenz bei 24 (40%) Patienten größer und bei 36 (60%) Patienten kleiner als der Median.

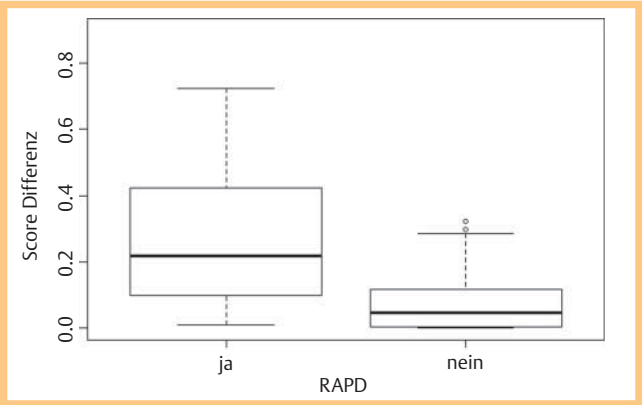

Abb. 3 Absolute Differenz im Gesichtsfeldscore in beiden Gruppen.

Dies lässt sich sehr gut mittels einer ROC-Kurve darstellen (Receiver Operating Characteristics), wo sich die Seitendifferenz mit einer AUC (area under curve) von 0,81 als ein guter Prädiktor für RAPD zeigt (▶ **Abb. 4**).

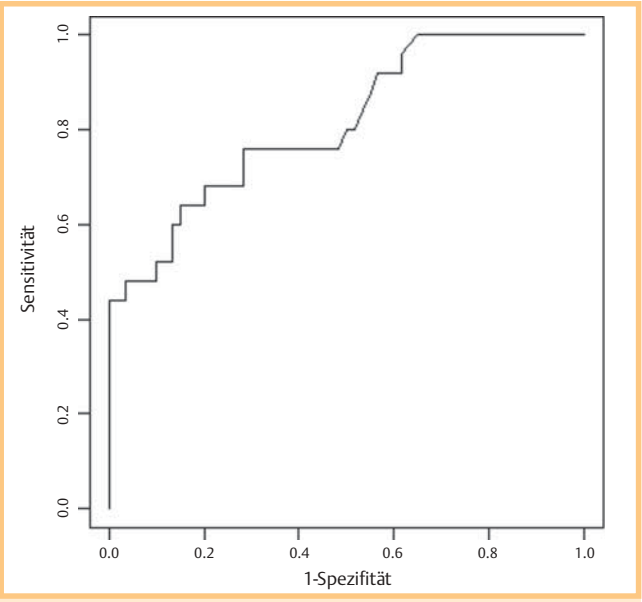

Abb. 4 ROC-Kurve für die Seitendifferenz im Gesichtsfeldbefund als Prädiktor für einen RAPD (AUC = 0,81).

Diskussion

Das Ziel unserer retrospektiven Studie war zu zeigen, wie oft ein RAPD bei Glaukompatienten beobachtet wird und ob ein Verhältnis zum Gesichtsfeldbefund besteht. Bei etwa einem Drittel der Patienten der Glaukomsprechstunde wurde ein RAPD gefunden. Unsere Studie zeigte weiterhin, nicht überraschend, dass bei Glaukompatienten mit RAPD die Seitendifferenz im Gesichtsfeldbefund größer ist als bei Patienten ohne RAPD. Patienten mit RAPD hatten zudem stärker fortgeschrittene Gesichtsfeldausfälle als solche ohne.

Als Schwäche der Studie kann man anführen, dass die Patienten Klinikpatienten sind und deshalb vielleicht nicht die Verteilung in einer Praxis widerspiegeln. Ähnliche Zahlen wie in dieser Studie finden sich aber auch an anderer Stelle. Jonas et al. untersuchten RAPD mittels einer Infrarot-Video-Kamera des Octopus-Perimeters. Sie fanden einen RAPD bei 7 von 17 Glaukompatienten und schließen daraus, dass eine quantitative Pupillometrie bei Glaukomdiagnostik hilfreich sein kann [5]. Lankaranian et al. verglichen 3 Methoden zur Erkennung vom RAPD bei Glaukompatienten. Mit dem klassischen Swinging-Flashlight-Test wurde bei 29% der Glaukompatienten ein RAPD entdeckt [6]. Unsere Studie fand einen RAPD bei 34% der Glaukompatienten. Man kann demnach bei ungefähr einem Drittel der Glaukompatienten einen RAPD erwarten.

Wir glauben, dass der potenzielle Beitrag eines RAPD bei der Beurteilung eines Glaukomschadens unterschätzt und im klinischen Alltag zu wenig genutzt wird. Trotz aller Einfachheit, Verfügbarkeit und Objektivität wird der Swinging-Flashlight-Test im Rahmen von Glaukomdiagnostik nicht routinemäßig durchgeführt, obwohl er manchmal sensitiver als pupillometrische Verfahren sein kann [2]. Leider gibt es nur einzelne Studien über den Beitrag des Swinging-Flashlight-Tests beim Glaukom. In der oben genannten Studie von Lankaranian et al. [6] konnte ein RAPD mit automatischer Pupillografie bei 56% der Glaukompatienten, mit dem klassischen Swinging-Flashlight-Test bei 29% der Patienten und mit einer besonderen Vergrößerungstechnik mittels + 20 dpt-Linse bei 60% der Patienten nachgewiesen werden. Dieser Test wurde aber erst nach dem üblichen Swinging-Flashlight-Test durchgeführt, sodass eine gewisse Voreingenommenheit der Untersucher nicht auszuschließen ist. 60% RAPD erscheinen nach unserer Erfahrung zu hoch. Kalaboukhova et al. untersuchten das Vorliegen eines RAPD bei Glaukompatienten und gesunden Probanden mittels Infrarotpupillometrie. Sie stellten fest, dass ihr Test eine glaukomatöse Optikusneuropathie mit einer Sensitivität von 86,7% bei einer Spezifität von 90% erkennen kann, die allerdings für einen Screening-Test immer noch zu niedrig ist [7].

Es wurde schon mehrfach versucht, den objektiven Swinging-Flashlight-Test mit subjektiven Methoden zu vergleichen. In allen im Folgenden zitierten Arbeiten wurden allerdings unterschiedliche Erkrankungen der vorderen Sehbahn bewertet, worunter das Glaukom nur einen kleinen Teil darstellte. Die erste Arbeit zu diesem Thema publizierte Thompson 1982 [8]. Durch eine Analyse von Goldmann-Gesichtsfeldern kam er zu einer Unterteilung des Gesichtsfelds in 60 einzelne Parzellen, von denen jede einen RAPD von 0,05 log-Einheiten repräsentieren sollte. Lagreze und Kardon untersuchten die Korrelation zwischen RAPD und retinalem Ganglienzellverlust. Sie stellten eine signifikante Korrelation fest mit Korrelations-Koeffizienten von 0,7 für das Humphrey-Gesichtsfeld und 0,63 für das Goldmann-Gesichtsfeld [9].

Wilhelm et al. [4] untersuchten bei 98 Patienten mit Optikusneuropathien unterschiedlicher Pathogenese die Korrelation vom RAPD mit Sehschärfe, zentraler Lichtunterschiedsempfindlichkeit (zLUE) und Gesichtsfeldbefund bei überschwelliger Rasterperimetrie. Während Visus und zLUE nur eine schwache Korrelation mit dem RAPD zeigten, korrelierte die Anzahl der nicht gesehenen Prüfpunkte bei der 30°-Perimetrie mäßig mit dem RAPD. Ein nicht gesehener Punkt entsprach einem RAPD von etwa 0,01 log-Einheiten. Ihre Ergebnisse hinsichtlich der Korrelation vom Gesichtsfeldausfall und RAPD sind gut vergleichbar mit denen anderer Autoren, die Schwellenperimetrie verwendeten. Es zeigte sich also, dass es möglich ist, durch Zählen der nicht gesehenen Prüfpunkte bei überschwelliger Perimetrie das Ausmaß des pupillomotorischen Empfindlichkeitsverlusts ebenso gut abzuschätzen wie durch Bestimmung des Gesamtverlusts bei schwellenbestimmender Perimetrie.

Zur Quantifizierung des Gesichtsfeldausfalls hatten Wilhelm et al. alle absoluten Ausfälle mit 1, alle relativen, unabhängig von der Tiefe, mit 0,5 bewertet und addiert. In unserer Studie haben wir eine ähnliche Methode benutzt. Diese Formel berücksichtigt zwar nicht die Exzentrizität der Defekte und die Tiefe des relativen Defekts, allerdings spiegelt das Raster von TAP und Octopus die lokal unterschiedliche pupillomotorische Empfindlichkeit der Netzhaut dadurch wider, dass es zentral verdichtet ist. Auch wird bei den meisten Glaukompatienten in unserer Klinik für die Verlaufskontrollen immer noch die schwellennah-überschwellige Perimetrie verwendet, bei der keine genauen lokalen Schwellen oder Gesamtverlust in dB (Mean Defect) bestimmt werden.

Abb. 1 und **Abb. 2** zeigen aber, dass es auch unter den Patienten ohne RAPD klar asymmetrische Gesichtsfeldbefunde gab. Ein Skotom bedeutet nicht unbedingt einen kompletten Verlust der Ganglienzellen. Es kann nur eine Dysfunktion der Ganglienzellen ohne einen aktuellen Verlust an Neuronen zeigen. Eine andere Erklärung bietet die unterschiedliche Basis beider Untersuchungsmethoden. Während bei Perimetrie schwellennah Lichtstimuli angeboten werden, wird ein RAPD mit klar

überschwelligen Lichtintensitäten getestet. Möglicherweise untersuchen beide Methoden auch verschiedene Ganglienzellpopulationen mit anderen rezeptiven Feldern, die von einer glaukomatösen Optikusneuropathie unterschiedlich betroffen sein können und deren unterschiedliche Eigenschaften zu den Abweichungen zwischen Perimetrie und RAPD beitragen können. Diese Überlegungen werden auch durch die letzten Erkenntnisse zum pupillomotorischen Einfluss der Melanopsin-enthaltenden lichtempfindlichen retinalen Ganglienzellen unterstützt [10, 11]. Das visuelle System ist streng retinotop, seine Schädigung würde also perimetrisch nachweisbare Ausfälle verursachen, während durch Schädigung des Kanals mit Melanopsin-Ganglienzellen ein RAPD zu erwarten wäre [12]. Unsere eigene Forschung, deren Ergebnisse noch nicht publiziert wurden, lässt vermuten, dass die pupillomotorischen rezeptiven Felder in ihrer Verteilung der visuellen Empfindlichkeit der Netzhaut entsprechen, allerdings viel größer sind als die klassischen rezeptiven Felder. In einem Netzhautgebiet mit beschädigten retinalen Ganglienzellen könnten die übrigen pupillomotorisch wirksamen Ganglienzellen außerhalb dieses Areals immer noch stimuliert werden. Also könnte ein zwar (zwischen beiden Augen) asymmetrischer, aber kleiner Gesichtsfeldausfall ohne Einfluss auf die Pupillenreaktion bleiben.

Es stellt sich die Frage, ob ein RAPD vor einem Gesichtsfeldausfall entstehen kann. Das könnte dadurch verursacht sein, dass bereits eine größere Anzahl Neuronen ausgefallen sein muss, bevor es zu einem messbaren Gesichtsfeldausfall kommt [13], während ein RAPD auch durch eine diffuse Herabsetzung der LUE zustande kommen kann. Gerade bei diesen Patienten würde der RAPD die zusätzliche Information beisteuern, dass der Schaden bereits größer ist, als sich nach dem Gesichtsfeldbefund vermuten ließe. In der Studie von Lagreze und Kardon [9] konnten anhand der Regressionsanalyse Patienten mit deutlichem RAPD und relativ kleinem Gesichtsfelddefekt bestimmt werden und umgekehrt. In ihrer Studie war der Swinging-Flashlight-Test so sensitiv wie die Perimetrie. In unserer Studie gab es keine Patienten mit RAPD, die keinen Gesichtsfeldausfall aufwiesen. Im Falle eines RAPD war wenigstens ein minimaler Gesichtsfelddefekt immer vorhanden.

Somit ist der Swinging-Flashlight-Test nicht als Ersatz, sondern als Ergänzung der Perimetrie aussagekräftig. Sein Vorhandensein zeigt ein fortgeschritteneres Stadium an. Der entscheidende Vorteil ist allerdings, dass diese Untersuchung objektiv und unabhängig vom Patienten ist. Dies ist vor allem dann bedeutend, wenn ein Patient bei der Perimetrie keine verlässlichen Angaben macht. Damit ist bei einer Zunahme der Patienten mit Demenz immer häufiger zu rechnen. Ein RAPD kann somit eine Verschlechterung anzeigen und bei der Interpretation der Gesichtsfelder helfen. Auch das Verschwinden eines RAPD kann eine Verschlechterung anzeigen, wenn sich das bislang bessere an das schlechte Auge annähert.

Schlussfolgerung

Der relative afferente Pupillendefekt tritt ungefähr bei einem Drittel der Patienten mit Offenwinkelglaukom auf. Er begleitet vorwiegend stärker ausgeprägte Gesichtsfeldausfälle und Gesichtsfeldausfälle mit einer großen interokularen Differenz. Sein Fehlen bedeutet aber nicht, dass kein Gesichtsfeldausfall vorliegt und umgekehrt kann ein RAPD bei scheinbar minimalen Gesichtsfeldausfällen vorhanden sein. Wir raten, den Swinging-Flashlight-Test bei Glaukompatienten routinemäßig anzuwenden.

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NEURO-OPHTHALMOLOGY

Pupil campimetry in patients with retinitis pigmentosa and functional visual field loss

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Abstract
Background The aim of our study was to test in a small series of cases if pupil perimetry can prove real concentric visual field loss in retinal degeneration and distinguish from feigned visual field loss.
Methods By means of infrared-video-pupillography, light responses to perimetric stimuli were recorded. The stimulus pattern consisted of 41 stimuli presented in the central 30° visual field. Stimulus intensity was 140 cd/m^2. 5 healthy subjects, 6 patients with retinitis pigmentosa and 2 patients with suspected functional visual field loss were examined.
Results Pupil perimetry was able to reproduce the visual field in retinitis pigmentosa very well. Normal subjects and patients with suspected feigned visual field loss showed normal pupillomotor fields, different from the findings in retinitis pigmentosa.
Conclusions This study provides sufficient evidence that pupil campimetry is applicable for differentiating between retinal dystrophy and functional concentric visual field loss. Possible residual light sensitivity of the blind retina due to melanopsin ganglion cells is obviously not sufficient to provide a pupillary light response to perimetric stimuli.

Keywords Pupil campimetry · Pupil perimetry · Retinitis pigmentosa · Concentric visual field loss · Functional visual field loss

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Introduction

To diagnose a retinal degeneration like retinitis pigmentosa (RP) is usually not a problem. However, there are occasionally patients with normal fundus appearance showing severely constricted fields. This might be non-organic visual loss, either feigned or psychogenic. To disclose non-organic visual field loss by objective methods may be a challenging issue in ophthalmology. If expert opinion is required, for example in social court issues, objective methods are necessary. At first an electroretinogram would be done of course, however, reduced ERG does not necessarily imply visual field loss and blinking or otherwise poor compliance might produce reduced ERG responses. It is therefore desirable to have an additional tool. Also, in the light of the emerging gene therapy in ophthalmology an objective visual field test would be helpful.

Pupil perimetry or campimetry also represents an objective method of testing the visual field by examining the pupillary response to focal light stimuli projected onto the retina. It is therefore principally suited as a tool to distinguish organic from non-organic visual loss. Before applying pupil perimetry in cases with constricted visual fields it needs to be clarified that it is really possible to demonstrate organic constricted fields. Although it is not likely that the recently decribed melanopsin retinal ganglion cells would respond to short and dim stimuli [1, 2] one could argue that residual pupillary light reaction might be possible in blind areas of the visual field. The aim of our study was to show in a small series of cases that pupil perimetry can demonstrate real concentric visual field loss in retinal degeneration and distinguish from feigned visual field loss and normal visual fields.

Methods

For the purpose of this study, a group of 5 healthy subjects, 6 patients with retinitis pigmentosa and 2 patients with feigned concentric visual field loss were examined.

Patients with retinitis pigmentosa included in our study suffered from advanced disease of both eyes and had fulfilled the following inclusion criteria: visual field reduced to the central 10° or less; last ERG less than half a year ago, with a marked reduction of amplitudes and increase in latencies in both full-field and the multifocal ERG; typical ocular signs of RP; no other ocular disease which could interfere with the visual field or pupil light reaction. The study group of patients with RP consisted of 4 females and 2 males aged 29 to 71 years (median 48.5 years).

Two male patients with presumed concentric functional visual field loss aged 27 and 29 years were recruited from our neuro-ophthalmological clinic. Subjective visual acuity was bilateral light perception in one and 0.3 right and 0.5 left in the other patient. Both patients pretended to have markedly constricted visual field. The diagnosis of feigned visual loss was based on the absence of any objective sign of visual loss in any test including electrophysiologic testing and on inconsistency of vision and observed behaviour.

As control subjects served 5 healthy subjects with normal ophthalmological findings, normal pupil light reaction and normal visual field in both eyes. The control group consisted of 4 females and 1 male aged 26 to 56 years (median 27 years).

The study was approved by the local institutional ethics committee and followed the tenets of the Declaration of Helsinki. All participants received written information about the pupillometry and gave their written consent.

All subjects underwent a thorough ophthalmological examination including either static perimetry, using Tübingen Automatic Perimeter, or Goldmann 90° kinetic perimetry of both eyes. Finally, the computerized infrared (IR) pupil campimetry was performed. In all subjects both eyes were tested consecutively, one eye always being covered with a black eye patch during the test. The pupillographic device consisted of a computer, a 19 inch CRT screen for the stimulus presentation and a small fixation control display. Stimuli were presented on the computer screen at a distance of 20 cm from the subject's eye. Blinds around the device prevented straylight in the room from disturbing the measurement. The pupil reaction was recorded by means of an IR-sensitive video camera. The stimulus pattern consisted of 41 stimuli presented in the visual field centre and three concentric rings within the central 30° visual field. Stimulus diameter was 4°. For all stimuli white light was used, stimulus intensity was 140 cd/m^2 with a constant background luminance of 2.7 cd/m^2. Each stimulus was presented for 200 ms every 2000 ms. A small red spot was presented constantly for fixation. The perimetry program presented each stimulus at each tested location four times. If the pupil size could not be recorded four times without problems (e.g. of blinks), the stimulus was presented more often until four recordings of the pupil size were done for each stimulus. The pupillary response was analysed for each pupil record. Afterwards the four pupillary responses were averaged. Using these averaged values the further analysis was done.

In all groups the pupil fields were compared to the standard visual fields obtained on the same day both by a subjective assessment of an experienced observer and statistical evaluation. For statistical analysis the mean of the pupil light reaction in the centre of the visual field and at the eccentricity of 10, 20 and 30 degrees, was calculated in each subject. The median, mean, standard deviation, minimum and maximum were calculated in the control and RP group.

To compare the RP group with the control group, the pupil responses at individual eccentricities were analysed using a two-tailed Wilcoxon rank-sum test. Due to the small number of patients with non-organic visual field loss, their results were not evaluated by descriptive statistics or the non-parametric test, but the actual pupil response discussed in comparison to the other two groups.

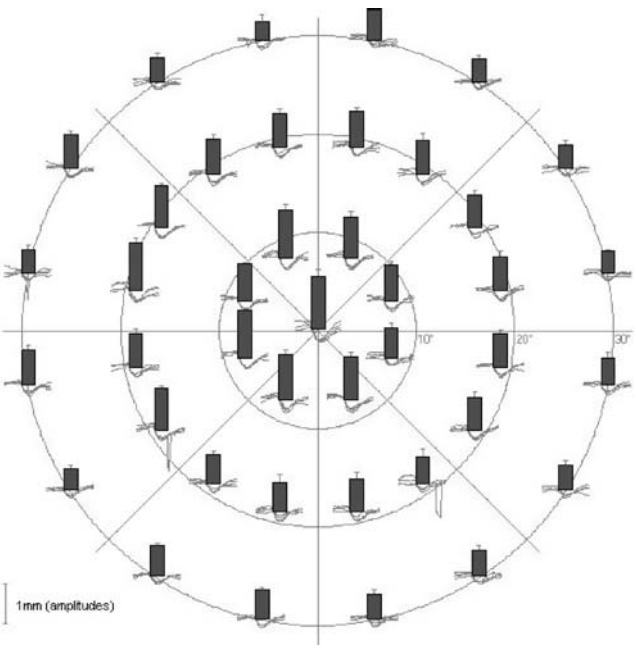

Fig. 1 Pupillomotor field in a healthy person. The column represents the mean value of pupil light response in mm at each tested location in the visual field. The mean value is calculated as an avarage of individual amplitudes of four displayed pupillographic curves. The error bar above the column represents the standard error (SE) of the mean value

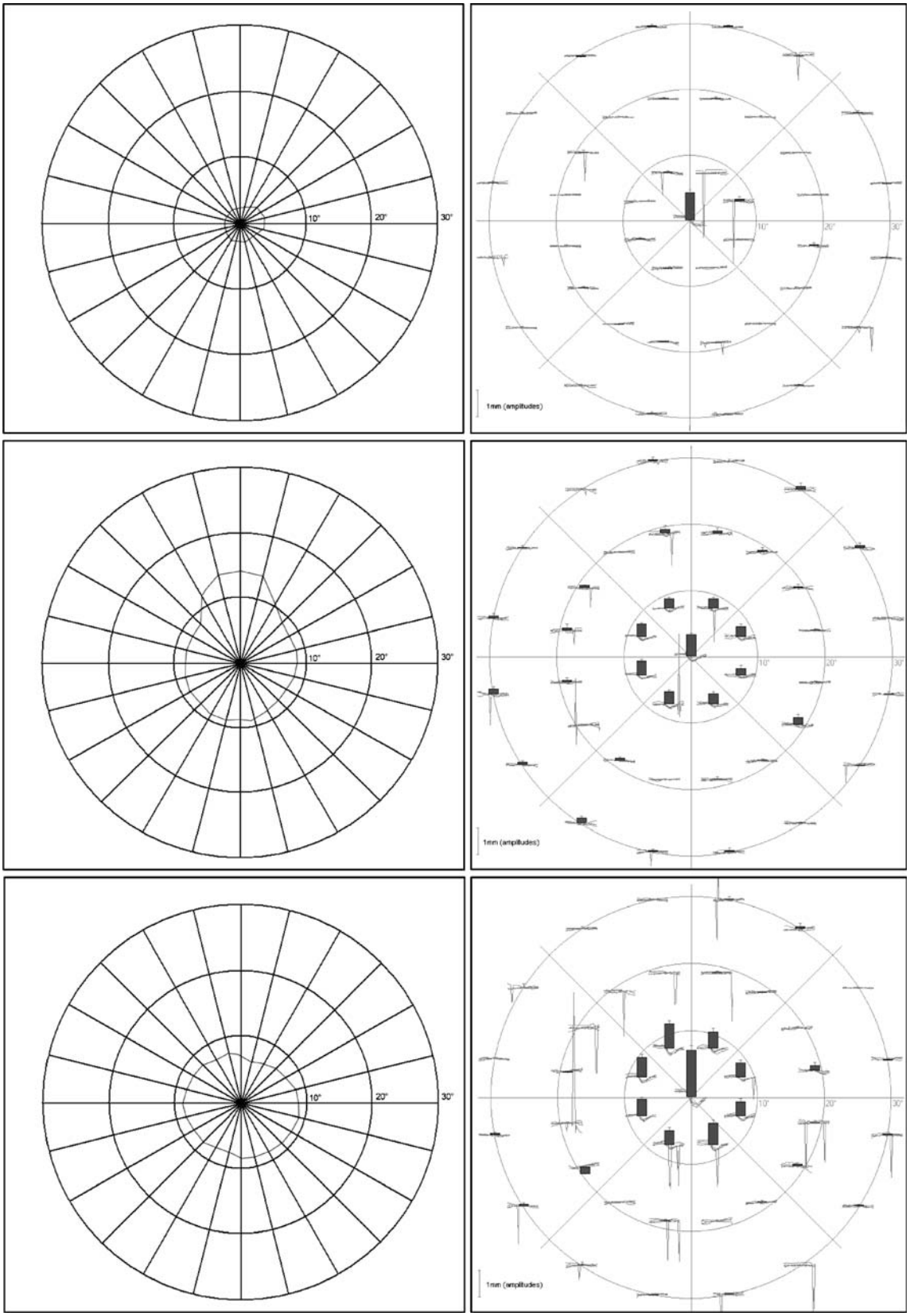

Fig. 2 Pupillomotor field in 6 patients with retinitis pigmentosa and the corresponding 30° visual field in Goldmann perimeter

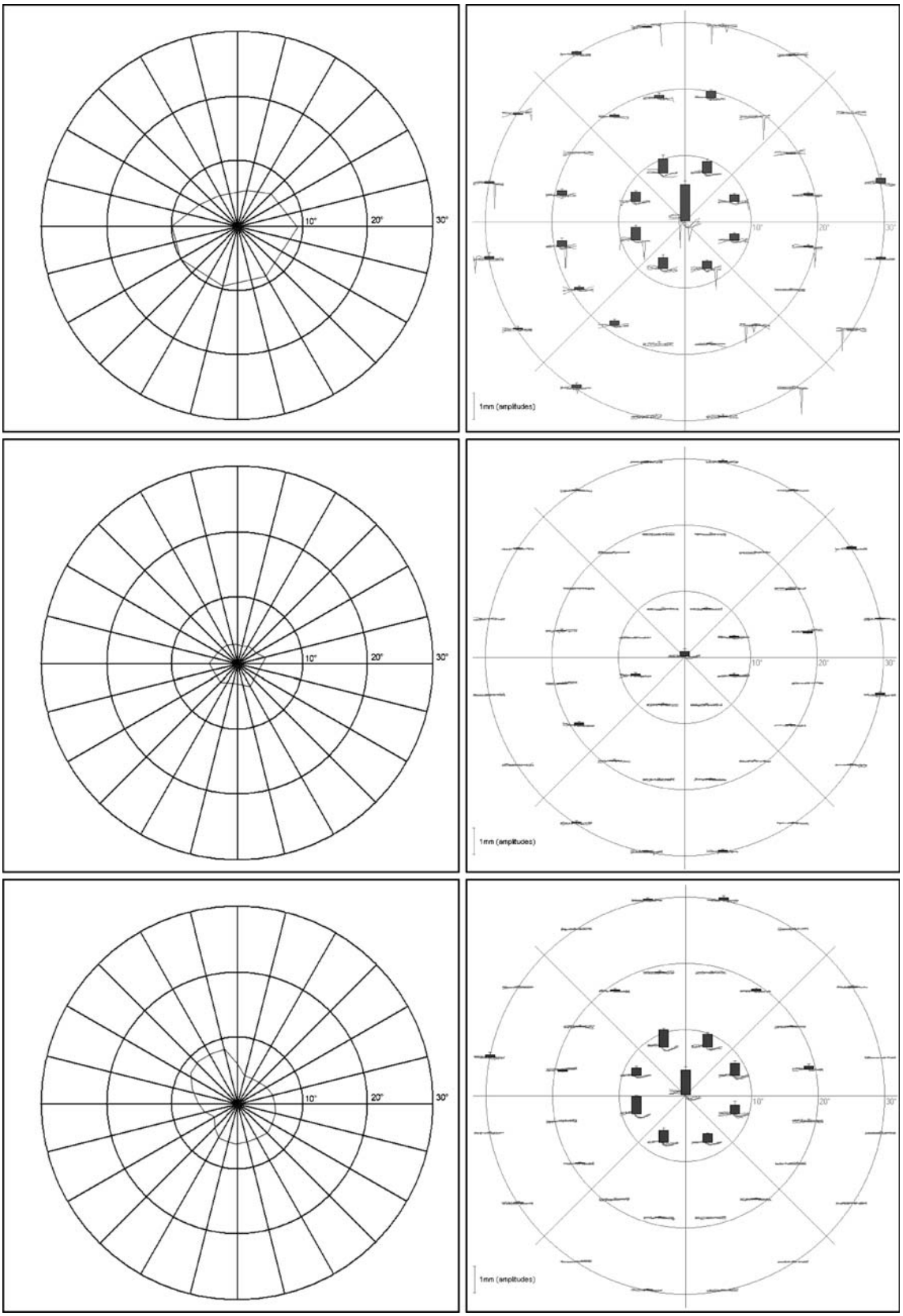

Fig. 2 (Continued)

Results

Pupil campimetry in control subjects showed pupil light reaction at all tested locations in the visual field with the highest amplitude in the centre of the visual field and a decrease towards periphery (Fig. 1). In patients with retinitis pigmentosa whose visual field was constricted to the central 3 to 10°, the pupil reaction was present only within the preserved visual field. No pupillary response could be recorded outside the area where Goldmann V4 was seen (Fig. 2). The median, mean, standard deviation, minimum and maximum of the pupil light reaction in the centre of the visual field and at the eccentricity of 10, 20 and 30 degrees in the control and RP groups, are listed in Table 1.

In the two patients with suspected feigned visual field loss one patient (1) pretented that he had a concentric visual field loss up to the central 10° on both eyes. There was no visible ocular pathology. The second patient (2) could identify only a few stimuli close to the centre of the visual field in both eyes during the visual field test. Ocular fundus of this patient showed only typical myopic changes. A relative afferent pupillary defect was not present with either of these patients. Magnetic resonance imaging scans of the brain and optic nerve had not revealed any pathology. Pupil campimetry in both patients showed a well evocable pupil reaction at all tested locations, with no evidence of any concentric constriction of the visual field in either eye (Fig. 3). The actual pupil reaction [mm] at defined eccentricities of the visual field for both patients is listed in Table 2.

The pupil responses differed significantly between the control subjects and the RP patients in the centre of the visual field ($p=0.029$), as well as at the eccentricity of 10, 20 and 30 degrees (all $p=0.006$). The pupil constriction amplitude of patients with feigned visual field loss resembled the results of the control subjects and differed from the results of RP patients especially at 10, 20 and 30 degrees eccentricity.

Table 1 Characteristics of pupil light reaction in the group of control subjects and RP patients

	Eccentricity	Median [mm]	Mean [mm]	SD	Minimum [mm]	Maximum [mm]
Control group	0°	1.80	1.76	0.36	1.25	2.26
	10°	1.23	1.22	0.27	0.91	1.65
	20°	1.04	1.03	0.24	0.71	1.33
	30°	0.81	0.87	0.22	0.56	1.09
RP group	0°	1.01	1.04	0.52	0.22	1.75
	10°	0.42	0.34	0.27	0.01	0.69
	20°	0.02	0.04	0.04	0.01	0.09
	30°	0.04	0.07	0.09	0.01	0.25

Median, mean, standard deviation, minimum and maximum are obtained from the mean values calculated for each subject at different eccentricities

Discussion

Pupil perimetry was able to reproduce the visual field in retinitis pigmentosa very well. Pupil perimetry in patients with functional concentric visual field loss did not show a pattern similar to retinitis pigmentosa at all. On the contrary, it confirmed normal functions in allegedly blind areas of the visual field, thereby ruling out a severe retinal dystrophy.

This is in accordance with other studies dealing with the clinical applications of pupil perimetry which have shown that most diseases affecting the retina and the visual pathway cause pupil field scotomata which match the defects found in standard perimetry [3, 4, 5, 6]. Visual field defects in pupil campimetry can be recognized by a reduced or absent pupil light reaction within these areas.

Not much information exists about the pupillary visual field in retinitis pigmentosa. Alexandridis et al. [7] showed that it is possible to objectify visual loss in patients with retinitis pigmentosa by means of the pupillography. However, in his experiments he did not use pupil perimetry but central threshold measurement.

Use of pupil campimetry to test patients with functional visual loss has been investigated by other studies, as well [4, 5, 8, 9, 10]. To our knowledge, only two studies [8, 9] included a few patients with retinitis pigmentosa. Moore et al. [8] included 2 patients with retinitis pigmentosa, who showed no pupil response in the peripheral field, similar to ours. Based on the data of 17 patients with suspected functional visual field loss, the authors called pupil perimetry a method, which can objectively substantiate functional field loss when focal pupillary responses are normal but visual threshold is not. Yoshitomi et al. [9] also examined 2 patients with retinitis pigmentosa and found a congruence between conventional and pupil perimetry. Rajan et al. [10] conducted a study on 3 patients with presumed functional visual field loss respecting the midlines. They concluded that in cases of functional visual field loss where the pattern is not consistent with retro-chiasmal disease, pupil perimetry can provide objective evidence for normal visual fields. Kardon et al. [4] tested pupil perimetry in normal subjects and patients with various visual field defects. One patient in their study group with functional hemifield loss demonstrated a completaly normal pupil field.

Pupil perimetry has its limitations too. First, only the central 30° of the visual field can be tested. Pupil light reaction elicited by light stimuli further in the periphery is only subtle and variable and can be hardly registered by

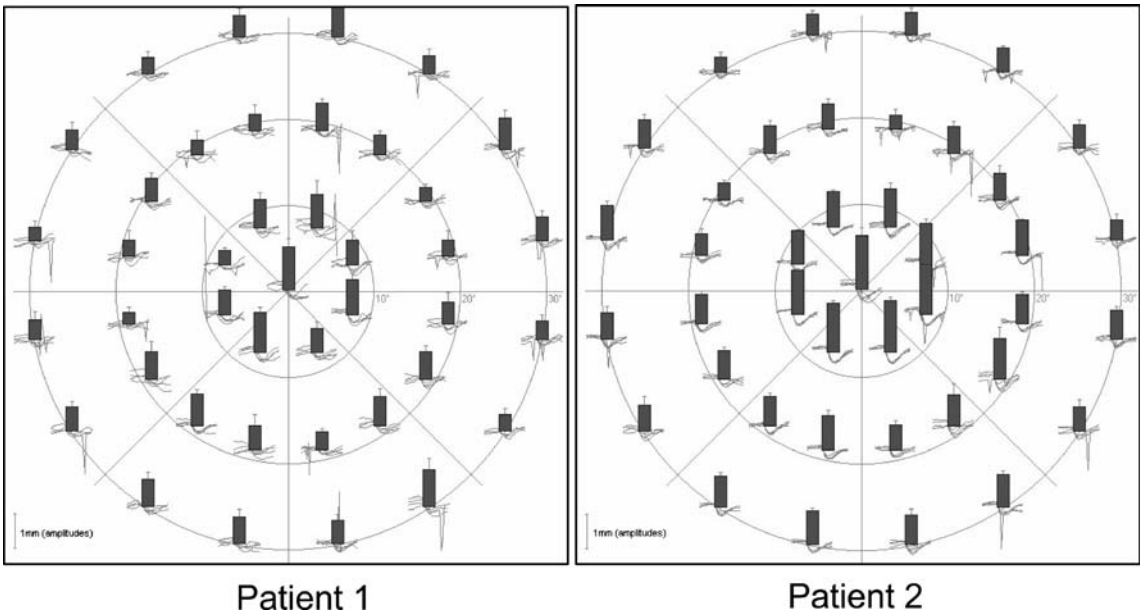

Fig. 3 Pupillomotor fields of 2 patients with feigned concentric visual field loss. During standard visual field test, patient 1 could identify only a few stimuli close to the centre of the visual field, patient 2 gave a visual field of 10°. However, their pupillograms at all tested locations are normal, giving no evidence of any concentric visual field loss. For further explanation of the graphs, see Fig. 1

current techniques. Second, it is accompanied by a greater variability in the measurements than the standard perimetry [11] and cannot be performed in patients with marked efferent pupillary disorders. Reduced pupil contraction can also be due to supranuclear inhibition (fear, stress), small pupil size, autonomic neuropathy or systemic drugs with anticholinergic effects. Such a pupil field might appear constricted, however, all responses are reduced, the central and the peripheral. According to our results, the appearance of a pupil field in retinitis pigmentosa patients is typical and should not be mistaken. Third, there is the unavoidable problem of straylight which might pretend a pupil light response in a blind area of the visual field. Fortunately, this played a minor role in our retinitis pigmentosa cases as demonstrated in Fig. 2. The responses outside the functional visual field area are absent or very small. However, when trying to map small defects, straylight may frustrate such an attempt.

Table 2 Mean pupil light reaction [mm] in the centre of the visual field and at the eccentricity of 10, 20 and 30 degrees in two patients with feigned visual field loss

	0°	10°	20°	30°
Patient 1	1.59	1.27	0.83	0.80
Patient 2	1.28	0.85	0.66	0.71

Again, these values were calculated from the mean values at a particular eccentricity in the visual field

Pupillary function in patients with retinitis pigmentosa needs also to be discussed in the context of new knowledge on retinal anatomy. Recent studies in mammals [12] have provided overwhelming evidence that ocular photoreception is not limited to rods and cones. A small subset of retinal ganglion cells expressing melanopsin has been shown to be directly photosensitive. These retinal ganglion cells project to the olivary pretectal nuclei, the retino-recipient area responsible for the pupillary light reflex, and the suprachiasmatic nuclei, the circadian pacemaker in the brain [13, 14]. They do not serve vision and might be spared in retinal cone-rod-dystrophies.

Experiments on rodless and coneless mice have shown that pupillary light response persists in the absence of rods and cones. It could be argued that those ganglion cells might provide light responses even in the blind visual field of retinitis pigmentosa patients. However, melanopsin exerts influence only at high irradiances and does not respond to short stimuli but rather to sustained stimuli. Probably, the rod/cone and melanopsin system together provide the full dynamic range of the normal pupillary reflex [15]. Thus, light stimuli used in our experiments were below the threshold of the photosensitive ganglion cells in the affected regions of the retina.

In conclusion, this study provides sufficient evidence that pupil campimetry is applicable in differential diagnosis of retinal dystrophy and functional concentric visual field loss. To determine specificity and sensitivity further studies with more patients are necessary.

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Glaukomerkennung mittels der Pupillenkampimetrie

Glaucoma Screening by Means of Pupil Campimetry

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Schlüsselwörter
- Pupille
- Glaukom
- Perimetrie
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Key words
- pupil
- glaucoma
- perimetry
- glaucoma screening

Zusammenfassung

Hintergrund: Ziel der Studie war festzustellen, ob eine pupillografische Untersuchung des Gesichtsfelds mittels Pupillenkampimetrie glaukomatöse Gesichtsfeldveränderungen aufdecken kann und somit für Glaukom-Screening geeignet wäre.

Patienten und Methoden: Es wurden 20 Patienten mit Offenwinkelglaukom und 30 gesunde Probanden mittels der Pupillenkampimetrie untersucht. Alle Glaukompatienten hatten einen glaukomatösen Gesichtsfelddefekt an mindestens einem Auge. Das Reizmuster bestand aus 17 weißen Lichtreizen, die im zentralen 30°-Gesichtsfeldbereich, besonders im Bjerrum-Bereich, dargeboten wurden. Der Stimulusdurchmesser war 6°. Jeder Stimulus wurde für 200 ms alle 2000 ms präsentiert. Es wurden insgesamt 3 Prüfpunkt-Leuchtdichten getestet (16,4 cd/m^2; 27,1 cd/m^2 und 40,5 cd/m^2). Die einzelnen Pupillenlichtreaktionen (PLR) an allen geprüften Punkten im Gesichtsfeld, deren Summen und Teilsummen wurden zwischen beiden Gruppen mit dem 2-seitigen Zweistichproben-t-Test verglichen. Die Trennschärfe der Methode beim Glaukom wurde mit ROC-Kurven (receiver operating characteristics) bewertet.

Ergebnisse: Die durchschnittliche PLR war bei Glaukompatienten an allen Messorten im Gesichtsfeld niedriger als bei gesunden Probanden. Auch bei der Summenbildung der Amplituden waren die Werte der Glaukompatienten geringer. Signifikante Unterschiede in der PLR zeigten sich vor allem im zentralen und parazentralen Gesichtsfeld. Die besten AUC-Werte (area under the curve) wurden unter Verwendung der höchsten Helligkeit erzielt, der größte AUC-Wert lag bei 0,769.

Schlussfolgerung: Obgleich der Unterschied der PLR zwischen Glaukompatienten und der Kontrollgruppe statistisch signifikant war, waren die erzielten AUC-Werte zu gering, um die gewünsch-

Abstract

Background: The aim of the study was to find out if pupillographic assessment of the visual field by means of pupil campimetry can identify glaucomatous visual field defects and as such be used for glaucoma screening purposes.

Patients and Methods: 20 patients with open angle glaucoma and 30 healthy persons were examined by means of pupil campimetry. All glaucoma patients had a glaucomatous visual field defect in at least one eye. The stimulus pattern consisted of 17 white-light stimuli which were presented within the 30° visual field, particularly in the Bjerrum region. The stimulus diameter was 6°. Each stimulus was presented for 200 ms and the interval between the stimuli was 1800 ms. Three stimulus intensities (16.4 cd/m^2; 27.1 cd/m^2 and 40.5 cd/m^2) were tested. The individual pupil light reaction (PLR) amplitudes at all examined locations in the visual field, their sums and partial sums were compared between both groups by the two-sided two-sample t test. The diagnostic performance of the method in glaucoma diagnosis was evaluated by ROC curves (receiver operating characteristics).

Results: The average PLR at all locations in the visual field was reduced in glaucoma patients compared to healthy persons. The sums of the PLR were reduced in glaucoma patients as well. Significant differences in the PLR were found especially in the central and paracentral visual fields. The best AUC values (area under the curve) were reached with the highest stimulus intensity, the highest AUC value overall was 0.769.

Conclusion: Although the difference in PLR between glaucoma patients and the control group was significant, the reached AUC values fell short of being ideal for screening purposes. A surprising finding was that the most central pupil response was reduced by the same amount as that in the Bjerrum region.

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te Sensitivität und Spezifität für ein geeignetes Glaukom-Screening zu erreichen. Ein überraschender Befund war, dass die Pupillenantwort auf den zentralsten Reiz im gleichen Umfang reduziert war wie in der Bjerrum-Region.

Einleitung

Einer von 40 Erwachsenen über 40 Jahre leidet an Glaukom mit einer Beeinträchtigung des Sehens. Das bedeutet, dass 60 Millionen Menschen weltweit Glaukom haben, und 8,4 Millionen davon sind blind auf beiden Augen. Sogar in entwickelten Ländern bleibt die Hälfte von Glaukompatienten unerkannt [1]. Und doch ist die Frühdiagnose bei dieser Erkrankung von höchster Bedeutung. Durch Therapie lässt sich der Glaukomschaden verhindern oder zumindest aufhalten.

Nach geeigneten und universalen Screening-Tests auf Glaukom wird also seit Langem dringend gesucht. Diese Verfahren müssen auch Nichtaugenärzten zugänglich sein, sie müssen schnell und einfach sein und sollten möglichst wenig von der Mitarbeit des Patienten und vom Können und der Erfahrung des Untersuchers abhängen.

Ein mögliches objektives Verfahren ist die pupillografische Prüfung der visuellen Afferenz. Ein Glaukom beginnt nur selten symmetrisch und somit hat ein Glaukom in aller Regel einen relativen afferenten Pupillendefekt im schlimmer betroffenen Auge zur Folge [2]. Auch ist das Gesichtsfeld selten symmetrisch betroffen. Es sollte sich demnach beim Glaukom eine deutlichere Streuung der pupillomotorischen Empfindlichkeit im Gesichtsfeld finden als beim Normalen. Das Ziel unserer Studie war zu zeigen, ob eine pupillografische Untersuchung des Gesichtsfeldes mittels Pupillenkampimetrie glaukomatöse Gesichtsfeldveränderungen aufdecken kann und somit für Glaukom-Screening geeignet wäre.

Patienten und Methoden

Für diese Studie wurden 20 Glaukompatienten mit Offenwinkelglaukom, Pseudoexfoliationsglaukom, Pigmentdispersionsglaukom oder Normaldruckglaukom untersucht. Die Patientengruppe bestand aus 12 Frauen und 8 Männern (Durchschnittsalter 58,4 ± 10,1 Jahre). Alle Patienten hatten einen glaukomatösen Gesichtsfelddefekt an mindestens einem Auge. Die Ausschlusskriterien waren wie folgt: Engwinkelglaukom; Netzhauterkrankung; Optikusneuropathie (außer Glaukomneuropathie); Amblyopie; Strabismus; Z. n. intraokularem chirurgischen Eingriff (außer einer nicht komplizierten Katarakt-Extraktion); Anamnese einer intraokularen Entzündung; Medikamenteneinnahme mit Einwirkung auf die PLR; gestörte PLR; fortgeschrittener Glaukomschaden des Gesichtsfeldes mit Beeinträchtigung der Sehschärfe, der einen Vergleich beider Gesichtsfeldhälften und eine gute Fixation während der Pupillenuntersuchung verhindern würde; schwer wiegende Grunderkrankungen, die gegen eine Teilnahme an der Studie sprechen. Als Kontrollgruppe dienten 30 gesunde Personen (Durchschnittsalter 58,0 ± 10,2 Jahre), davon 18 waren Frauen und 12 Männer. Zu den Einschlusskriterien zählten für die gesunden Probanden Visus 1,0; Augendruck < 21 mmHg; ein physiologischer Augenbefund und eine normale Pupillenlichtreaktion (PLR). Die Studie wurde durch die Ethik-Kommission der Medizinischen Fakultät in Tübingen genehmigt, und ein schriftliches Einverständnis zur Studienteilnahme von jedem Probanden verlangt.

Jeder Proband wurde am Untersuchungstag ophthalmologisch untersucht (Visusprüfung, Spaltlampenmikroskopie, Prüfung der PLR und Fundusbeurteilung). Die Gesichtsfelduntersuchung fand bei Glaukompatienten am selben Tag wie die Pupillenbeurteilung statt. Das zentrale 30° Gesichtsfeld wurde mittels statischer Rasterperimetrie mit dem Tübinger Automatik Perimeter oder dem Octopus 101 Perimeter untersucht.

Schließlich wurde bei allen Probanden die Pupillenperimetrie (Kampimetrie) durchgeführt. Diese Methode ist auf dem Prinzip einer Infrarot-Video-Pupillografie aufgebaut. Die pupillenkampimetrische Messeinrichtung besteht aus einem 19 Zoll Bildschirm, auf dem die Lichtreize (Stimuli) dargeboten werden, einer Infrarot-sensitiven Videokamera zur Aufzeichnung der PLR, einem kleinen Monitor für die ständige Überwachung der Fixation sowie einem Computer mit einem weiteren Monitor zur Steuerung des Messprogramms. Die Untersuchung findet in einem abgedunkelten Raum statt. Die Lichtstimuli werden auf dem Bildschirm etwa 20 cm vom Auge des Probanden präsentiert. Der Patient wird aufgefordert, während der Messung so wenig wie möglich zu blinzeln und einen Punkt in der Mitte des Bildschirms zu fixieren. Bei allen Probanden wurde in dieser Studie nur ein Auge untersucht, das andere Auge war mit einer lichtdichten Augenklappe abgedeckt.

Das Reizmuster bestand aus 17 weißen Lichtreizen, die im zentralen 30°-Gesichtsfeldbereich dargeboten wurden, besonders zwischen 10° und 20° oberhalb und unterhalb des Fixationsorts (= Bjerrumbereich), wo sich die Nervenfaserbündeldefekte beim Glaukom meistens finden. Der Stimulusdurchmesser war 6°. Jeder Stimulus wurde für 200 ms alle 2000 ms präsentiert. Es wurden insgesamt drei unterschiedliche Prüfpunkt-Leuchtdichten H1 = 16,4 cd/m^2, H2 = 27,1 cd/m^2 und H3 = 40,5 cd/m^2 nacheinander in unabhängigen Messreihen getestet. Die Hintergrundbeleuchtung wurde auf 0,7 cd/m^2 konstant eingestellt. Das Perimetrie-Programm wiederholte jeden Stimulus vier Mal, um intraindividuelle Schwankungen auszugleichen. Wenn die Aufzeichnung unzulänglich war (z. B. wegen Blinzeln), wurde der Stimulus mehrfach dargeboten, bis vier verlässliche Aufnahmen der PLR zur Verfügung standen. Anhand der vier pupillografischen Kurven der PLR pro Messort wurde der Mittelwert der Reflexamplitude in mm bestimmt. Dieser Durchschnittswert wurde dann für die weitere Analyse benutzt.

Das Primärkriterium der statistischen Analyse war die Amplitude der PLR auf die Testreize an allen geprüften Punkten im Gesichtsfeld und deren Vergleich bei Gesunden und Glaukompatienten. Da von einer Normalverteilung der Werte ausgegangen werden konnte, wurde für die statistische Analyse der t-Test verwendet. Um die Aussagekraft der Methode umfassend zu prüfen, wurden außer dem Vergleich der PLR an Einzelpunkten im Gesichtsfeld zwischen Glaukompatienten und Gesunden auch deren Summen, Teilsummen und Differenzen zwischen dem oberen und unteren Halbfeld verglichen und jeweils die ROC-Kurven gebildet. Schließlich wurde noch der Ausgangs-Pupillendurchmesser vom Anfang der Untersuchung an allen geprüften Stellen im Gesichtsfeld zwischen beiden Gruppen verglichen. Engere Pupillen konnten nämlich zur reduzierten retinalen Beleuchtung und somit zur geringeren Pupillenkontraktion führen.

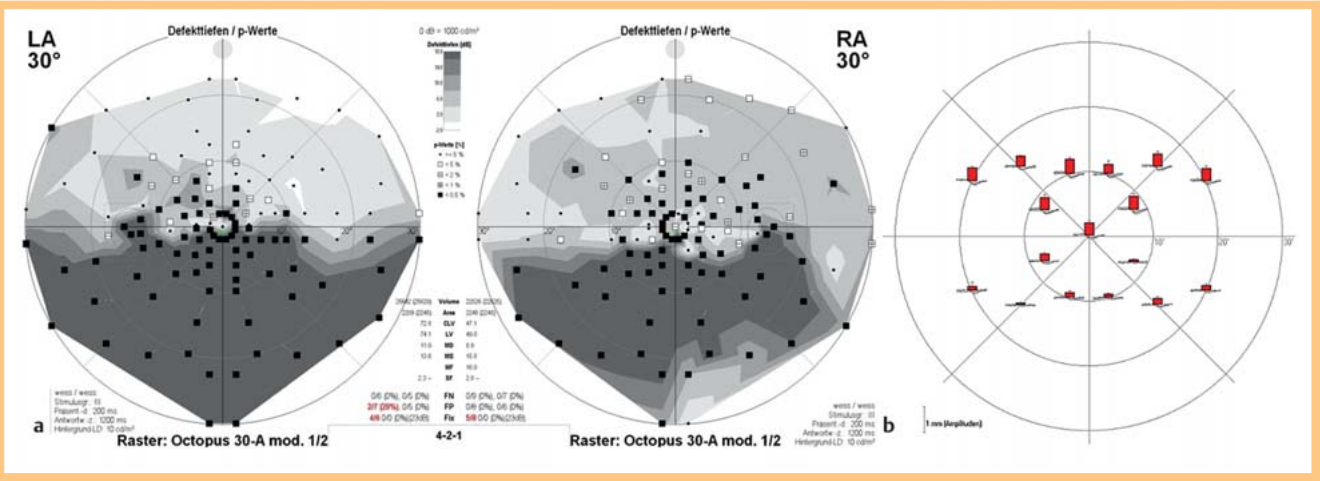

Abb. 1 **a** Die Gesichtsfelduntersuchung zeigt bei diesem Glaukompatienten ausgedehnte Gesichtsfeldausfälle im unteren Halbfeld beider Augen (Gerät Octopus 101, Haag Streit). **b** Der Gesichtsfelddefekt am linken Auge konnte mittels der Pupillenkampimetrie bei H1 gut dargestellt werden. Die Höhe der roten Balken spiegelt die Intensität der Pupillenlichtreaktion am entsprechenden Ort im Gesichtsfeld wider.

Ergebnisse

Zur Veranschaulichung der Darstellbarkeit der glaukomatösen Gesichtsfelddefekte mittels der Pupillenkampimetrie sind die Ergebnisse der Pupillenkampimetrie und automatischer Perimetrie von 2 Glaukompatienten dargestellt. Bei einem Patienten verursachte ein Glaukom große Nervenfaserbündeldefekte im unteren Halbfeld beider Augen. Diese Defekte bilden sich pupillenkampimetrisch sehr gut ab, die PLR ist im unteren Halbfeld erniedrigt (**Abb. 1**). Bei dem anderen Patienten hatte das Glaukom einen typischen Nervenfaserbündeldefekt im Bjerrum-Bereich am linken Auge zur Folge. Dieser Defekt konnte mittels der Pupillenkampimetrie nicht nachgewiesen werden (**Abb. 2**).

Zur Schematisierung und Standardisierung des Untersuchungsablaufs wurden die 17 Testorte im Gesichtsfeld vom Zentrum aus gegen den Uhrzeigersinn von M0 bis M16 durchnummeriert (**Abb. 3**). Aus dem Vergleich der Amplituden der PLR an 17 Einzelpunkten im Gesichtsfeld ergab sich, dass die durchschnittliche PLR bei Glaukompatienten an allen Messorten niedriger als bei gesunden Probanden war. Der t-Test zeigte signifikante Unterschiede zwischen beiden Gruppen an den Messorten M2, M4, M7 und M8 ($p < 0{,}05$) unter Verwendung von Helligkeit 1, an den Messorten M1, M2, M5, M6, M8, M9 und M12 ($p < 0{,}05$) bei Helligkeit 2 und an den Messorten M0 bis M15 ($p < 0{,}05$) bei Helligkeit 3, wobei der Unterschied an den Messorten M0 bis M2 und M4 bis M8 am deutlichsten war ($p < 0{,}01$). Die Differenz zwischen der PLR beider Gruppen wird mittels der grafischen Darstellung für Helligkeit 3 deutlich – an allen Messorten im Gesichtsfeld verläuft die Kurve der Amplitudenmittelwerte der Gesunden oberhalb der Kurve der Patienten (**Abb. 4**).

Der Ausgangs-Pupillendurchmesser bei Glaukompatienten war im Mittelwert 6,37 ± 1,06 mm. Bei gesunden Probanden lag der Mittelwert bei 6,93 ± 1,34 mm. Die Pupillendurchmesser der Glaukompatienten waren an allen Stellen im Gesichtsfeld kleiner als diejenigen der gesunden Probanden, der Unterschied war aber mit einer einzigen Ausnahme (Messort M0, $p = 0{,}046$) statistisch nicht signifikant.

Um die diagnostische Trennschärfe der Methode zu beurteilen, wurden für alle Messorte und alle Leuchtdichten ROC-Kurven angefertigt. Alle Kurven lagen dabei oberhalb der Winkelhalbierenden, die Fläche unter der Kurve (AUC) war also immer größer als 0,5. Die größten AUC-Werte wurden an jedem Testort unter Verwendung der Helligkeit 3 (40,5 cd/m²) erzielt, diese Stimulusleuchtdichte konnte also zwischen den Glaukompatienten und gesunden Probanden am besten unterscheiden (**Abb. 5**). Der größte AUC-Wert von 0,769 wurde bei Helligkeit 3 am Messort Nr. 5 erreicht. Da sich die Leuchtdichte 3 als beste für die Unterscheidung zwischen beiden Gruppen gezeigt hat, wurde in den weiteren Analysen nur diese Leuchtdichte verwendet.

Als nächstes wurden die Summen von Amplituden der PLR bei Helligkeit 3 von M0 bis M16 (30°-Gesichtsfeld), von M0 bis M4 (zentrales Gesichtsfeld) und von M0 bis M8 (zentrales und parazentrales Gesichtsfeld) gebildet und diese zwischen Glaukompatienten und gesunden Probanden verglichen. Dabei zeigte sich, dass die Glaukompatienten auch bei der Summenbildung der Amplituden jeweils geringere Werte aufwiesen als die Kontrollgruppe. Im t-Test ergab sich erneut ein statistisch signifikanter Unterschied zwischen beiden Gruppen. Geringere p-Werte wurden dabei für das zentrale und parazentrale Gesichtsfeld erzielt – Messorte M0 bis M8 (**Tab. 1**). Die erzielten AUC-Werte überschritten für jeden Summenvergleich den Wert 0,7 (**Tab. 2**), allerdings waren diese nicht größer als beim Vergleich von Einzelpunkten bei Helligkeit 3.

Als letztes wurden noch die Differenzen der Amplituden der PLR von entsprechenden Stellen im oberen und unteren Gesichtsfeld berechnet und diese zwischen Glaukompatienten und Probanden verglichen. Diese Analyse wurde erneut nur für die Helligkeit 3 durchgeführt. Zu erwarten wäre, dass ein asymmetrischer Glaukomschaden in oberer und unterer Retina zu einem größeren Unterschied zwischen den Amplitudenwerten der PLR des oberen und unteren Gesichtsfelds führen könnte als bei der Kontrollgruppe und somit der Betrag der jeweiligen Differenz größer wäre. Außer dem Vergleich von Messorten M5 und M8 zeigte der t-Test in diesem Fall allerdings keinen signifikanten Unterschied zwischen beiden Gruppen. Auch die AUC-Werte (0,369–0,647) führten dabei zu keiner Verbesserung der Güte der Methode.

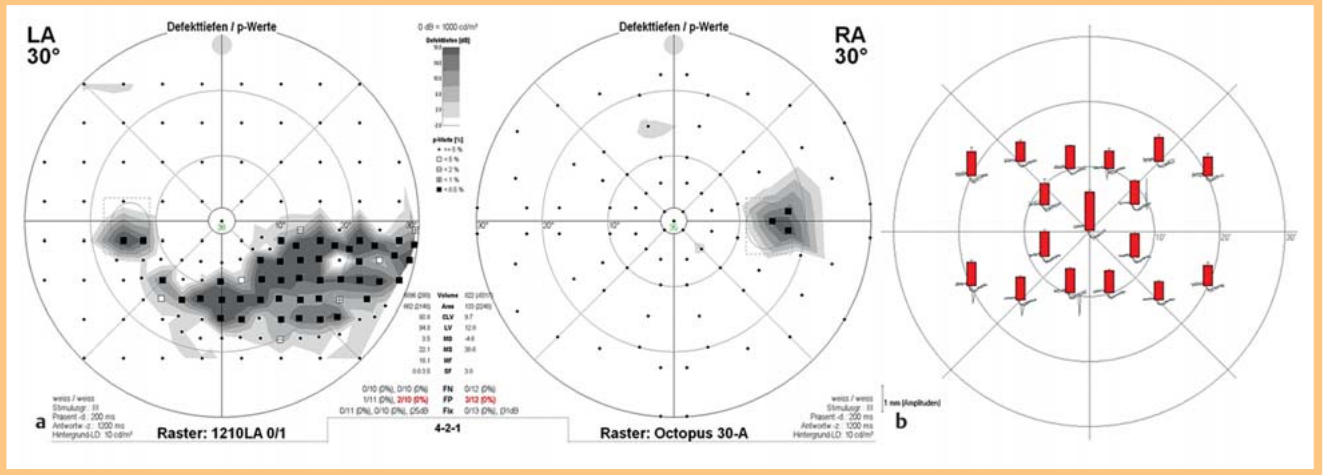

Abb. 2 **a** Die Gesichtsfelduntersuchung zeigt bei diesem Glaukompatienten einen Nervenfaserbündeldefekt im unteren Halbfeld des linken Auges (Gerät Octopus101, Haag Streit). **b** Der Gesichtsfelddefekt am linken Auge ließ sich mittels der Pupillenkampimetrie in diesem Fall nicht gut nachweisen. Die Höhe der roten Balken spiegelt die Intensität der Pupillenlichtreaktion am entsprechenden Ort im Gesichtsfeld wider.

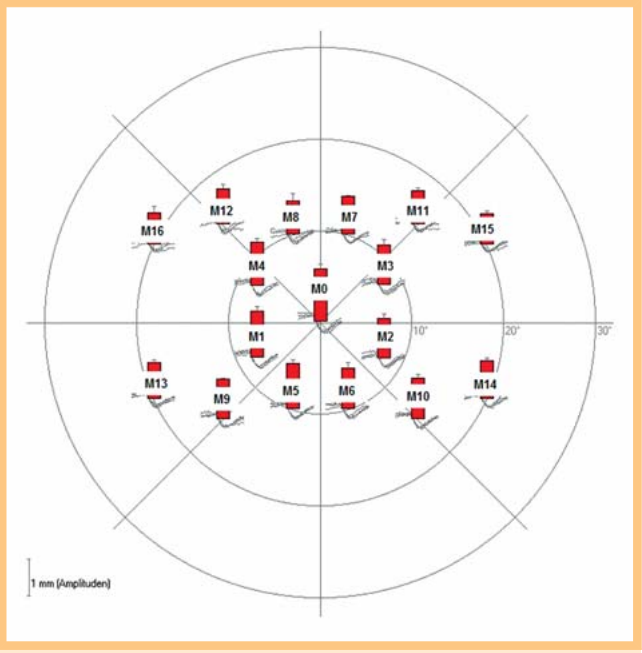

Abb. 3 Schematische Darstellung der Lokalisation der Messorte M0 bis M16 im 30°-Pupillengesichtsfeld.

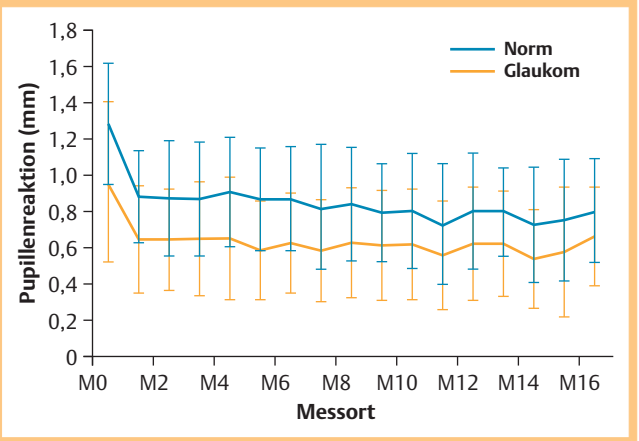

Abb. 4 Vergleich der Mittelwerte der Pupillenreaktion bei Glaukompatienten und gesunden Probanden und ihre Standardabweichung an Messorten M0 bis M16 bei Helligkeit 3.

Diskussion

Diese prospektive Studie zeigte einen signifikanten Abfall der Amplitude der PLR der Glaukompatienten gegenüber der Norm an allen geprüften Orten im 30°-Gesichtsfeld. Die mögliche klinische Anwendung der Methode wurde mittels ROC-Kurven bewertet, welche die für ein geeignetes Glaukom-Screening erforderliche Trennschärfe aber nicht erreichen konnten. Summen- oder Differenzenbildung führten dabei zu keiner relevanten Verbesserung der AUC-Werte gegenüber der Auswertung der Einzelpunkte. Unsere Studie erbrachte allerdings interessante Erfahrungen, die als Ausgangspunkte für zukünftige Versuche dienen können.

Gegenüber der ursprünglich beabsichtigten Früherkennung zeigte diese Studie auf, dass sich Glaukomatöse nicht nur in ihrer Schwellenwahrnehmung von Normalbeobachtern unterscheiden. Perimetrien sind meistens schwellenbestimmend. Die Pupillenkampimetrie prüft dagegen Antworten auf überschwellige Lichtreize. Die Glaukompatienten der Studie unterschieden sich von den Normalbeobachtern umso mehr, je weiter überschwellig der verwendete Lichtreiz war. Diese und auch die folgenden diskutierten Ergebnisse haben möglicherweise grundsätzliche Bedeutung für das Verständnis des Sehens und die Art des Schadens beim Glaukom.

Ein typischer glaukomatöser Gesichtsfelddefekt wird durch bogenförmige Defekte, nasale Sprünge oder andere Muster gekennzeichnet, die dem Verlauf von Nervenfasern auf der Netzhaut entsprechen und das Gesichtsfeldzentrum aussparen [3]. Ein Schaden im Gesichtsfeldzentrum mit einer Beeinträchtigung der Sehschärfe wird erst im Terminalstadium vom Glaukom erwartet. Erstaunlicherweise lieferte in unserer Studie auch der zentral gelegene Messort M0 eine deutlich abgeschwächte PLR der Glaukompatienten, und die höchsten AUC-Werte wurden besonders

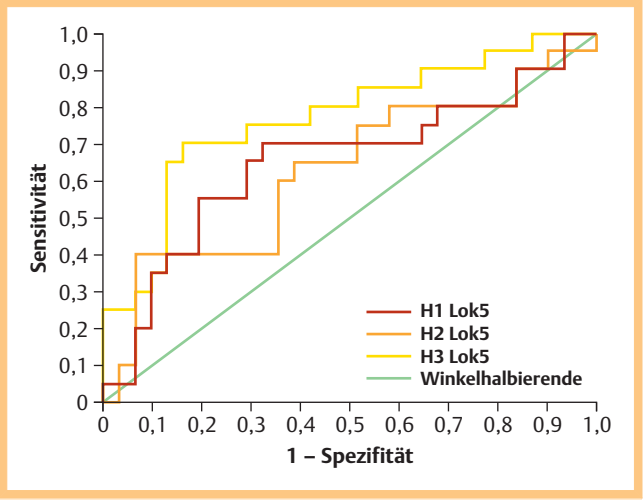

Abb. 5 ROC-Kurven am Testort M5 unter Verwendung der Stimulusleuchtdichten H1, H2 oder H3.

Tab. 1 Mittelwerte der Summen der Pupillenreaktion [mm] bei gesunden Probanden und Glaukompatienten unter Verwendung der Stimulusleuchtdichte 3 und der p-Wert beim Summenvergleich zwischen Glaukompatienten und gesunden Probanden.

Summe N/G		MW der Pupillenreaktion	SD	p-Wert
M0–M16	N	14,44	4,84	0,0067
M0–M16	G	10,85	4,93	
M0–M4	N	4,81	1,45	0,0028
M0–M4	G	3,57	1,56	
M0–M8	N	8,22	2,60	0,0025
M0–M8	G	6,00	2,67	

MW = Mittelwert, N = Norm, G = Glaukompatienten, SD = Standardabweichung

Tab. 2 AUC-Werte der Summenvergleiche.

Summen	AUC
M0–M16	0,702
M0–M4	0,721
M0–M8	0,727

im zentralen und parazentralen Gesichtsfeld erreicht. Die Summenbildung von parazentralen Stellen M0 bis M8 lieferte die besten Ergebnisse. Auch perimetrische Studien mit lokal verdichtetem Raster zeigten, dass es in Augen mit nur mäßigem Glaukomschaden Gesichtsfelddefekte im perizentralem Gesichtsfeld gibt, vor allem im oberen Halbfeld [4]. Das zentrale und parazentrale Gesichtsfeld scheint also bei Glaukompatienten funktionell früher beeinträchtigt zu sein als gedacht. Das könnte zu wesentlichen Problemen beim Lesen, Autofahren oder anderen Aktivitäten führen, deren Meisterung vom intakten parazentralen Gesichtsfeld abhängt.

Der Effekt von kleineren Pupillen auf die reduzierte PLR bei Glaukompatienten konnte in dieser Studie weitgehend ausgeschlossen werden. Bei Glaukompatienten zeigte sich zwar die Tendenz zu engeren Pupillen, jedoch wäre ein Unterschied dieser Größenordnung erst bei deutlich größeren Fallzahlen mit ausreichender Power nachzuweisen. Über die Pupillenweite bei Glaukompatienten gibt es in der Literatur keine klaren Aussagen. Eine Doktorarbeit aus unserer Forschungsgruppe zeigte, dass die Pupillen bei Patienten mit primärem Offenwinkelglaukom tatsächlich enger sind als bei Gesunden (unveröffentlichte Ergebnisse). Über die Ursache kann man nur spekulieren. Engere Pupillen können durch ein höheres Alter verursacht werden [5], und die meisten Glaukompatienten sind ältere Menschen. Jedoch waren beide Gruppen in unserer Studie in ihrem Altersaufbau sehr ähnlich. Man könnte auch argumentieren, dass es sich um die Wirkung von Miotika handeln könnte. Heutzutage wird aber Pilocarpin bei den Offenwinkelglaukomen so gut wie nicht mehr verwendet, und bei den bevorzugten Therapiemöglichkeiten wie Prostaglandinanaloga oder Betablocker wurde keine Wirkung auf die Pupillengröße gefunden [6, 7]. Eine weitere Erklärung könnte sein, dass Patienten mit primärem Offenwinkelglaukom eine geringere zentrale Hemmung des pupillokonstriktorischen Edinger-Westphal-Kerns haben und die Pupillen dadurch kleiner werden [5]. Das würde zu der aktuellen Definition vom Glaukom als einer neurodegenerativen Erkrankung des zentralen Nervensystems passen. Hier öffnet sich auf jeden Fall ein interessantes Gebiet weiterer Forschung.

Der pupillografische Ansatz beim Glaukom sollte auch im Kontext neuer Erkenntnisse der retinalen Anatomie diskutiert werden. Außer den klassischen Fotorezeptoren (Zapfen und Stäbchen) gibt es in der Netzhaut eine kleine Gruppe an intrinsisch fotosensiblen retinalen Ganglienzellen (RGCs), die Melanopsin enthalten und am Pupillenlichtreflex beteiligt sind [8]. Da die Melanopsin-RGCs allerdings besser auf anhaltende und helle (> 100 cd/m²) Lichtreize antworten [9], lagen die Beleuchtungsdichten unserer Stimuli unterhalb der Schwelle der Melanopsin-RGCs und konzentrierten sich auf das Zapfen-Stäbchen-System. Nun stellt sich noch die Frage, ob die Melanopsin-RGCs bei Glaukom ausgespart werden und in der Lage sein könnten, auch in Bereichen absoluter Skotome eine PLR hervorzurufen. Kankipati et al. untersuchten eine anhaltende Pupillenkonstriktion nach dem Ausschalten vom farbigen Lichtstimulus („post-illumination pupil response"), die gerade durch Melanopsin-RGCs gesteuert wird. Sie stellten fest, dass diese anhaltende Pupillenkonstriktion bei Glaukompatienten im Vergleich zur Norm signifikant erniedrigt ist und mit dem Ausmaß vom Gesichtsfeldverlust umgekehrt korreliert [10]. Es scheint also, dass die Melanopsin-RGCs bei Glaukom auch betroffen sind und keine „zusätzliche" PLR in beschädigten retinalen Arealen ermöglichen.

Über den Einsatz von Pupillografie beim Glaukom wurde in der letzten Zeit einiges geforscht. Kalaboukhova et al. untersuchten das Vorliegen eines RAPD bei Glaukompatienten und gesunden Probanden mittels Infrarotpupillometrie. Sie stellten fest, dass ihr Test eine glaukomatöse Optikusneuropathie mit einer Sensitivität von 86,7% bei einer Spezifität von 90,0% erkennen kann, die allerdings für einen Screening-Test immer noch zu niedrig ist [11]. Chen et al. untersuchten bei Glaukompatienten die Asymmetrie der PLR auf große, im oberen und unteren Halbfeld spiegelbildlich gelegte Lichtreize. Die PLR wurde als der Kontrastausgleich („contrast balance" – relative Sensitivität auf obere und untere Lichtreize) und die Kontraktionsamplitude auf einzelne Lichtreize ausgewertet. Die Werte des Kontrastausgleichs unterschieden sich beim Glaukom signifikant von der Norm und entdeckten den Gesichtsfelddefekt in 70% der Patienten. Allein nach der Pupillenkontraktion konnten 60% der Glaukompatienten erkannt werden. Wenn der Kontrastausgleich und die Pupillenkontraktion zusammen ausgewertet wurden, entstand für die Unterscheidung von Glaukompatienten eine ROC-Kurve mit einer AUC von 0,83. Die Trennschärfe der Kontraktionsamplitude allein,

was für den Vergleich mit unseren Ergebnissen vorteilhafter wäre, wurde in dieser Studie nicht überprüft [12]. Wride et al. untersuchten dieselbe Methode bei 30 Glaukompatienten und 30 gesunden Probanden mit dem Gerät The Pupilmetrix™ PLR60 (Applied Neurodiagnostics Ltd., Cramlington, United Kingdom). Die erzielte Sensitivität der Methode war sogar 93,1% bei einer Spezifizität von 76,7%. Die Übereinstimmung mit der klinischen Diagnose eines Glaukoms lag bei 84,7% [13]. Eine andere Methode zur Glaukomerkennung mit der Pupillenperimetrie haben Asakawa et al. benutzt [14]. Anhand ihrer Experimente bei gesunden Probanden berechneten sie eine „normale" Pupillenkontraktion an allen geprüften Stellen im Gesichtsfeld. Mit diesen Werten verglichen sie dann das 85. Perzentil der Pupillenkontraktion der Glaukompatienten und berechneten für jeden Ort die Abweichung von der Norm. Auf diese Weise legten sie einen allgemeinen Grenzwert der Abweichung fest, der zwischen Patienten und gesunden Probanden unterscheiden sollte. Der Mangel dieser Studie besteht allerdings darin, dass bei der Berechnung der Abweichung (pattern deviation) die Exzentrizität der Punkte im Gesichtsfeld nicht berücksichtigt wurde.

Im Allgemeinen können beim Glaukom Veränderungen in der PLR erfasst werden, die man auf verschiedenen Wegen untersuchen kann, allerdings scheinen sie nicht so eindeutig zu sein, dass man sie nach derzeitigem Stand für Screening-Zwecke benutzen könnte.

Schlussfolgerung

Unsere Studie zeigte, dass die PLR auf fokale Stimuli im 30°-Gesichtsfeld bei Glaukompatienten schwächer ausfällt als bei der gesunden Kontrollgruppe. Signifikante Abfälle der Amplituden gegenüber der Norm fanden sich besonders im zentralen und parazentralen Gesichtsfeld unter Verwendung der hellsten geprüften Stimulusleuchtdichte. Hier zeigten sich auch die größten AUC-Werte. Obgleich dieser Unterschied der Amplitudenwerte des PLR zwischen Glaukompatienten und der Kontrollgruppe statistisch signifikant nachweisbar war, waren unter den in dieser Arbeit gegebenen Messbedingungen und -einstellungen die erzielten AUC-Werte zu gering, um die gewünschte diagnostische Trennschärfe für ein geeignetes Glaukom-Screening zu erreichen.

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Aktueller Stand der pupillenbasierten Diagnostik der glaukomatösen Optikusneuropathie

Eine Pupillenuntersuchung wird routinemäßig primär bei neuroophthalmologischen Patienten durchgeführt. Jedoch kann die Pupille auch bei anderen ophthalmologischen Erkrankungen nützliche Informationen liefern. Manche Tests sind schon lange etabliert, manche beruhen auf den neuen Erfahrungen aus der Pupillenforschung, die ein neues Licht auf die Anatomie, Physiologie und Pathologie des Pupillenlichtreflexes werfen. Dieser Beitrag gibt einen Überblick über die pupillenbasierten diagnostischen Methoden und deren Einsatzmöglichkeiten in der Glaukomdiagnostik.

Seit Pilokarpin aus der Glaukomtherapie so gut wie verschwunden ist und die Mehrzahl der Patienten mit Medikamenten therapiert wird, welche die Pupillen unbeeinflusst lassen, ist die Pupillenlichtreaktion ein interessantes glaukomdiagnostisches Verfahren geworden. Die Pupillenreaktion bietet eine objektive Möglichkeit, die Funktion zu prüfen. Ein Problem stellt die große interindividuelle Variabilität der Pupillenlichtreaktion dar, die es praktisch unmöglich macht, ohne weitere Information zu entscheiden, ob ein Lichtreflex noch normal oder pathologisch ist. Sehr viel weniger variabel sind hingegen interokulare Unterschiede oder intraokulare Unterschiede zwischen verschiedenen Gesichtsfeldarealen. Deshalb spielen vergleichende Untersuchungen, Swinging-flashlight-Test und Pupillenperimetrie die größte Rolle und sollen hier besondere Berücksichtigung finden.

Relativer afferenter Pupillendefekt bei Glaukom

Ein relativer afferenter Pupillendefekt (RAPD) bedeutet, dass die Pupillenreaktion unterschiedlich ausfällt, je nachdem von welchem Auge sie ausgelöst wird. Im Falle einer üblicherweise normalen efferenten Pupillenansteuerung unterscheiden sich dabei die direkten Lichtreaktionen beider Augen, aber auch die direkte und die konsensuelle Reaktion desselben Auges sind ebenfalls unterschiedlich. Ein RAPD begleitet praktisch immer eine einseitige oder asymmetrische bilaterale Läsion der anterioren Sehbahn im Bereich von Sehnerv, Chiasma oder Tractus opticus.

Das primäre Offenwinkelglaukom betrifft zwar meist beide Augen, beginnt und verläuft aber oft asymmetrisch. Somit kann eine glaukomatöse Optikusneuropathie einen RAPD zur Folge haben. Tatsächlich tritt ein klinisch identifizierbarer relativer afferenter Pupillendefekt ungefähr bei einem Drittel der Patienten mit Offenwinkelglaukom auf [2, 8, 22, 26].

Ein RAPD lässt sich mit dem Swinging-flashlight-Test (Pupillen-Wechselbelichtungstest) feststellen. Dieser Test wird folgendermaßen durchgeführt: In einem möglichst dunklen Raum wird der Patient aufgefordert, ein Objekt in einigen Metern Abstand zu fixieren. Das Licht eines Ophthalmoskops wird in einem Winkel von 45° aus ca. 30 cm von unten auf jeweils ein Auge gerichtet. Dann bewegt man mehrfach das Licht rasch von einem Auge zum anderen und beobachtet dabei die direkten Lichtreaktionen beider Pupillen. Beide Pupillen müssen bei diesem Test gleich lang (ca. 2 s) aus gleichem Abstand und im gleichen Winkel beleuchtet werden. Der Wechsel zwischen beiden Augen sollte mindestens 5-mal wiederholt werden. Liegt ein RAPD vor, dann erweitern sich bei Belichtung des betroffenen Auges entweder beide Pupillen ohne vorausgehende Kontraktion, oder diese Kontraktion wird (im Seitenvergleich) weniger ausgiebig ausfallen (◘ **Abb. 1**). Der RAPD lässt sich mittels Graufiltern oder einem automatisierten Verfahren quantifizieren. Die Graufilter werden in den Lichtstrahl des Untersuchungslichtes gehalten, um die Beleuchtung des besseren Auges zu reduzieren. Schrittweise (ausgehend vom schwächsten Filter) werden Graufilter verschiedener Dichte geprüft. Geringere Dichten als 0,3-log-Einheiten sind normalerweise nicht notwendig und bei Filterdichten über 1,5-log-Einheiten wird die Messung recht ungenau. Deshalb sind Stufen von 0,3, 0,6, 0,9, 1,2 und 1,5 sinnvoll. Diese kann man aus 0,3, 0,6 und 0,9 kombinieren (z. B. fotografische ND-Filter 2-fach, 4-fach und 8-fach). Solche Graufilter sind entweder im Fotofachhandel oder bei verschiedenen Firmen erhältlich, wie z. B. GULDEN Ophthalmics in den USA oder bei Fa. HÜBEL in Olfen, Deutschland. Die Dichte des Filters, die den RAPD ausgleicht, entspricht dem Maß des RAPD [31]. Der automatische Swinging-flashlight-Test ist v. a. in

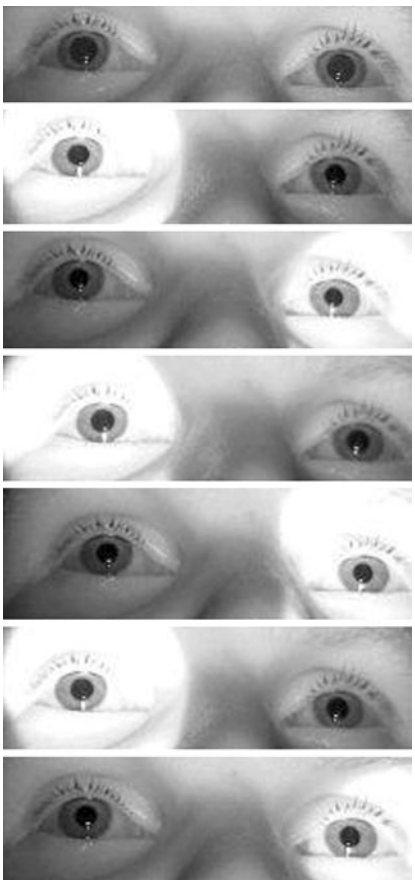

Abb. 1 ▲ Ausschnitte aus dem Infrarotvideo eines Glaukompatienten ohne Gesichtsfeldausfälle. Man sieht einen kleinen, aber reproduzierbaren Unterschied in der Pupillenweite: Bei Beleuchtung rechts sind die Pupillen weiter, es besteht also ein RAPD rechts. Im Video sieht man auch, dass sich die Pupillen bei Beleuchtung rechts weniger ausgiebig kontrahieren

klinischen Studien sinnvoll, in denen die Untersuchereinflüsse ausgeschlossen werden müssen [30].

Der Ausprägungsgrad des RAPD hängt vom Ausmaß des Ganglienzellverlusts und somit von dem Gesichtsfeldverlust ab. Lagrèze und Kardon [15] untersuchten die Korrelation zwischen RAPD und retinalem Ganglienzellverlust bei Glaukom und anderen Sehnerverkrankungen. Sie stellten eine signifikante Korrelation zwischen dem RAPD und dem Ganglienzellverlust mit Korrelationskoeffizienten von 0,7 für das „Humphrey-Gesichtsfeld" und 0,63 für das „Goldmann-Gesichtsfeld" fest. Der Ganglienzellverlust wurde aus der Fläche des Gesichtsfeldverlustes geschätzt. Schiefer et al. [22] fanden, dass das Ausmaß des RAPD am stärksten mit dem Gesichtsfeldparameter „loss volume" korreliert und am wenigsten mit der zentralen Lichtunterschiedsempfindlichkeit. Skorkovská et al. [26] zeigten, dass der RAPD bei Glaukom vorwiegend stärker ausgeprägte Gesichtsfeldausfälle und Gesichtsfeldausfälle mit einer großen interokularen Differenz begleitet. Sein Fehlen bedeutet aber nicht, dass kein Gesichtsfeldausfall vorliegt und umgekehrt kann ein RAPD bei minimalen oder gar nicht darstellbaren Gesichtsfeldausfällen vorhanden sein. Bruckmann et al. [2] zeigten, dass Glaukompatienten mit einem RAPD eine größere Differenz zwischen den Gesichtsfeldbefunden beider Augen aufweisen als solche ohne.

» Der Swinging-flashlight-Test ist schnell und patientenunabhängig

Der Swinging-flashlight-Test hat den entscheidenden Vorteil, dass diese Untersuchung schnell und patientenunabhängig (objektiv) ist. Der Test sollte als Ergänzung der Perimetrie betrachtet werden und ist besonders wertvoll, wenn Patienten nicht in der Lage sind, zuverlässige Angaben zu machen. Nicht selten findet sich eine ausgeprägte Streuung zwischen perimetrischen Untersuchungen, sodass sich oft nicht von einer Kontrolle zur nächsten sagen lässt, ob eine Verschlechterung eingetreten ist. Das Auftreten oder die Zunahme eines RAPD kann aber eine Verschlechterung objektivieren und bei der Interpretation der Gesichtsfelder helfen. Allerdings kann auch die Verringerung oder gar das Verschwinden eines RAPD eine Verschlechterung anzeigen, wenn sich das bislang bessere funktionell dem schlechteren Auge annähert.

Der Swinging-flashlight-Test hat demnach seinen Platz in der Glaukomdiagnostik, und zwar bei der Objektivierung einer Verschlechterung bei nicht eindeutigen perimetrischen Angaben. Ein RAPD kann auch anzeigen, dass ein „präperimetrisches" Glaukom auf dem Weg ist, dieses Attribut zu verlieren.

Pupillenperimetrie bei Glaukom

Eine Gesichtsfelduntersuchung ist obligatorischer Bestandteil der Glaukomdiagnostik. Allerdings ist die konventionelle Perimetrie eine „subjektive", d. h. patientenabhängige Untersuchungsmethode, die von vielen Faktoren beeinflusst werden kann. In klinischen Studien mit Glaukompatienten liegt die Rate unzuverlässiger Gesichtsfeldbefunde bei ≥10% [14]. Die Test-Retest-Variabilität der automatischen Perimetrie ist besonders in den geschädigten Gesichtsfeldbereichen hoch, was die Verlaufskontrolle erschwert [6]. Bei objektiven Tests könnten derartige Probleme geringer sein.

Die Pupillenperimetrie (bzw. -kampimetrie, wenn ein Monitor verwendet wird) stellt eine objektive Methode zur Gesichtsfelduntersuchung mittels der Pupillenlichtreaktion dar. Diese Methode basiert auf dem Prinzip der Infrarot-Video-Pupillographie, kombiniert mit einer perimetrischen Lichtreizdarbietung. Als Antwort dient nicht das Betätigen eines Schalters, sondern die pupillographisch gemessene Reaktion der Pupillen. Diese Antwort kann quantifiziert werden. Es ist bekannt, dass die Pupillenlichtreaktion – abgesehen vom Schwellenbereich und vom Sättigungsbereich (sehr heller Reiz) – linear mit dem Logarithmus des Lichtstromes auf die Netzhaut korreliert. Somit hat man ein relativ einfaches Verfahren, das bei bekannter Reizgröße und Helligkeit die retinale Empfindlichkeit an der untersuchten Stelle angibt. Die Reize müssen allerdings relativ groß und/oder hell sein, was zum einen die räumliche Auflösung begrenzt und das Risiko einer Streulichtantwort anstelle einer echten lokalen Antwort beinhaltet. Eine typische pupillenkampimetrische Messeinrichtung, wie wir sie verwenden, besteht aus einem Bildschirm, auf dem die Lichtreize dargeboten werden, einer Infrarot-sensitiven Videokamera zur Aufzeichnung der Pupillenreaktion, einem kleinen Monitor für die ständige Überwachung der Fixation sowie einem Computer mit einem weiteren Monitor zur Steuerung des Messprogramms. Die Untersuchung findet in einem abgedunkelten Raum statt. Die Lichtstimuli werden auf dem Bildschirm etwa 20 cm vom Auge des Probanden präsentiert. Über die Fixation hinaus ist keine Mitwirkung des Patienten erforderlich. Beide Augen werden getrennt untersucht [24, 25].

Es wurde gezeigt, dass bei den meisten Erkrankungen der Netzhaut und der Sehbahn die durch die klassische perimetrische Untersuchung festgestellten Skotome in der Pupillenkampimetrie reproduzierbar sind [13, 24]. Klinisch wird die Pupillenkampimetrie v. a. als objektiver Beweis bei Verdacht auf Simulation von Gesichtsfelddefekten eingesetzt [25].

» Klinisch wird die Pupillenkampimetrie v. a. bei Verdacht auf Simulation von Gesichtsfelddefekten eingesetzt

Wie erwähnt, beginnt ein Glaukom nur selten symmetrisch. Somit ist das Gesichtsfeld auch nur selten symmetrisch betroffen. So wäre zu erwarten, dass sich beim Glaukom größere Unterschiede in der pupillomotorischen Empfindlichkeit im Gesichtsfeld finden als beim Normalen. Diese Hypothese untersuchte eine eigene Studie, deren Ergebnisse erstmals beim 29. Internationalen Pupillen-Colloquium vorgestellt wurden [26]. Ziel war es zu zeigen, ob eine pupillographische Untersuchung des Gesichtsfeldes mittels Pupillenkampimetrie glaukomatöse Gesichtsfeldveränderungen aufdecken kann und somit für ein Glaukom-Screening geeignet wäre. Das Stimulusmuster bestand aus 17 Lichtreizen, vorzugsweise im Bjerrum-Bereich des oberen und unteren Halbfelds lokalisiert, wo die Glaukomdefekte am ehesten entstehen.

Die Ergebnisse zeigten, dass die Pupillenlichtreaktion auf fokale Stimuli im 30°-Gesichtsfeld bei Glaukompatienten schwächer ausfällt als bei der gesunden Kontrollgruppe (**Abb. 2a,b**). Signifikante Abfälle der Amplituden gegenüber der Norm fanden sich besonders im zentralen und parazentralen Gesichtsfeld. Obwohl sich statistisch signifikante Unterschiede der Amplitudenwerte der Pupillenlichtreaktion zwischen Glaukompatienten und der Kontrollgruppe zeigten, waren die erzielten AUC-Werte („area under the curve"), welche die diagnostische Genauigkeit der Methode repräsentieren, zu gering, um die gewünschte Sensitivität und Spezifität für ein geeignetes Glaukom-Screening zu erreichen. Ein wichtiges Ergebnis der Studie war allerdings, dass der zentral gelegene Messort eine deutlich abgeschwächte Pupillenlichtreaktion bei Glaukompatienten zeigte. Dies stimmt nicht mit der klassischen Vorstellung vom Ablauf der Gesichtsfeldverschlechterung beim Glaukom überein, in dem das Gesichtsfeldzentrum erst in terminalen Stadien der Erkrankung betroffen wird. Perimetrische Untersuchungen mit zentral verdichteten Rastern konnten in Augen mit nur mäßigem Glaukomschaden bereits Gesichtsfelddefekte im perizentralem Gesichtsfeld nachweisen [7, 23]. Das zentrale und parazentrale Gesichtsfeld scheint also bei Glaukompatienten funktionell früher beeinträchtigt zu sein als in früheren Studien angenommen.

Die Ergebnisse anderer Studien sind bezüglich des potenziellen Beitrags der Pupillenperimetrie zur Glaukomdiagnostik widersprüchlich. Kardon [11] berichtete, dass man bei Glaukompatienten nur wenig Korrelation zwischen dem „Pupillenfeld"- und dem Gesichtsfeldverlust sieht. Kalaboukhova et al. [9] berichteten, dass die automatisierte Infrarotpupillometrie eine glaukomatöse Optikusneuropathie mit einer Sensitivität von 86,7% bei einer Spezifität von 90% detektieren kann; allerdings sind diese Werte für einen vollwertigen Screening-Test immer noch zu niedrig [9]. Andere Arbeiten, liefern dagegen optimistischere Ergebnisse [4, 33]. Die methodischen Randbedingungen, v. a. die Stimuluseigenschaften, sind aber sehr unterschiedlich. Die Pupillenkampimetrie kann Veränderungen in der Pupillenreaktion bei glaukomatöser Optikusneuropathie entdecken. Bezüglich der genauen Modalitäten ihrer möglichen klinischen Anwendung besteht noch weiterer Forschungsbedarf.

Multifokale Pupillographie bei Glaukom

Andere objektive Methoden zur Gesichtsfelduntersuchung basieren auf multifokalen Stimuluspräsentationen. Diese Techniken ermöglichen eine simultane Ableitung der elektrischen Aktivität aus zahlreichen Netzthautbereichen. Die Stimuli werden in der Form eines Wabenmusters angezeigt, dessen Kontrast sich periodisch ändert, aber nie wiederholt (sog.

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Aktueller Stand der pupillenbasierten Diagnostik der glaukomatösen Optikusneuropathie

Zusammenfassung

Zwischen der Pupillenreaktion von Glaukompatienten und gesunden Probanden gibt es Unterschiede, die mit verschiedenen Techniken erfasst werden können. Die Methoden beruhen auf der (frühzeitigen) Asymmetrie in der visuellen Afferenz, auf der Untersuchung des Gesichtsfeldes mittels fokaler Lichtreize oder auf Stimulationsmethoden in Analogie zu multifokalen elektrophysiologischen Tests. Aktuelle Ergebnisse der Pupillenforschung beziehen intrinsisch lichtempfindliche (Melanopsin-haltige) Ganglienzellen in die Glaukomdiagnostik ein. Die bisherigen Ergebnisse der Pupillenuntersuchungen bei Glaukompatienten ermutigen zu weiterer Forschung auf diesem Gebiet, da nach geeigneten objektiven Screening-Verfahren für Glaukom ständig gesucht wird.

Schlüsselwörter

Pupille · Glaukom · Optikusneuropathie · Pupillenperimetrie · Multifokale Pupillographie

Current state of pupil-based diagnostics for glaucomatous optic neuropathy

Abstract

There are considerable differences between pupillary reactions to light in glaucoma patients and healthy subjects which can be identified by various techniques. These methods are based on the early asymmetry of the afferent conduction in the visual pathway, on the examination of the visual field by focal light stimuli or on visual stimuli in analogy with multifocal electrophysiological tests. Latest findings in pupillary research also suggest a possible use of the intrinsically photosensitive (melanopsin expressing) retinal ganglion cells in glaucoma diagnostics. The current results of pupillary experiments in glaucoma patients are encouraging for further research in this field because suitable objective screening methods for glaucoma are continually being sought.

Keywords

Pupil · Glaucoma · Optic neuropathy · Pupil perimetry · Multifocal pupillography

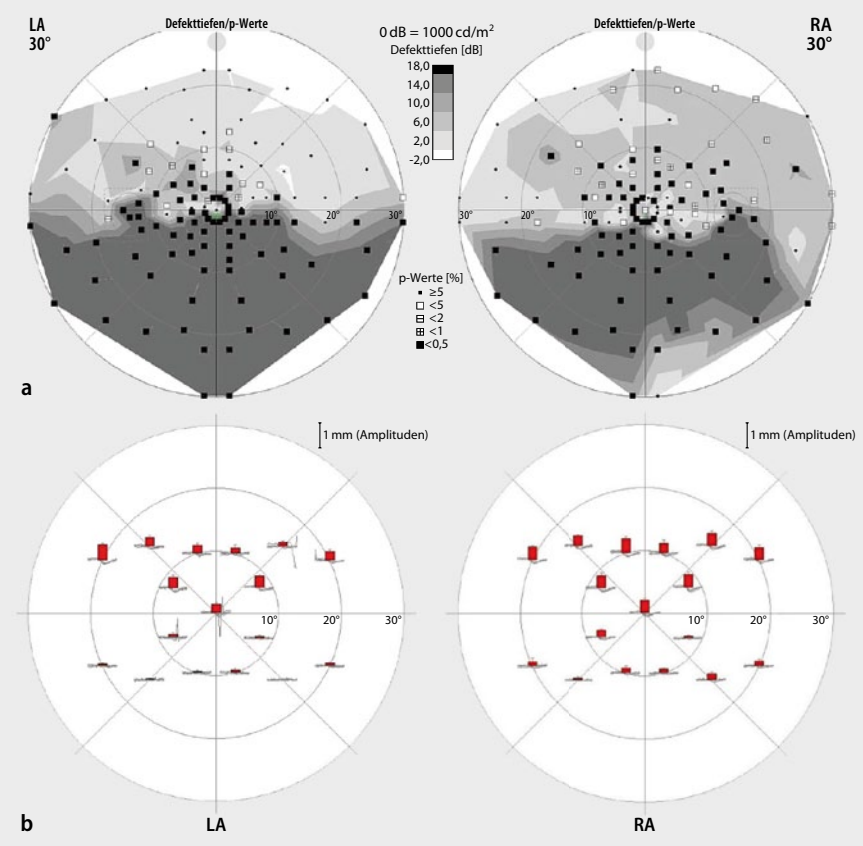

Abb. 2 ▲ **a** Die Gesichtsfelduntersuchung am Octopus-101-Perimeter (Haag Streit, Köniz, Schweiz) zeigt bei diesem Glaukompatienten ausgedehnte Gesichtsfeldausfälle im unteren Halbfeld beider Augen (schwellenbestimmende Perimetrie). *LA* linkes Auge, *RA* rechtes Auge. **b** Die Gesichtsfelddefekte konnten auch mittels der Pupillenkampimetrie (Pupil Research Lab, Center for Ophthalmology, Tübingen) gut dargestellt werden. Die Höhe der roten Balken spiegelt die Intensität der Pupillenlichtreaktion am entsprechenden Ort im Gesichtsfeld wider. *LA* linkes Auge, *RA* rechtes Auge

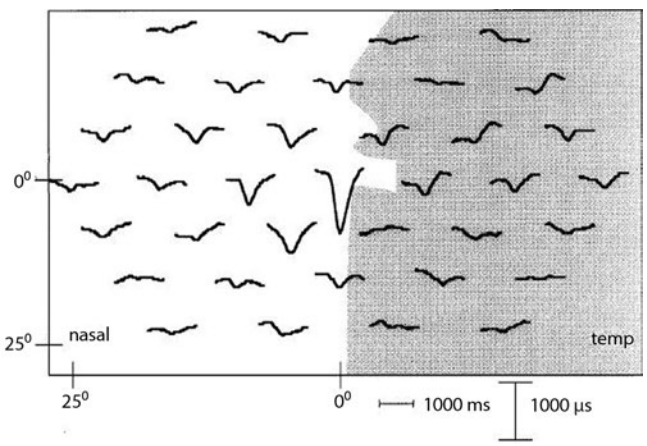

Abb. 3 ▲ Multifokales Pupillogramm vom rechten Auge bei einem Patienten mit Hypophysenadenom mit temporalem Gesichtsfeldverlust. Das perimetrisch nachgewiesene Skotom ist grau hinterlegt. Pupillenantworten sind im Vergleich zur nasalen Gesichtsfeldhälfte erniedrigt. (Mit freundl. Genehmigung aus [32]; http://www.iovs.org/)

M-Sequenz). Man könnte auf diesem Weg ein multifokales ERG ableiten. Der Einsatz der multifokalen Elektroretinographie (mfERG) kann beim Glaukom allerdings nicht funktionieren, da Bipolarzellen, Müller-Zellen und Rezeptoren nicht betroffen werden. Multifokale visuell evozierte Potenziale (mfVEPs) waren bei der Detektion von glaukomatösen Gesichtsfelddefekten erfolgreicher [5]. Auch das „pattern ERG" (PERG) ist grundsätzlich geeignet, um Schädigungen der Ganglienzellschicht nachzuweisen. Es wurde gezeigt, dass beim Glaukom typische Veränderungen im PERG auftreten, die sogar gewissermaßen die Konversion der okulären Hypertension zum Glaukom voraussagen oder für Langzeitverlaufskontrollen angewandt werden können [1]. Auch beim multifokalen PERG (mfPERG) wurden bei Glaukompatienten signifikante Veränderungen, v. a. im Gesichtsfeldzentrum, gefunden, die mit Fortschreiten der Erkrankung zunehmen [28]. Vor diesem Hintergrund hat die multifokale Pupillographie Chancen.

Das Untersuchungskonzept besteht darin, den auswertenden Computer dahingehend zu „täuschen", dass man ihm statt der erwarteten Netzhautantwort den als elektrisches Potenzial „getarnten" Pupillendurchmesser zuspielt. Die M-Sequenz-Technik ist nämlich ein hervorragendes Verfahren, Rauschen bei einer Messung zu reduzieren, was die Elektroretinographie revolutioniert hat. Die Studie von Wilhelm et al. [32] zeigte, dass die multifokale pupillographische objektive Perimetrie einen Gesichtsfelddefekt nachweisen kann. In dieser Studie wurden 37 Hexagone innerhalb des 25°-Gesichtsfelds stimuliert (**Abb. 3**). Das wesentliche Problem bei der Abbildung von Gesichtsfelddefekten war allerdings ein niedriges Signal-Rausch-Verhältnis, das die Dauer der Untersuchung auf 30 min pro Auge verlängerte. In weiteren Arbeiten wurde die Methode durch die Verwendung von zeitlich und räumlich reduzierten multifokalen Stimuli verbessert, was sich auch bei mfVEPs bewährt hatte. Die simultane Stimulation beider Augen mit nur 24 Stimuli innerhalb des 30°-Gesichtsfelds lieferte nach dem Vergleich von Pupillenkontraktionsamplituden bei Glaukompatienten und gesunden Probanden einen AUC-Wert von 0,84, womit sich die diagnostische Genauigkeit derjenigen der automatischen Perimetrie annähert. Wichtig war auch, dass die Untersuchung nur 4 min dauerte [19]. Eine weitere Studie mit mehreren und kleineren

Testbereichen (40 Stimuli innerhalb des 60°-Gesichtsfelds) zeigte, dass die Pupillenantwort bei Glaukompatienten im Vergleich zur Norm bezüglich der Amplitude signifikant geringer, hinsichtlich der Antwortkurve kürzer und bezüglich der Latenz verlängert war. Die höchsten AUC-Werte (0,86 für alle Gesichtsfeldbefunde und 1,0 für mäßig und schwer betroffene Gesichtsfelder) lieferte eine Diskriminanzfunktion, in die sowohl die Pupillenamplitude als auch die Breite der Pupillenantwort einbezogen wurde [3].

» Die multifokale Pupillographie könnte als Ergänzung zur konventionellen Perimetrie dienen

Die Sensitivität der multifokalen Pupillographie erreicht also die diagnostische Genauigkeit von den heutzutage verwendeten Glaukom-Screening-Verfahren und könnte als Ergänzung zur konventionellen Perimetrie dienen. Der Test ist kurz, wenig belastend und nur gering von einer Fehlrefraktion oder einer Linsentrübung abhängig [3]. Die bisherigen Ergebnisse ermutigen zur Weiterentwicklung dieser Methode (u. a. Normwertdefinition, Feinabstimmung von Stimuluseigenschaften).

Melanopsin-Ganglienzellen und Glaukom

Die Pupillenfunktion von Glaukompatienten muss auch im Kontext neuer Erkenntnisse der retinalen Morphologie diskutiert werden [29]. Aktuelle Studien zeigen, dass die okuläre Photorezeption nicht nur auf Zapfen und Stäbchen limitiert ist, sondern dass auch eine kleine Gruppe an intrinsisch photosensitiven retinalen Ganglienzellen (ipRGCs) existiert. Diese retinalen Ganglienzellen sind an der Steuerung des zirkadianen Rhythmus [17] sowie am Pupillenlichtreflex [16] beteiligt, nicht aber am unmittelbaren Sehvorgang. Die Expression des Opsin-Photopigments Melanopsin, dessen spektrales Empfindlichkeitsmaximum bei 479 nm liegt (blaues Licht), ermöglicht offenbar diesen ipRGCs, eigenständig auf Licht zu reagieren. Der volle dynamische Umfang des normalen Pupillenlichtreflexes kann aber nur durch das Zusammenspiel der Melanopsin RGCs und des Zapfen/Stäbchen-Systems erreicht werden, die in ihrer Funktion komplementär sind [18].

Um die Funktion der verschiedenen Photorezeptoren untersuchen zu können, werden in aktuellen Studien farbige Lichtreize zum Auslösen der Pupillenlichtreaktion verwendet. Die Funktion von Stäbchen und Zapfen wird mittels blauer und roter Lichtreize niedriger Intensität untersucht. Die Funktion der Melanopsin-RGCs wird mittels blauer Lichtreize hoher Intensität getestet. Mit letztgenanntem Stimulus konnte selbst bei komplett blinden Retinitis-pigmentosa-Patienten Pupillenantworten nachgewiesen werden [12].

Es wurde die Auffassung vertreten, dass manche Subpopulationen retinaler Ganglienzellen durch das Glaukom bevorzugt betroffen werden [20]. Dieses Konzept führte zur Entwicklung spezifischer perimetrischer Strategien [21]. Es wird zu überprüfen sein, inwieweit die Melanopsin-RGCs spezifisch durch das Glaukom betroffen sind. Die Studie bei Kankipati et al. [10] zeigte, dass die Melanopsin-RGCs bei normalen Probanden nach dem Ausschalten des blauen Lichts eine nachhaltige Pupillenkonstriktion hervorrufen, die „post-illumination pupil response" (PIPR) genannt wurde. Dieses Phänomen (PIPR) war bei Glaukompatienten im Vergleich zu gesunden Probanden signifikant kleiner und korrelierte umgekehrt mit dem Gesichtsfeldverlust. Die Autoren schlagen eine Verwendung dieser Methoden in der Klinik vor. Ihre Sensitivität und Spezifität muss allerdings noch überprüft werden.

Fazit für die Praxis

- **Zwischen der Pupillenreaktion bei Glaukompatienten und gesunden Probanden gibt es signifikante Unterschiede, die diagnostisch verwendet werden können.**
- **Der Swinging-flashlight-Test sollte bei Glaukompatienten routinemäßig angewandt werden – hauptsächlich dann, wenn die perimetrischen Befunde nicht zuverlässig sind.**
- **Die Pupillenperimetrie/-kampimetrie bietet sich als eine „objektive Gesichtsfelduntersuchung" bei Verdacht auf Simulation von Gesichtsfelddefekten an; ihre Rolle in der Glaukomdiagnostik muss noch weiter untersucht werden.**
- **Die multifokale Pupillographie scheint für ein Glaukom-Screening geeignet.**

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Interessenkonflikt. Die korrespondierende Autorin weist für sich und seine Koautoren auf folgende Beziehungen hin: Die Autoren geben an, dass keine Interessenkonflikte in Bezug auf diese Thematik bestehen. Prof. Dr. Ulrich Schiefer hat Consultant-Status gegenüber HAAG-STREIT Inc., Köniz, Schweiz, und der Fa. Servier, Paris, Frankreich.

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Die Fähigkeit zu sehen bringt Selektionsvorteil

Paläontologen aus Berlin bestätigen die bedeutsame Rolle des Augenlichts für den evolutionären Erfolg. Untersucht wurden versteinerte Exemplare verschiedener Klassen wirbelloser Meerestiere, um zeitliche Änderungen in der Vielfalt von blinden und sehenden Gruppen herauszuarbeiten. Der Besitz von Augen lässt sich entweder direkt an den Fossilien erkennen oder über Verwandtschaftsverhältnisse mit rezenten Arten ableiten. Wenn man alle der über 17.000 analysierten Gattungen über erdgeschichtliche Zeiträume betrachtet, zeigt sich in den Gesteinsschichten des Kambriums ein deutlicher Anstieg von sehenden Arten. Dies deuten die Wissenschaftler als einen Effekt des Auftauchens der ersten großen Räuber vor etwa 520 Millionen Jahren. Augen wurden plötzlich gebraucht, sowohl zum Aufspüren von Beute als auch zur rechtzeitigen Flucht. Auch in den langen Zeiträumen nach dem Kambrium war der Besitz von Augen ein Garant für evolutionären Erfolg. In diesem Zusammenhang wurde die Anzahl der Gattungen innerhalb solcher Klassen vergleichen, die sowohl blinde als auch sehende Vertreter beherbergen. Diese detaillierten Analysen innerhalb der Trilobiten, Muscheln, Schnecken und Seesterne sowie deren Verwandten zeigten einheitlich eine Zunahme in der Anzahl von sehenden Gattungen im Vergleich zu den blinden Vertretern. Das Sehvermögen bildet dementsprechend einen Selektionsvorteil in vielen ökologischen Nischen. Die Fähigkeit zu sehen stellte also einen entscheidenden evolutionären Faktor dar.

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NEUROPHTHALMOLOGY

Investigation of summation mechanisms in the pupillomotor system

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Abstract
Background To ascertain whether the pupillary response amplitude shows spatial summation of responses with increasing size of retinal stimulation, and to examine the pupillary responses for evidence of surround inhibition, analogous to that found in the receptive fields of the retinal ganglion cells.
Methods By means of infrared-video-pupillography, the pupil reaction to stimuli of increasing size (1–15°) was measured in 30 normal subjects. Four different retinal locations (0°, 20° and 40° eccentricity on the upper temporal retina and 20° eccentricity on the lower nasal retina) were examined at four different stimulus luminances (17, 47, 87 and 140 cd/m^2).
Results When the average log amplitude of the pupil light reaction from the 30 subjects is plotted as a function of the log area of the stimulus, a bi-linear response is observed, which is most pronounced for the two higher luminances. The intersection points of the two linear responses are 2.01° in the fovea, 2.80° at 20° upper temporal retina, 2.85° at 20° lower nasal retina and 4.86° at 40° upper temporal retina.
Conclusions This study suggests that pupillomotor summation areas consist of both summation and inhibitory zones. They show larger diameters than receptive fields of retinal ganglion cells and do not appear to reflect pupillary summation areas of the pretectal olivary nucleus luminance neurons.

Keywords Pupil · Receptive field · Pupil perimetry · Campimetry

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Introduction

Automated threshold perimetry has become a standard for the evaluation of retinal and optic nerve function in patients with visual field loss. Properties of the stimulus in standard perimetry are based on longstanding experience and knowledge about retinal receptive fields. Hartline in 1940 introduced the concept of a receptive field to describe the spatial properties of retinal ganglion cells in frogs [1]. The classic centre-surround receptive field organization of ganglion cells was discovered some years later in cats [2] and monkeys [3]. Their psychophysical equivalents, i.e., concentric areas of summation and inhibition found using subjective methods, have been named perceptive fields [4]. They are thought to be the basis of the relationship between the threshold luminance and size of stimulus, as described by the Ricco [5] and Piper laws [6] on complete and partial summation.

Pupil perimetry or campimetry represents an objective method of testing the visual field by examining the pupillary light response (PLR) normally to threshold focal light stimuli projected onto the retina. Visual field defects in pupil campimetry can be recognized by a reduced or absent pupil light reaction within these areas. Studies dealing with the clinical applications of pupil campimetry have shown that most diseases affecting the retina and the visual pathway caused pupil field scotomata, which match the defects found in standard perimetry [7–10]. The PLR has been shown in cats and monkeys to be most likely mediated by ON luminance neurons in the pretectal olivary nucleus (PON), which project

to the Edinger-Westphal (EW) nucleus [11–13]. The axons of the EW nucleus synapse on ciliary ganglion neurons that innervate the constrictor muscle of the iris. Newer findings have shown that the preganglionic parasympathetic neurons are not exactly located in the human EW nucleus [14].

The aim of this study was to obtain information about pupillomotor summation areas, i.e., areas of the retina that, when stimulated, show evidence for spatial summation and possibly inhibition of the pupillary response. This has not previously been investigated in humans. To gain information about the spatial characteristics of the pupillary response, we recorded the change in pupil diameter caused by stimuli of increasing size at four different retinal eccentricities, each with four different stimulus luminances.

Materials and methods

Computerized infrared (IR) pupil campimetry was performed in 30 normal subjects aged 18 to 32 years (10 males, 20 females, mean age 27.4±3.1 SD). The subjects were recruited from the staff and students of the University Eye Hospital in Tübingen. The study was approved by the local institutional ethics committee and followed the tenets of the Declaration of Helsinki.

All subjects fulfilled the following inclusion criteria: best-corrected visual acuity 1.0 or better, intraocular pressure below 21 mmHg, intact anterior and posterior segment of the eye, normal 30° visual field, no relative afferent pupillary defect and no history of a serious eye disease. Refractive error was limited to ±4 diopters. In all subjects, only the right eye was tested; the other eye was covered with a black eye patch.

The pupillographic device consisted of a computer, a 19 in. cathode ray tube (CRT) screen for the stimulus presentation and a third monitor for a continuous monitoring of fixation by observation. Stimuli were displayed on the computer screen at a distance of 20 cm from the subject's eye. A small red spot was presented for fixation. Blinds around the device prevented stray light from the room from disturbing the measurement. The pupil reaction was recorded by means of an infrared-sensitive video camera. The pupil edges could be determined by the contrast of the dark fundus and a very light iris infrared reflex. Spatial resolution was about 0.01 mm. During the test, the examiner could observe the quality of fixation, the stimulus sequence, as well as the continuous pupillographic curve. For all stimuli, white light was used and four stimulus intensities were tested (17, 47, 87 and 140 cd/m^2) with a constant background luminance of 2.7 cd/m^2. The stimulus was presented for 200 ms every 2000 ms. The CRT was switched on at least 30 min. before the tests. For each stimulus intensity, 12 stimuli were tested with diameters of: 1°–10° in one degree steps, 12° and 15°, in order of increasing size.

We examined three different locations in the upper temporal visual field quadrant: 0°, 20° and 40° eccentricity, as well as at 20° in the lower nasal visual field quadrant (−20°), alternating between them in order to avoid adaptation.

The perimetry program presented each stimulus at each tested location four times. If the pupil size could not be recorded four times without artefacts (e.g., blinks), the stimulus was presented more often until four valid recordings of the pupil size were obtained for each stimulus. The pupillary response (i.e., the change in pupil diameter) was analysed for each pupil record.

In data analysis, the average of the pupillary response amplitudes of all subjects was calculated for each stimulus location and intensity. The logarithms of these averaged values were plotted against the logarithm of the area of the stimulus and a piecewise linear fit of the data was calculated (broken stick). The break and offset were determined.

The broken-stick fit may fail in the sense that the break lies, e.g., between the lowest two log area values. In this case, the fit is not defined well anymore, because every value for the break between the both lowest values gives the same result. Therefore, in this case the break was set between the two lowest points (0.2).

It is possible that a simple linear regression analysis could perform just as well in terms of statistical significance of the regression analysis. However, in this study, no hypothesis testing was done via inferential statistics and the data were analysed exploratively. If there are no effects, the data should be distributed more or less randomly and no consistent differences should be seen, e.g., when comparing different locations.

Results

The results obtained from the centre of the visual field are shown in Fig. 1, where the average log amplitude of the pupil light reaction (in mm) from the 30 subjects is plotted as a function of the log area (in deg^2) of the stimulus. The four panels show the results for four different intensities: 17, 47, 87 and 140 cd/m^2. The curves have been fit by a broken-stick (or segmented) regression line, often used to fit data that contain a threshold or change point, thus obtaining a bi-linear fitting.

In Figure 2, plotted as in Fig. 1, we show the results obtained at an eccentricity of 20 deg in the upper temporal quadrant of the visual field. In Fig. 3, data at 40° eccentricity in the upper temporal quadrant are presented. Again, the data points can be fit by a bi-linear function, which becomes more evident at higher stimulus intensities. Furthermore, in the periphery, the transition occurs with larger stimulus areas than in the centre of the visual field.

The point of transition (log area deg^2) of the best fit lines for different stimulus intensities and visual field locations is

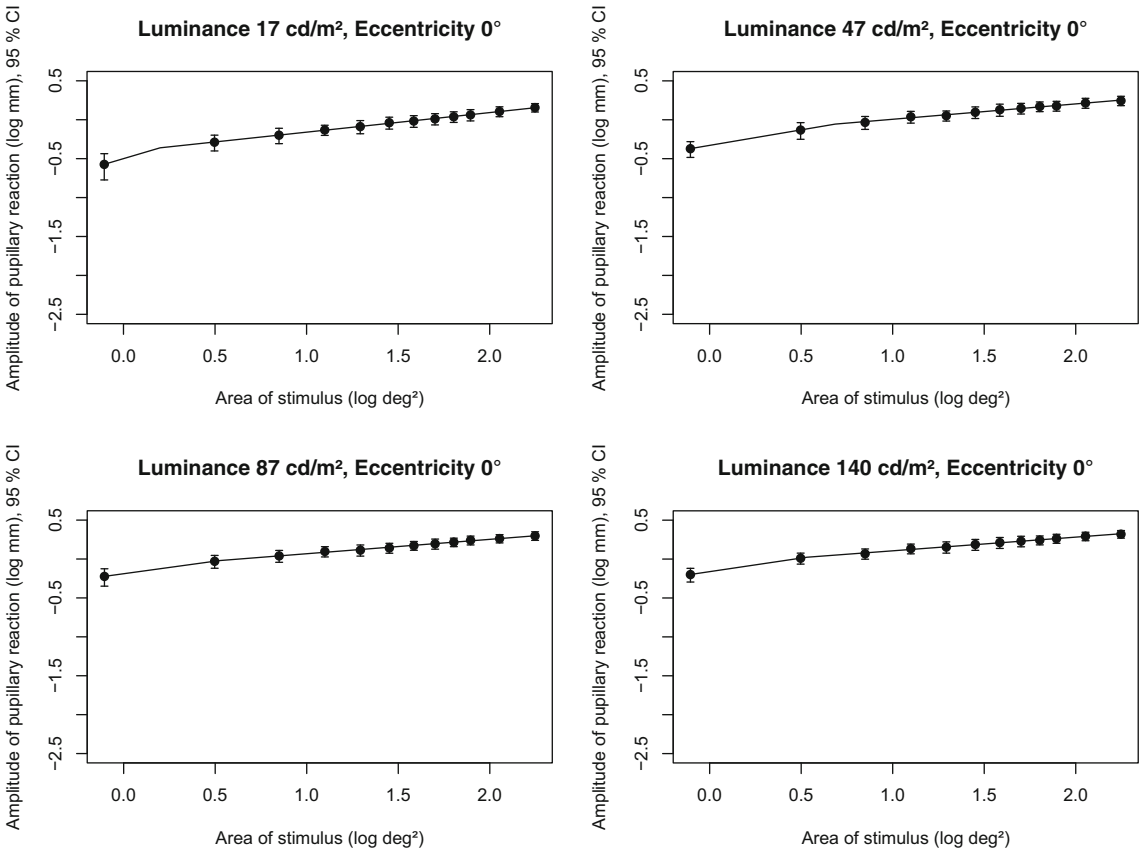

Fig. 1 The average log amplitude of the pupil light reaction in the centre of the visual field is plotted as a function of the log area of the stimulus. The four panels show the mean results and their 95 % confidence intervals (CI) for four different intensities: 17, 47, 87 and 140 cd/m^2

shown in Table 1. In Table 2, we show the results calculated for the corresponding diameter of the centre of the pupillary summation areas.

Discussion

In this study, we examined the pupil responses evoked by increment spots of increasing diameter at different retinal locations and at different stimulus intensities. When the average log amplitude of the pupil light reaction is plotted as a function of the log area of the stimulus, a bi-linear curve can be observed (Figs. 1, 2, 3). The change in the pupil response to smaller and larger stimuli can be particularly observed at higher stimulus intensities (87 and 140 cd/m^2). The gain of the two-phase stimulus–response curve for smaller stimuli is different from that for larger stimuli, and resembles the relationship between threshold energy of light stimulus and stimulus diameter known from psychophysical experiments [2, 3]. In comparing the two methods, however, it should be borne in mind that the psychophysical methods use threshold measurements, whereas here we measured the amplitude of the pupil response. The two-phase response in pupil size indicates that with increasing spot diameter, the response profile of the summation area alters. We hypothesize that the break in this stimulus–response curve might give an estimation of the size of the pupillomotor summation area. When the stimulus becomes larger than the assumed summation area and invades an inhibitory surround, the stimulus response decreases.

Our results indicate that pupillomotor summation areas are larger than receptive fields of a retinal ganglion cell, their size increases with eccentricity in the visual field and the pupillomotor sensitivity of the retina decreases with distance from the fovea, in agreement with our knowledge about retinal receptive fields measured psychophysically [15].

The size of the centre of the pupillomotor summation area for a stimulus intensity 87 cd/m^2 is 2.06, 3.74, 2.33 and 5.46 deg diameter in the centre of the visual field and at 20, −20 and 40°, respectively (Table 2). The size of the on-centre for stimulus intensity 140 cd/m^2 in the centre of the visual field and at the eccentricity of 20, −20 and 40° is 2.08, 2.71, 2.65 and 3.57 deg diameter, respectively (Table 2). In receptive fields of a retinal ganglion cell, the antagonistic surround drops out at low luminances and the size of the centre increases [2, 3]. Our results indicate that the size of the pupillomotor summation area is larger at a stimulus intensity of 87 cd/m^2 than at 140 cd/m^2, i.e., their size also decreases with increasing illumination. On the other hand, with large

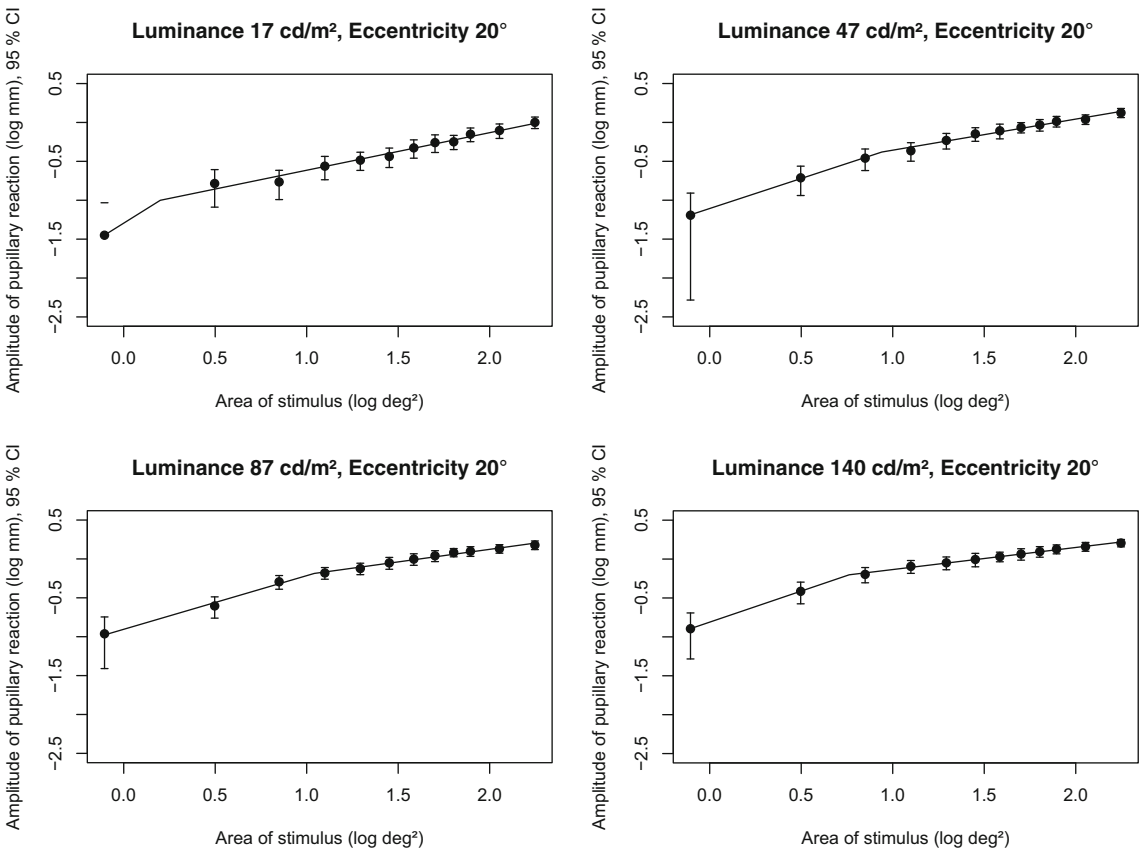

Fig. 2 The average log amplitude of the pupil light reaction at the eccentricity of 20° is plotted as a function of the log area of the stimulus. The four panels show the mean results and their 95 % confidence intervals (CI) for four different intensities: 17, 47, 87 and 140 cd/m^2

and bright stimuli, stray light may become an issue, which can unfortunately never be fully eliminated in pupil measurements. Intraocular scatter of light, however, probably contributes only little to the pupillary response to a focal stimulus: If scatter dominated the response, then any pupillary field defect detected by pupil campimetry would tend to disappear as brighter stimulus intensities were used.

In our study, we find, however, a large variability of pupil responses, especially to the smaller stimuli. In general, we must be aware that pupillary light responses are noisy and variable, both intraindividually and interindividually. The same might be true for pupillary visual field. It might therefore be useful to look at each individual data set to see if a bilinear fit is possible. We did this and found that in approximately 50 % of the subjects, such a bilinear trend could clearly be identified; however, in the other half of the subjects, the variability of the pupillary responses was too marked to establish a bi-linearity. We therefore decided to use the average of all subjects for the calculations. Especially in the 0° position (Fig. 1), it may additionally be criticized that the first line is determined by only one data point. However, the responses for sizes 2 to 11 can almost perfectly be fitted by a straight line; only the smallest stimulus does not fit onto this line. We therefore assume that the pupillomotor summation area is larger than the first stimulus and smaller than the second. Of course, we cannot state that the numbers resulting from the data analysis do really represent the summation area for the pupillary light response; however, we get at least an idea about the range where we have to assume the sizes of the pupillomotor summation areas. Variability of pupillary responses is much more pronounced than psychophysical thresholds.

Additionally, we have to be aware that pupillary responses might be generated by two different systems with different summation areas: by the rod and cone system and by the melanopsin ganglion cells that have been shown to be directly photosensitive [16]. It is probable that together, the rod/cone and melanopsin systems provide the full dynamic range of the normal pupillary reflex [17]. At a low stimulus intensity that is focal, most of the pupil response will likely be photoreceptor-mediated pupil responses, but at the brighter light intensities, there may be also additional intrinsic activation. However, melanopsin exerts an influence only at high irradiances and responds better to sustained stimuli than short stimuli. Thus, the light stimuli used in our experiments were probably below the threshold of the photosensitive ganglion cells and focused on the rod-cone system.

There is no information about pupillomotor summation areas in the literature. Comparison of the pupillary and

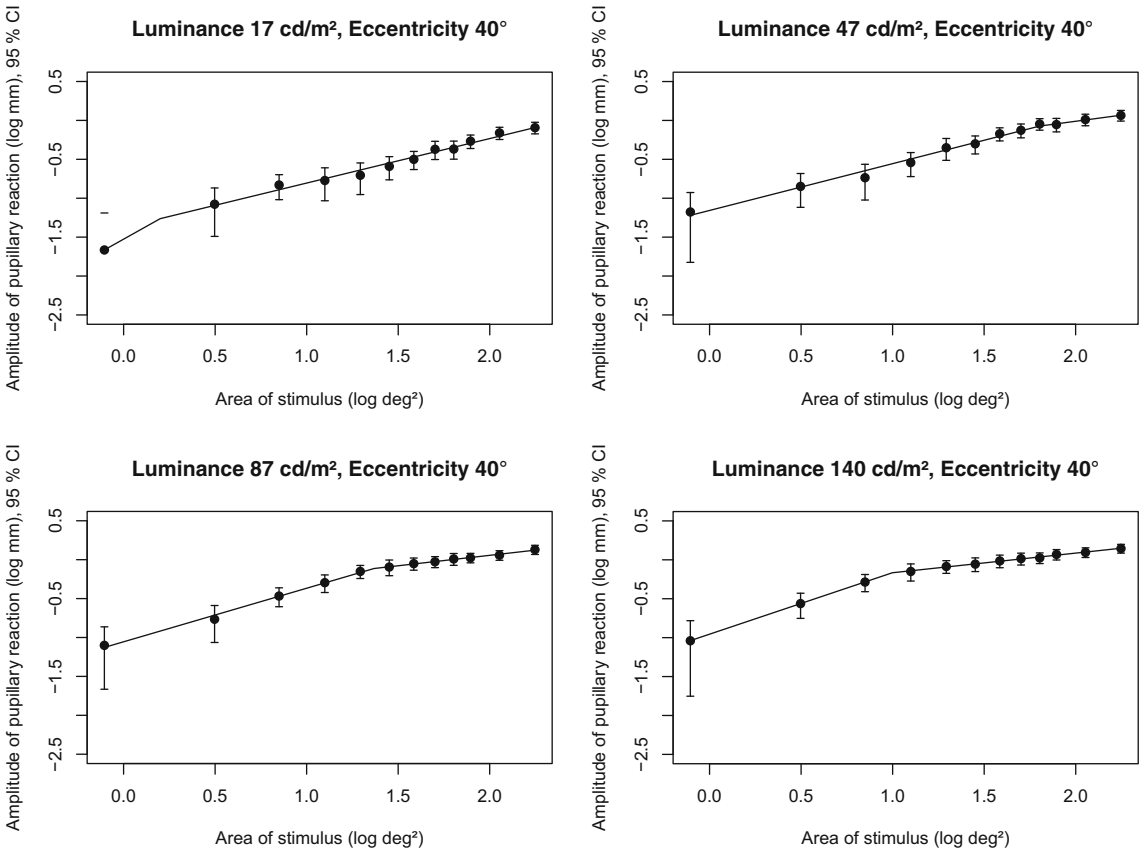

Fig. 3 The average log amplitude of the pupil light reaction at 40° eccentricity is plotted as a function of the log area of the stimulus. The four panels show the mean results and their 95 % confidence intervals (CI) for four different intensities: 17, 47, 87 and 140 cd/m^2

sensory threshold in relation to the area, duration and localization of the stimulus at different levels of adaptation has been studied in the fovea and at 20° nasal by Alexandridis [18]. His results show that threshold measurements of the pupillomotor response curve both in peripheral and central stimulation are in agreement with Ricco's law up to a stimulus size of 30° diameter and that larger stimuli follow Piper's law. With sensory threshold measurements, Ricco's law holds only for smaller stimulus sizes, especially in the periphery. However, Alexandridis investigated summation effects of pupillomotor threshold, but did not define any receptive fields. The experiments of Krastel et al. suggest that the pupil is influenced by opponency mechanisms. In their study, the thresholds for the phasic pupil light reflex are shown to closely parallel the peaks and troughs of the sensory sensitivity curve ascribed to opponency [19].

In conclusion, the results of our study show that the pupillary light reaction is related to the size, intensity and retinal location of the stimulus. The relationship between size and pupil reaction can with caution be considered as biphasic and can be fit by two intersecting lines. These results are reminiscent of receptive field behavior, and suggest that pupillomotor summation areas might exist within the pupillary pathway. They show larger diameters than the receptive fields of the retinal ganglion cells, but respect the summation rules valid for the retinal receptive fields. If this is so, stimuli used in

Table 1 Mean break (log area deg^2)

Stimulus intensity [cd/m2]	Eccentricity [deg]			
	0	20	–20	40
17	0.20	0.20	0.20	0.20
47	0.69	0.94	1.29	1.80
87	0.52	1.04	0.63	1.37
140	0.53	0.76	0.74	1.00

Table 2 Diameter of pupillomotor summation areas (deg)

Stimulus intensity [cd/m2]	Eccentricity [deg]			
	0	20	−20	40
17	1.42	1.42	1.42	1.42
47	2.49	3.33	5.00	9.00
87	2.06	3.74	2.33	5.46
140	2.08	2.71	2.65	3.57
Mean of all stimulus intenstities	2.01	2.80	2.85	4.86

pupil perimetry should be larger than the stimuli used in standard visual perimetry to counteract this difference.

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The authors confirm to have full control of all primary data and agree to allow Graefe´s Archive for Clinical and Experimental Ophthalmology to review their data upon request.

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Farmakologické testy u Hornerova syndromu - kazuistika.

Cesk Slov Oftalmol 2016;72(2):39-43

FARMAKOLOGICKÉ TESTY U HORNEROVA SYNDROMU

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SOUHRN

V kazuistice je prezentován případ pacientky, která byla na naše oddělení odeslána pro rok trvající anizokorii. Kromě anizokorie pacientka žádné subjektivní potíže neměla. Zornice na pravém oku byla o více než 1 mm širší než zornice vlevo. Přímá fotoreakce byla výbavná na obou očích, na levém oku byl patrný dilatační deficit. Byla přítomna lehká ptóza horního víčka vlevo. Nález na předním i zadním segmentu byl na obou očích bez patologie, jen na levém oku byla duhovka poněkud světlejší. Oční nález ukazoval na Hornerův syndrom, jehož příčinu se však nepodařilo zjistit. V kazuistice je poukázáno na problémy spojené s farmakologickými testy pro průkaz Hornerova syndromu a jsou uvedeny alternativy kokainového testu s ohledem na látky, které jsou v současné době v České republice dostupné.
Klíčová slova: anizokorie, Hornerův syndrom, kokainový test, fenylefrin

SUMMARY

PHARMACOLOGICAL TESTS FOR HORNER SYNDROME – CASE REPORT

The case report presents a patient, who was examined at our department due to anisocoria that was present for more than one year. Besides the anisocoria the patient had no other pathological symptoms. The pupil on the right eye was larger than on the left eye by more than 1mm. Photoreaction was present on both eyes with a dilatation deficit on the left eye. There was also a slight ptosis on the left. The anterior and posterior eye segment was normal, only the iris of the left eye was slightly decoloured. The ophthalmological finding was pointing to Horner syndrome on the left side. The cause of the syndrome was not found. The case report discusses current problems of pharmacological pupillary tests used in Horner syndrome. Alternatives to the standard cocaine test are proposed, with respect to substances currently available in the Czech Republic.
Keywords: anisocoria, Horner syndrome, cocaine test, phenylephrine

Čes. a slov. Oftal., 72, 2016, No. 2, p. 39–43

ÚVOD

Hornerův syndrom shrnuje příznaky jednostranné obrny sympatického nervového systému. Na postižené straně je zornice pro inaktivitu musculus dilatator pupillae užší a je přítomna ptóza horního víčka v důsledku parézy Müllerova svalu. Dolní víčko naopak lehce vystoupí, protože jsou postiženy i sympatikem inervované retraktory dolního víčka. Enoftalmus je tedy pouze zdánlivý, způsobený zúžením oční štěrbiny z obou stran, a z klasické triády příznaků „ptóza, mióza, enoftalmus“ dnes popisujeme jen první dva [10, 11].

Hornerův syndrom se vyskytuje relativně vzácně, proto je důležité si nejdříve ověřit, zda se o toto onemocnění opravdu jedná. To je možné pomocí farmakologických pupilárních testů, z nichž některé dokáží také rozlišit preganglionární nebo postganglionární postižení. Spolehlivě lze Hornerovu zornici bez ohledu na lokalizaci léze identifikovat kokainovým testem: po instilaci 5% kokainu do obou očí se zdravá zornice po 60 minutách rozšíří, neboť kokain zablokuje zpětnou resorpci noradrenalinu do nervových zakončení a tím prodlouží jeho působení na sval. U Hornerova syndromu je ale uvolňování tohoto neurotransmiteru sníženo nebo zcela chybí a kokainový blok je proto bez efektu. Hornerova zornice se po aplikaci kokainu nerozšíří.

Obstarat kokainové kapky pro průkaz Hornerova syndromu bylo dříve relativně snadné, protože se kokain v očním lékařství používal jako anestetikum. Dnes je však kokain v praxi obtížně dostupný a jeho skladování je vázáno přísnými pravidly pro zacházení s omamnými látkami. Také další látky jako například hydroxyamfetamin, pholedrin nebo tyramin, které se pro farmakologické testy v minulosti používaly, nejsou v lékárnách dostupné. Proto se začaly při diagnostice Hornerova syndromu zkoušet jiné substance, které jsou snadno a rychle k dispozici. Jedná se zejména o nepřímá sympatomimetika působící jako agonisté na receptorech pro noradrenalin. Z nich se v zahraničí etabloval apraclonidin, vyráběný jako antiglaukomatikum ve formě HVLP přípravku, který u nás však není registrovaný. V České republice lze z alternativních surovin sehnat pouze adrenalin nebo fenylefrin. Hyfroxyamfetamin, pholedrin, tyramin ani apraclonidin předepsat nelze.

Fenylefrin je obsažen v HVLP přípravku Neosynephrin (10% roztok fenylefrinu), který má většina očních lékařů v ordinaci. 1% roztok fenylefrinu působí na principu denervační hypersenzitivity musculus dilatator pupillae k jeho specifickému neurotransmiteru nebo farmakologickým agonistům, která se vyvine při postganglionární poruše sympatické inervace. Hornerova zornice by se měla po instilaci 1%

fenylefrinu rozšířit, naopak zdravá zornice nikoli. V následující kazuistice bych ráda popsala příklad využití fenylefrinu při farmakologickém průkazu Hornerova syndromu a zároveň diagnostické rozpaky, které mohou anizokorii způsobenou Hornerovým syndromem provázet.

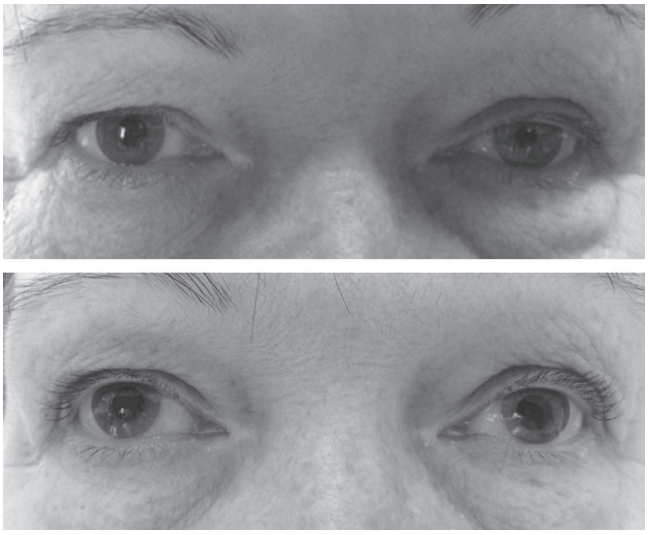
KAZUISTIKA

V lednu 2015 se na naše oddělení dostavila šedesátiletá pacientka za účelem vyšetření anizokorie, která u ní byla zjištěna náhodně již před rokem při předpisu brýlí u sektorového oftalmologa. Pacientka žádné subjektivní potíže neměla, celkově se léčila jen s hypertenzí. Zornice na pravém oku byla širší než na oku levém. Během posledního roku paní absolvovala řadu vyšetření, která však nevedla ke stanovení diagnózy ani příčiny anizokorie. Za patologickou byla vždy považována širší zornice na pravém oku.

Po zjištění anizokorie byla pacientka odeslána svým očním lékařem nejdříve k sektorovému neurologovi, kde byla v objektivním nálezu zjištěna distální senzomotorická polyneuropatie a na magnetické rezonanci (MR) hlavy popsány nespecifické hyperintenzity v mozku supratentoriálně. Pro tento nález byla pacientka odeslána do centra pro roztroušenou sklerózu naší nemocnice, kde bylo toto onemocnění vyloučeno, změny na MR označeny spíše jako degenerativní a k rozšíření diagnostiky anizokorie doporučen odběr protilátek proti boreliím a ultrazvuk magistrálních tepen. Nález na krčních tepnách byl v pořádku, IgG protilátky proti Borrelia burgdorferi však vyšly pozitivní, proto byla pacientka odeslána na kliniku infekčních chorob. Tam byla hladina protilátek proti boreliím označena za „běžnou“, ale s ohledem na anizokorii doporučena lumbální punkce, která by umožnila stanovit hladinu protilátek přímo v mozkomíšním moku. Pacientka se však lumbální punkce bála, proto byla svou oční lékařkou odeslána ještě na konzultaci k nám.

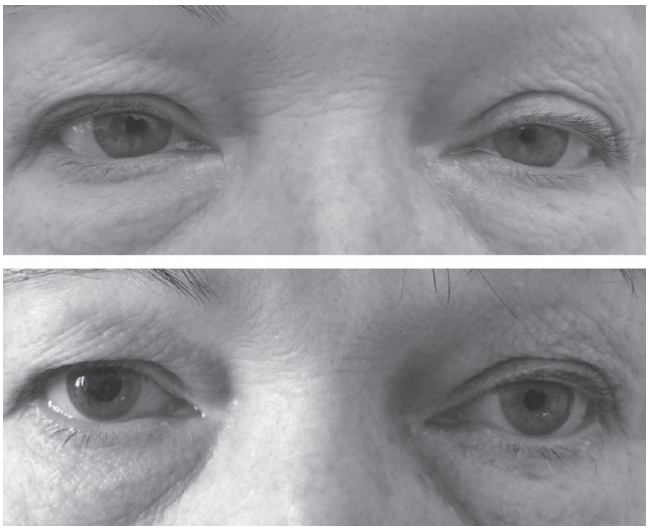
Při vyšetření na našem pracovišti byla zornice na pravém oku širší, rozdíl v průměru zornice pravého a levého oka byl více než 1 mm. Přímá fotoreakce byla přítomna na obou očích, na levém oku byl patrný dilatační deficit. Horní víčko levého oka bylo lehce pokleslé a na cílený dotaz pacientka uvedla, že si podle fotek poklesu horního víčka sama všimla. Okulomotorika byla v normě, diplopii pacientka neudávala. Zraková ostrost byla na obou očích 1,0 naturálně, nitrooční tlak v normě a zorné pole intaktní. Nález na předním i zadním segmentu byl na obou očích bez patologie, byla patrná jen diskrétní heterochromie, světlejší byla duhovka na oku levém.

Oční nález ukazoval na Hornerův syndrom vlevo. Pro průkaz tohoto syndromu by se měl v ideálním případě provést kokainový test. Když jsem však v naší ústavní lékárně začala shánět kokain, zjistila jsem, že by se musel kokain speciálně objednat, kapky by stály 1 500 Kč a jeho předpis by byl značně komplikovaný. Začala jsem tedy hledat jinou alternativu. V západní Evropě používaný apraclonidin není v ČR registrovaný a mimořádný dovoz jednoho balení těchto kapek by byl nereálný. Rozhodla jsem se tedy vyzkoušet 1% roztok fenylefrinu, který jsem si nechala připravit v lékárně naředěním 10% fenylefrinu (Neosynephrine-POS). Změřila jsem průměr zornice pravého a levého oka za stejných světelných podmínek před aplikací a jednu hodinu po aplikaci jedné kapky 1% roztoku fenylefrinu do spojivkového vaku obou očí. Před aplikací byl průměr zornice pravého oka 5 mm, levého oka 3 mm. Hodinu po aplikaci 1% fenylefrinu byl průměr zornice pravého oka 5 mm, levého 5 mm a rovněž se zlepšil pokles horního víčka vlevo (obr. 1). Výsledek testu ukázal na postganglionární lézi sympatiku vlevo.



Obr. 1 Průměr zornice pravého oka byl před aplikací 1% fenylefrinu 5 mm, levého oka 3 mm (nahoře). Hodinu po aplikaci 1% fenylefrinu se průměr zornice pravého oka nezměnil, na levém oku se zornice rozšířila a rovněž se zlepšil pokles horního víčka vlevo (dole). Výsledek testu ukázal na postganglionární lézi sympatiku vlevo

Pro potvrzení efektu 1% fenylefrinu jsem se ze studijních důvodů přece jen rozhodla provést také kokainový test. Po



Obr. 2 Před aplikací kokainu měla zornice na pravém oku šířku 3 mm, na levém oku 2 mm (nahoře). Hodinu po nakapání kokainu se pravá zornice rozšířila na 5 mm, průměr levé zornice se nezměnil (dole). Kokainový test potvrdil, že se jedná o Hornerův syndrom

složitém vyřizování mi bylo povoleno vyzvednout si mimořádně speciální recept na opiáty, na očním už totiž žádné takové recepty nemáme. V lékárně jsem pak objednala přípravu 5% kokainových očních kapek. Kokainový test jsme s pacientkou provedly s odstupem jednoho měsíce od předchozího testu. Opět jsem změřila šíři zornice obou očí, aplikovala jsem do spojivkového vaku každého oka jednu kapku 5% kokainu a průměr zornice změřila znovu po jedné hodině za stejných světelných podmínek. Před aplikací kokainu měla zornice na pravém oku šířku 3 mm, na levém oku 2 mm. Hodinu po nakapání kokainu se pravá zornice rozšířila na 5 mm, průměr levé zornice se nezměnil (obr. 2). Kokainový test jednoznačně potvrdil, že se jedná o Hornerův syndrom.

U pacientky tedy byla diagnostikována postganglionární forma Hornerova syndromu. Pro doplnění diagnostiky byl proveden rentgen plic, který neprokázal žádné patologické změny na plicích nebo v oblasti horní hrudní apertury, a vyšetření štítné žlázy, to bylo rovněž v normě. Protože byl Hornerův syndrom přítomný již více než rok, na což ukazovala i lehká heterochromie duhovky, dosavadní vyšetření nezjistila žádnou patologii a pacientka byla bez jiných obtíží nebo příznaků, rozhodla jsem se stav jen sledovat. Zároveň nebyl důvod pro provedení zvažované lumbální punkce na klinice infekčních chorob.

DISKUSE

Nejnápadnějšími příznaky Hornerova syndromu jsou mióza a ptóza se zúžením oční štěrbiny. Fotoreakce je u Hornerova syndromu dobře výbavná, protože parasympatikus a tedy funkce musculus sphincter pupillae je intaktní. Je však přítomný dilatační deficit, který lze při vyšetření zornicových reakcí ve tmě zaregistrovat buď pomocí infračervené kamery, nebo pozorováním zornice při použití druhého, slabšího zdroje světla, kterým osvětlujeme zornici zespodu. Anizokorie je u Hornerova syndromu měnlivá, vždy větší za šera nebo při emocích, protože se zdravá zornice více rozšíří [11].

Pokud leží léze před bifurkací karotidy, tedy před odstupem sympatických vláken pro sekreci potu a regulaci teploty v obličeji, může se k projevům Hornerova syndromu přidat anhidróza a zarudnutí poloviny obličeje na postižené straně. U vrozených a perinatálně vzniklých obrn sympatiku se vyskytuje heterochromie duhovky. Postižená duhovka si totiž uchová šedomodrou barvu novorozenecké iris, protože rozvoj pigmentace duhovky vyžaduje intaktní sympatickou inervaci. Také u dospělého s dlouhotrvajícím Hornerovým syndromem dochází po letech ke ztrátě pigmentu duhovky [11].

Dráha sympatiku se táhne od hypothalamu k druhému hrudnímu obratli, ve stěně karotidy zpět vzhůru přes sinus cavernosus, dále spolu s n. abducens a n. ophthalmicus skrz orbitu až k musculus dilatator pupillae a Müllerovu svalu horního víčka. V jejím průběhu dochází k přepojení na dvou místech – v centrum ciliospinale a v ganglion cervicale superius. Příčina Hornerova syndromu se může nacházet v oblasti centrálního neuronu (od hypothalamu k centrum ciliospinale), preganglionárního – prvního periferního neuronu sympatiku (mezi centrum ciliospinale a ganglion cervicale superius) nebo postganglionárního – druhého periferního neuronu sympatiku (mezi ganglion cervicale superius a duhovkou).

Možných příčin syndromu je mnoho a zahrnují jak afekce naprosto benigní, tak i procesy velmi závažné, jako je disekce karotidy nebo nádory. Jejich došetření je však často obtížné. Pomoci může anamnéza nebo přidružené symptomy (tab. 1). Nicméně až u třetiny pacientů se i přes adekvátní diagnostiku pomocí zobrazovacích metod nepodaří příčinu zjistit. V takovém případě je vhodné pátrat, jak dlouho je Hornerův syndrom u pacienta přítomen, například pomocí starších fotek. Obecně, trvá-li Hornerův syndrom déle než rok, je nebezpečná příčina velmi nepravděpodobná. Pokud je přítomný kratší dobu, je vhodné provést zobrazení celého průběhu sympatické dráhy [11].

Tab. 1 Příčiny Hornerova syndromu a příslušné doprovodné příznaky a nálezy

Léze mozkového kmene	nystagmus, dysmetrie sakád, poruchy čití, hamiataxie
Syringomyelie	porucha vnímání bolesti a teploty, svalová atrofie
Výhřez ploténky	parézy, poruchy čití
Thoracic outlet syndrom	poruchy čití, obrny horních končetin
Tumor mediastina	kašel, městnání
Poškození plexus brachialis	parézy, předchozí trauma
Neuroblastom	palpační nález
Struma	změny hormonů štítné žlázy, palpační nález
Krční lymfom	palpační nález
Laterální krční cysta	palpační nález
Disekce karotidy	bolest, přechodné poruchy vidění a obrny
Karcinom paranazálních dutin (PND)	symptomy onemocnění PND
Tumor sinus cavernosus	paréza n. VI, poruchy čití v oblasti 1. větve n. V
Cluster headache	silné bolesti poloviny hlavy

Obecnou vlastností sympatického i parasympatického nervového systému je tzv. denervační supersenzitivita. Podle ní se orgán, který ztratí svou normální inervaci, stane více citlivým k chemickému transmiteru uvolňovanému z příslušných nervových zakončení. Při snížení nebo chybění impulzů ze sympatiku dochází k „up-regulaci" α1-receptorů musculus dilatator pupillae a tedy jeho větší citlivosti k noradrenalinu nebo jeho agonistům – sympatomimetikům [6].

Právě na podkladě denervační supersenzitivity dojde u postganglionární formy Hornerova syndromu k rozšíření zornice i po aplikaci ředěného roztoku fenylefrinu do spojivkového vaku. U zdravé osoby nebo pacienta s centrální či preganglionární formou Hornerova syndromu se zornice nerozšíří. U naší pacientky se zornice na levém oku rozšířila o 2 mm, na pravém oku se nezměnila, jedná se tedy o postganglionární postižení sympatické inervace vlevo. Zároveň se zlepšila ptóza horního víčka, což můžeme interpretovat rovněž jako důsledek adrenergního působení fenylefrinu.

Srovnání 1% fenylefrinu s 1% hydroxyamfetaminem při průkazu postganglionární léze sympatiku u Hornerova syndromu provedla ve své studii profesorka Danesh-Meyer. U 14 pacientů s Hornerovým syndromem způsobil fenylefrin rozšíření zornice u postganglionární formy v průměru o 1,9 mm, u léze centrálního nebo preganglionárního neuronu činila změna šíře zornice jen 0,25 mm a 0,5 mm. Šířka zdravé zornice se ve všech případech změnila v průměru pouze o 0,2 mm. Senzitivita fenylefrinu dosáhla v této studii 81 %, specificita 100 %. Pro srovnání senzitivita 1% hydroxyamfetaminu byla v této studii 93 % a specificita 83 %. 1% fenylefrin tedy představuje spolehlivou náhradu dříve používaného hydroxyamfetaminu, který není v lékárnách dostupný [3].

Alternativou k fenylefrinu může být v našich podmínkách další sympatomimetický preparát, a sice adrenalin. Ten v ředění 1‰ nepůsobí na šíři zornice na zdravém oku, ale podobně jako fenylefrin rozšíří díky denervační přecitlivělosti zornici s postganglionární lézí krčního sympatiku. Limitací je jedině jeho poněkud horší prostupnost rohovkou. Adrenalin 1‰ je povinnou součástí všech resuscitačních balíčků a měl by tedy být dostupný okamžitě. Cena jedné ampulky je pouhých 24 Kč.

Na principu denervační supersenzitivity působí na duhovku u Hornerova syndromu také sympatomimetikum apraclonidin 0,5%, který je v západní Evropě dostupný jako antiglaukomatikum Iopidine® od firmy Alcon. Zatímco u zdravé zornice nedojde k žádnému – nebo jen minimálnímu – rozšíření, Hornerova zornice se rozšíří výrazně a rovněž se zlepší ptóza. Kromě snadné dostupnosti spočívá výhoda testu s apraclonidinem také v tom, že lze změnu v šířce zornice odečíst již za 15 minut [1, 6]. V zemích, kde je apraclonidin registrovaný, je tento preparát nejlepší a nejjednodušší alternativou ke kokainu při farmakologickém průkazu Hornerova syndromu.

Námitkou proti užití apraclonidinu, fenylefrinu nebo jiného α1-sympatomimetika může být, že se zmíněná přecitlivělost adrenergních receptorů sympatiku vyvíjí pomalu. Je sice prokazatelná již za několik dnů, ale plně vyvinutá je až za 1–2 týdny [8]. Proto může být výsledek farmakologického testu u časné formy Hornerova syndromu falešně negativní [4, 7]. Například Falzon a kol. popsali případy dvou pacientů s postganglionární formou Hornerova syndromu, u kterých nebylo možné denervační supersenzitivitu prokázat pomocí 1% phenylephrinu po třech dnech trvání potíží, nýbrž až deset dní po rozvoji příznaků [5]. Na druhou stranu existují však i práce, které dokazují, že se denervační supersenzitivita rozvine naopak velmi rychle, dokonce během několika hodin [1]. Rozřešení by přinesla jedině studie s velkým počtem pacientů, což je však v případě Hornerova syndromu obtížné. Nicméně, jedná-li se o mladého člověka s anamnézou úrazu, bolestmi hlavy a podezřením na Hornerův syndrom, je vhodné co nejrychleji provést magnetickou rezonanci hlavy a krku, a to i bez farmakologických testů zornicových reakcí k vyloučení závažné disekce karotidy, která je nejčastější příčinou cévní mozkové příhody u pacientů mladších 50 let.

Na rozdíl od dospělých platí u dětí nadále, že je při podezření na Hornerův syndrom indikován kokainový test (u dětí do 1 roku s 2,5% kokainem), protože α1-sympatomimetika u nich mohou způsobit pokles krevního tlaku. Správná diagnóza Hornerova syndromu je u dětí důležitá zejména s ohledem na nebezpečí neuroblastomu [12].

ZÁVĚR

Přes veškeré nesnáze jsem se u naší pacientky k potvrzení diagnózy Hornerova syndromu dopracovala a mohla jsem ji uklidnit, že nalezení nějaké závažné příčiny je po tak dlouhé době spíše nepravděpodobné. Touto kazuistikou bych však chtěla upozornit hlavně na to, že kokainový test uvedený v učebnicích jako klasický test k průkazu Hornerova syndromu dnes většina oftalmologů v Evropě již neprovádí. Obtížná dostupnost kokainu, jeho vysoká cena a potíže s proskripcí jsou pro běžného oftalmologa zcela limitující. Snahou je tedy využívat pro diagnostiku Hornerova syndromu snadněji dostupné substance, jako je například fenylefrin, adrenalin nebo apraclonidin.

A jak by měl v dnešní době český oftalmolog postupovat při diagnostice Hornerova syndromu u dospělých pacientů? Doporučila bych správně vyšetřit zornicové reakce a při podezření na Hornerův syndrom provést test s 1% roztokem fenylefrinu nebo 1‰ adrenalinem. Pokud se Hornerův syndrom potvrdí, jsou v naší zemi pacienti z očního pracoviště odesílaní nejčastěji k neurologovi, který by se měl pokusit na základě anamnézy a přidružených symptomů odhadnout možnou příčinu Hornerova syndromu a podle toho indikovat další vyšetření, nejčastěji magnetickou rezonanci. Jedná-li se o Hornerův syndrom trvající méně než jeden týden, je nutné provést neurologické vyšetření akutně [11]. Nejsou-li k dispozici kapky pro potvrzení Hornerova syndromu, nemělo by se u pacientů s akutním, bolestivým nebo traumatickým rozvojem příznaků na výsledek farmakologického pupilárního testu čekat a oddalovat tak provedení zobrazovací metody [2].

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Oznámení

Prof. MUDr. Zoltán Oláh, DrSc. - osemdesiatpäť ročný

Profesor Oláh sa narodil v Komárne 27. 4. 1931 a prežil tu i svoje detstvo a adolescentný vek. V Komárne absolvoval gymnázium a potom hneď nastúpil na Lekársku fakultu UK v Braatislave, ktorú ukončil v roku 1956. Už počas štúdia sa venoval svojej obľúbenej anatómii a na Ústave anatómie pobudol celý rok po skončení štúdia. Morfologické princípy sa mu stali základom ďalšieho vedeckého výskumu na Očnej klinike, kde nastúpil v roku 1957 a zostal jej verný podnes. Z morfologicko-histologických problémov oka obhájil kandidátsku dizertáciu v roku 1965 na tému *„Štúdium priebehu včasných štádií reaktívnych zmien skléry po perforačnom poranení"*. Štúdium morfológie malígnych procesov vyústilo do habilitácie v roku 1970 témou *„Morfologický a klinicko-patologický rozbor výskytu a prognózy malígnych melanómov v uveálnom trakte oka".* A aby nebolo mikroskopie málo, tak do tretice v roku 1979 obhájil na podobnú tému (*Problémy hojenia a citia rán v oku*) doktorskú dizertačnú prácu.

Prednostom kliniky oftalmológie UK sa stal v roku 1976 a v roku 1981 bol menovaný za riadneho profesora oftalmológie. Pracovisko viedol až do roku 1997, odkedy pracoval až do roku 2008 na klinike na plný pracovný úväzok. Od tohto obdobia až doteraz chodí pravidelne 1–2x týždenne na kliniku a ako emeritný profesor odovzdáva svoje bohaté skúsenosti mladej oftalmologickej generácii.

Profesor Oláh bol mimoriadnym zjavom na oftalmologickej scéne bývalého Československa a neskôr Slovenska. Smelo, i keď skromne ho možno prehlásiť za jedného zo zakladateľov oftalmomikrochirurgie, najmä v oblasti inovácie operácie katarakty a implantácie vnútroočnej šošovky, operácií glaukómu, komplikovanejších úrazov oka, odlúpenej sietnice a vnútroočných nádorov. Bol pionierom v zavádzaní laserovej chirurgie a výpočtovej techniky do dennej praxe.

Vedecko-publikačne bol mimoriadne aktívny. Odprednášal na rôznych fórach doma a v zahraničí cca 450 prác a okolo 200 ich aj publikoval. Na rôzne témy vydal asi 10 monografií a vysokoškolských učebníc samostatne ako so svojimi spolupracovníkmi. Obdivuhodným fenoménom je pokračovanie experimentálnej práce so svojím spolupracovníkom doc. Veselovským v oblasti biochémie glaukómu i vo svojom vysokom veku.

Málokto sa môže pochváliť svojou vedeckou a pedagogickou školou, tak ako prof. Oláh. Za svojho života vyrástlo pod jeho vedením 5 univerzitných profesorov, 4 docenti a 25 doktorandov. Predstavuje to takmer celú graduovanú oftalmologickú kapacitu Slovenska za posledné desaťročia.

Okrem uvedenej plodnej liečebno-preventívnej, vedecko-výskumnej a pedagogickej činnosti sa venoval aj organizačnej práci. Bol dlhé roky predsedom Slovenskej oftalmologickej spoločnosti, členom výboru Československej oftalmologickej spoločnosti a zástupcom šéfredaktora časopisu Česko-slovenská oftalmologie. Podieľal sa na organizácii početných kongresov a rozličných odborných oftalmologických podujatí.

Vážený pán profesor, milý priateľ Zolo,

keď sa veľkého Izáka Newtona opýtali, čomu vďačí za svoje grandiózne dielo, odpovedal: *„Stál som na pleciach svojich predchodcov."* My Ti za celý Tvoj celoživotný výkon ďakujeme a s hrdosťou na Tvoje dielo nadväzujeme. Zároveň Ti želáme pevné zdravie a stále ten mladícky elán v odovzdávaní svojich skúseností svojim kolegom.

Prof. MUDr. Anton Gerinec, CSc.
Prof. MUDr. Peter Strmeň, CSc.
Doc. MUDr. Vladimír Krásnik, Ph.D.
Bratislava 5. 4. 2016

G. Skorkovská K, Wilhelm H.

Afferent pupillary disorders in postchiasmal lesions of the visual pathways.

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1863 von Karl Wilhelm v. Zehender im Zusammenwirken mit Theodor Sämisch und Albrecht von Graefe gegründet, um den Bedürfnissen des am Patienten tätigen Augenarztes in Klinik und Praxis zu dienen. Die Leser werden seitdem fortlaufend über Ergebnisse und Probleme der klinischen Forschung durch die Publikation von Originalarbeiten, Beobachtungen und Übersichtsartikeln unterrichtet.

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Afferente Pupillenstörungen bei postchiasmalen Läsionen der Sehbahn

Afferent Pupillary Disorders in Postchiasmal Lesions of the Visual Pathways

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Schlüsselwörter
- Pupille
- homonyme Hemianopsie
- Tractus opticus
- Sehbahn
- Pupillenperimetrie
- relativer afferenter Pupillendefekt

Key words
- pupil
- homonymous hemianopia
- optic tract
- visual pathways
- pupil perimetry
- relative afferent pupillary defect

Zusammenfassung

Klassischerweise betrachtet man die Pupillenbahn als einfachen Reflexbogen, bestehend aus den retinalen Ganglienzellen, mesenzephalen Interneuronen, N. oculomotorius und kurzen Ziliarnerven. Jedoch gibt es im Aufbau der afferenten Pupillenbahn einige Besonderheiten, die man bei der Beurteilung von typischen Krankheitsbildern mit Pupillenstörungen berücksichtigen muss und die bei der Topodiagnostik der Läsion sehr hilfreich sein können. Zusätzlich haben Untersuchungen von Patienten mit Läsionen der postgenikulären Sehbahn gezeigt, dass auch dabei Störungen der Pupillenlichtreaktion auftreten können. Die Pupillomotorik wird also nicht nur durch subkortikale Zentren gesteuert, sondern manche Komponenten der Pupillenreaktion sind auch durch die Sehrinde deutlich beeinflusst. Ziel dieses Beitrags ist es, verschiedene Begriffe und Befunde wie relativer afferenter Pupillendefekt und Hemihypokinesie der Pupille zu erklären.

Abstract

Classically, the pupillary pathway is considered as a simple reflex arc comprising retinal ganglion cells, midbrain interneurons, oculomotor nerve and short ciliary nerves. However, there are some specialties in the construction of the pupillary pathways that have to be kept in mind when dealing with diseases involving pupillary disorders. This may help to localise lesions. Additionally, studies in patients with lesions of the retrogeniculate pathways have shown that pupillary disorders are possible even with lesions not involving the classical reflex arc. The pupil is therefore not only controlled subcortically, some components are influenced by the visual cortex. The aim of this article is to clarify various findings and terms such as relative afferent pupillary defect and pupillary hemihypokinesia.

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Einleitung

Der Reflexbogen des Pupillenlichtreflexes, wie von Wernicke beschrieben [35], besteht aus vier Neuronen. Afferente Axone der retinalen Ganglienzellen verlaufen zuerst im Sehnerv. In der Chiasmaregion kreuzen die Axone aus der nasalen Netzhauthälfte in den kontralateralen Tractus opticus, die in der temporalen Netzhauthälfte entspringenden Axone verlaufen ipsilateral. Im letzten Drittel des Tractus opticus zweigen die pupillomotorischen Fasern von den sensorischen ab und verlaufen weiter im Brachium colliculi superioris in die Area praetectalis im dorsalen Mittelhirn. Von dort ziehen Interneurone zu beiden Edinger-Westphal-Kernen, die schließlich über parasympatische Fasern im N. oculomotorius den Pupillensphinkter innervieren. Das klassische anatomische Schema wurde allerdings durch klinische Beobachtungen der Pupillenstörungen bei verschiedenen Läsionen der Sehbahn wiederholt infrage gestellt, vor allem ist immer wieder eine kortikale Beteiligung am Pupillenreflex postuliert worden.

Ein relativer afferenter Pupillendefekt (RAPD) ist durch eine herabgesetzte Pupillenreaktion bei direkter Beleuchtung und eine normale konsensuelle Antwort bei Beleuchtung des kontralateralen Auges gekennzeichnet. Es ist ein wichtiges klinisches Zeichen, das typischerweise bei Läsionen der vorderen Sehbahn eintritt. Ein RAPD begleitet fast immer einseitige oder bilaterale asymmetri-

sche Sehnervschädigungen, Chiasma- und Traktusläsionen. Allerdings wird ein RAPD auch bei manchen supragenikulären Läsionen beobachtet.

RAPD bei Traktusläsionen (◉ Abb. 1)

Traktusläsionen sind durch eine kongruente oder inkongruente homonyme Hemianopsie, asymmetrische bilaterale Optikusatrophie – meist ohne Sehschärfebeeinträchtigung – und einen RAPD kontralateral zur Seite der Läsion gekennzeichnet. Bell und Thompson berichteten über vier Patienten mit einer Traktusläsion mit RAPD, kompletter homonymen Hemianopsie und guter Sehschärfe auf beiden Augen [5]. Im Gegensatz dazu fanden Savino et al. einen RAPD nur bei Patienten mit einer Herabsetzung der Sehschärfe [27]. Bei diesen Patienten war somit wahrscheinlich auch der ipsilaterale Sehnerv betroffen. Newman und Miller berichteten von zehn Patienten mit einer Traktusläsion, von denen ein RAPD nur in Fällen mit einer kompletten homonymen Hemianopsie und guter Sehschärfe zu bestätigen war [23]. Ähnlich wie Bell und Thompson [5] sind sie der Meinung, dass das Auftreten eines RAPD mehr vom Gesichtsfeldausfall als von der Sehschärfe abhängt. Sie betrachten das Vorliegen eines RAPD in Fällen mit homonymer Hemianopsie als ein Kriterium für die Unterscheidung zwischen einer Traktusläsion und einer retrogenikulär verursachten homonymen Hemianopsie [5, 23].

Die Pathogenese eines kontralateralen RAPD bei Traktusläsionen beruht möglicherweise auf einer höheren Photorezeptorenzahl in der nasalen Netzhauthälfte [24, 33], auf einem ungleichmäßigen Verhältnis der gekreuzten und ungekreuzten Fasern von 53:47 im Chiasma [20] und auf der Tatsache, dass die temporale Gesichtsfeldhälfte 60–70% größer ist als die nasale. Bei einer Traktusläsion werden Nervenfasern aus der kontralateralen nasalen und der ipsilateralen temporalen Netzhaut unterbrochen, wodurch der Input aus dem kontralateralen Auge erniedrigt wird und ein entsprechender RAPD entsteht.

Die eher unerhebliche temporo-nasale Asymmetrie der kreuzenden und unkreuzenden Nervenfasern der retinalen Ganglienzellen (53:47) vermag aber nicht die großen Unterschiede im RAPD-Ausmaß bei Patienten mit einer Traktusläsion zu erklären, das von 0,3 logE bis 1,0 logE reichen kann. Studien, die die lokale retinale pupillomotorische Empfindlichkeit mittels fokaler Lichtstimuli bei Pupillenperimetrie oder mittels Halbfeld-Stimulation gemessen haben, zeigten eine größere pupillomotorische Empfindlichkeit der nasalen Netzhaut (temporales Gesichtsfeld) im Vergleich zur temporalen Netzhaut. Das exakte Verhältnis von temporalem und nasalem Input im Tractus opticus bleibt aber nach wie vor unbekannt [8, 18, 29]. Schmid et al. untersuchten die Pupillenlichtreflexe nach einer Stimulation der nasalen und temporalen Netzhauthälfte innerhalb des zentralen 10°-Gesichtsfelds und schätzten die Proportion der gekreuzten zu den ungekreuzten afferenten pupillomotorischen Fasern auf 52:48. Sie sehen in diesem kleinen Unterschied keine hinreichende Erklärung für das Ausmaß des RAPD, wie man es bei Patienten mit einer Traktusläsion sieht [29].

Patienten mit einer Traktusläsion stellen ein einzigartiges Modell dar, Erkenntnisse über die Halbfeldorganisation des afferenten pupillomotorischen Systems zu gewinnen. Eine komplette Traktusläsion ermöglicht den Vergleich der Pupillenantwort aus der temporalen und nasalen Netzhauthälfte ohne den unerwünschten Einfluss vom Streulicht, weil sich immer nur das intakte Halbfeld am Pupillenreflex beteiligen kann. Gerade wegen Streulicht kann eine Abschätzung der Nervenfaserverteilung in der Pupillenbahn am gesunden Auge mit erhaltener Funktion beider Netzhauthälften nie genau erfolgen [17]. Kardon et al. verglichen bei fünf Patienten mit einer einseitigen Traktusläsion die Pupillenreaktion nach Lichtstimulation der nasalen und temporalen Gesichtsfeldhälfte mittels Infrarotpupillografie. Bei allen Patienten war die Pupillenreaktion in der erhaltenen temporalen Gesichtsfeldhälfte ipsilateral zur Seite der Traktusläsion größer als in der funktionellen kontralateralen nasalen Gesichtsfeldhälfte. Nach ihrer Meinung reflektiert ein RAPD bei Traktusläsionen den Unterschied in Lichtempfindlichkeit zwischen dem intakten temporalen und nasalen Halbfeld [17].

RAPD ohne Gesichtsfeldausfall (◉ Abb. 1)

Vor der Umschaltung der Axone der retinalen Ganglienzellen im Corpus geniculatum laterale weichen die pupillomotorischen Fasern ab und verlaufen in Brachium colliculi superioris zum ipsilateralen prätektalen Kern, wo sie auf das nächste Neuron der Pupillenbahn umgeschaltet werden. Das kleine Gebiet zwischen Tractus opticus und Area praetectalis, prätektale afferente Pupillenbahn genannt, befindet sich im dorsalen Mittelhirn und dessen einseitige Läsion hat einen kontralateralen RAPD ohne visuelle Beeinträchtigung zur Folge (keine Vermin-

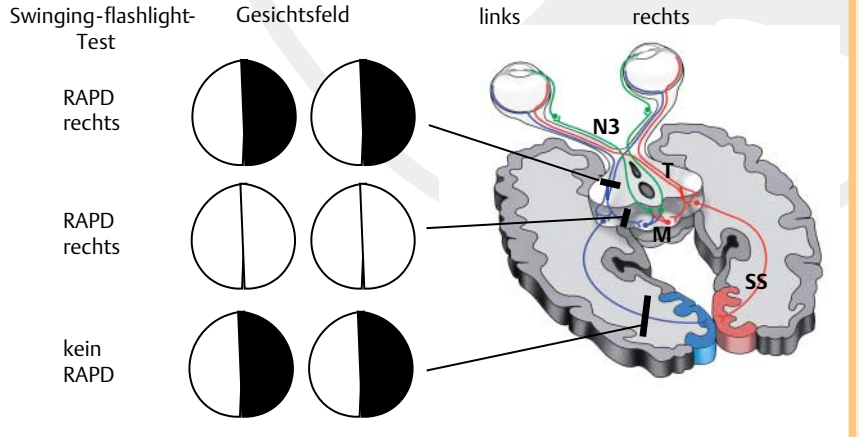

Abb. 1 Schematische Darstellung der verschiedenen Befunde anhand eines Verlaufsschemas der Pupillenbahn (T = Tractus opticus, M = Mittelhirn, SS = Sehstrahlung, N 3 = N. oculomotorius). Bei Traktusläsion resultieren eine homonyme Hemianopsie und ein relativer afferenter Pupillendefekt der Gegenseite. Bei Läsionen des Brachium colliculi superioris entsteht keine homonyme Hemianopsie, aber gleichfalls ein RAPD. Bei retrogenikulären Läsionen, die deutlichen Abstand zum Corpus geniculare laterale haben, entsteht eine homonyme Hemianopsie ohne relativen afferenten Pupillendefekt.

derung der Sehschärfe, kein Gesichtsfeldausfall, keine Optikusatrophie). Wenn die Läsion mehr proximal wäre (z. B. im Tractus opticus), würde es einen Gesichtsfeldausfall geben, und umgekehrt, wäre die Läsion mehr distal (z. B. im Edinger-Westphal-Kern), würde man eine Anisokorie sehen.

Einen RAPD ohne visuellen Schaden beschrieb als erster Behr 1913 bei zwei Patienten nach einem Gehirntrauma. Behr schlug als Ursache eine Läsion der afferenten Pupillenbahn im prätektalen Gebiet vor [4]. Ellis berichtete von einem Patienten mit einem Tumor im dorsalen Thalamus rechts und einem kontralateralen RAPD links ohne visuelle Beeinträchtigung [9]. Johnson und Bell stellten einen Patienten mit dorsalem Mittelhirn-Syndrom vor, bei dem nach der Rückbildung von okulomotorischen Störungen immer noch ein RAPD ohne visuellen Schaden feststellbar war [15]. In der Literatur gibt es noch weitere Berichte über Patienten mit einem einseitigen RAPD ohne jegliche Beeinträchtigung des Sehvermögens [10, 19, 31]. Alle sehen als Ursache eine Läsion der prätektalen afferenten Pupillenbahn im dorsalen Mittelhirn. 2008 gelang es nun Papageorgiou et al., bei einem solchen Patienten mittels Pupillenperimetrie zu zeigen, dass das pupillomotorische Gesichtsfeld ganz genau so aussah, wie man es bei einer Tractus-opticus-Läsion erwarten würde. Damit existiert ein Beleg dafür, dass der RAPD ohne visuelle Beeinträchtigung eine Variante des RAPD bei Traktusläsion ist, bei welcher der Läsionsort Richtung dorsales Mittelhirn verlagert ist und die visuellen Fasern ausgespart sind [26].

RAPD bei retrogenikulären Läsionen mit homonymem Gesichtsfeldausfall (◉ Abb. 1)

Das Auftreten eines RAPD in akuten homonymen Hemianopsien wird oft als Kriterium zur Differenzialdiagnose von prä- und retrogenikulären Läsionen benutzt. Bei erworbenem Schaden der Sehstrahlung oder der Sehrinde sollte keine Optikusatrophie und kein RAPD auftreten [5, 23]. 1985 wurde von Tychsen und Hoyt ein RAPD bei 2 Patienten mit einer kongenitalen okzipitalen Hemianopsie beschrieben. Ihre Erklärung dafür ist eine transsynaptische Atrophie des Tractus opticus nach einem intrauterinen oder perinatalen Schaden der supragenikulären Sehbahn, der wahrscheinlich auch die afferenten pupillomotorischen Fasern zur Area praetectalis im Mittelhirn einbezog [32]. Diese Entdeckung wäre plausibel und mit den bisherigen Erfahrungen in Einklang zu bringen.

Aber es gibt auch Studien bei erworbenen retrogenikulären Läsionen, die Befunde zeigen, die nicht mehr mit den bisherigen Modellen vereinbar sind: entweder ein RAPD kontralateral zur Seite der Läsion [25, 39] oder eine sogenannte pupilläre „Hemiakinesie“ oder „Hemihypokinesie“ [1, 6, 7, 11, 12, 14, 16, 25]. Wilhelm et al. stellten einen RAPD bei ungefähr der Hälfte ihrer Patienten mit einer supragenikulären homonymen Hemianopsie fest [39]. Die Analyse der Bildgebung zeigte, dass die Läsion näher als 10 mm am Corpus geniculatum laterale lag oder es einbezog, wenn ein RAPD bestand. Der Tractus opticus war bei allen Patienten unbeschädigt. Bei Läsionen, die mehr als 18 mm vom Corpus geniculatum laterale entfernt waren, gab es keinen RAPD. Die Autoren schließen daraus, dass der RAPD nicht durch eine Läsion der Sehbahn, sondern durch eine Läsion der Interneurone zwischen der Sehbahn und dem pupillomotorischen Zentrum in der Area praetectalis im Mittelhirn verursacht war [39]. Vor Kurzem erschien eine Arbeit von Papageorgiou et al., die sich erneut mit dem Verhältnis zwischen einem RAPD bei supragenikulären Läsionen und der Lage und dem Umfang der Läsion befasste. Ein RAPD von 0,3 – 0,9 logE kontralateral zur Seite der Läsion wurde bei 10 von 23 Patienten mit einem homonymen retrogenikulär verursachten Gesichtsfeldausfall festgestellt. Der Bereich, der bei Patienten mit RAPD typischerweise betroffen war, befand sich im proximalen Abschnitt der Sehstrahlung in der temporalen weißen Substanz [25]. Der Befund stützt die Hypothese, dass sich die Verbindung zwischen der Sehbahn und Area praetectalis im dorsalen Mittelhirn wahrscheinlich nahe beim Corpus geniculatum laterale befindet und bei den retrogenikulären homonymen Hemianopsien mit RAPD betroffen ist [4, 15, 19, 39].

Nach einigen Hypothesen könnte der RAPD bei supragenikulären Läsionen auch durch eine transsynaptische Degeneration erklärt werden, die durch Synapsen im Corpus geniculatum laterale weitergeleitet wird. Darüber hinaus wäre auch eine Schädigung der vermuteten kortiko-prätektalen Verbindung zur Area praetectalis denkbar [1, 7, 34]. Allerdings sollte in diesem Fall ein RAPD erst Monate oder sogar Jahre nach dem Ereignis entstehen. Nach Papageorgiou et al. [25] zeigte sich ein RAPD bei einem Patienten aber schon wenige Tage nach dem zerebralen Insult und eine Optikusatrophie konnte selbst vier Monate nach dem akuten Ereignis bei keinem der untersuchten Patienten nachgewiesen werden. Vier Monate sollten eine ausreichende Zeitspanne für die Entwicklung einer Optikusatrophie sein, die bei einer eventuellen transsynaptischen Degeneration zu erwarten wäre. Die umstrittene transsynaptische Degeneration bei Erwachsenen wurde auch von Miller und Newman infrage gestellt. Eine von ihnen post mortem untersuchte Patientin mit einer supragenikulären homonymen Hemianopsie wies 57 Jahre nach dem zerebrovaskulären Ereignis keine Zeichen einer Degeneration im Bereich der vorderen Sehbahn auf [22]. Die Hypothese scheint somit nicht haltbar.

Zusammenfassend lässt sich sagen, dass bei retrochiasmalen Läsionen unsere klassische Vorstellung von der Organisation der Pupillenbahn als eine Einheit nicht grundlegend infrage gestellt wird. Prä- und retrogenikuläre Läsionen lassen sich nach wie vor durch den RAPD unterscheiden, man muss nur beachten, dass auch bei einer Läsion im Gebiet der Area praetectalis ein RAPD auftreten kann. Anders ist es bei der in der Folge zu besprechenden Hemihypokinesie der Pupille bei retrogenikulären Läsionen.

Hemihypokinesie der Pupille

Die Pupillen-Hemihypokinesie ist vom RAPD zu unterscheiden: Pupillen-Hemihypokinesie (oder ggf. -akinesie) bedeutet eine erniedrigte oder völlig erloschene Pupillenreaktion auf perimetrische Lichtreize im Bereich der Gesichtsfeldausfälle bei Patienten mit einer retrochiasmalen Läsion der Sehbahn. Nach den klassischen Vorstellungen vom Verlauf der Pupillenbahn sollten Läsionen vor dem Corpus geniculatum laterale eine Hypokinesie zur Folge haben, postgenikuläre Läsionen hingegen nicht. Die ersten pupillenperimetrischen Versuche bei Patienten mit Läsionen der postgenikulären Sehbahn wurden schon von Harms [12] 1949 durchgeführt und haben die klassische Vorstellung des Pupillenreflexes nach Wernicke [35] infrage gestellt. Harms fand bei Kriegsheimkehrern mit Verletzungen des Okzipitalhirns herabgesetzte Pupillenreaktionen. Seine Veröffentlichungen wurden infrage gestellt und eine

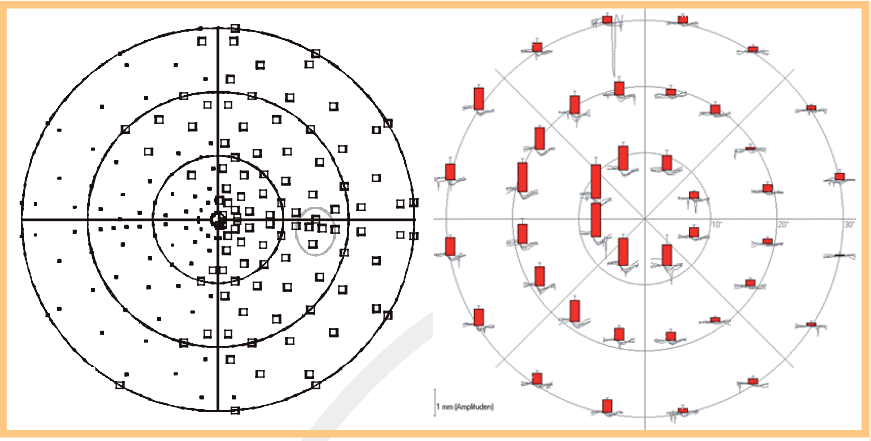

Abb. 2 Patient mit okzipitalem Astrozytom ohne Beteiligung des Tractus opticus und ohne Optikusatrophie. Links das konventionelle Gesichtsfeld (Tübinger Automatik Perimeter, 30°), rechts das pupillomotorische Gesichtsfeld. Die Höhe der kleinen Säulen steht für das Ausmaß der Pupillenkonstriktion. Es zeigt sich eine sehr gute Übereinstimmung.

transsynaptische Degeneration oder ein übersehener zusätzlicher prägenikulärer Schaden wurde postuliert. Harms' Gegenargument, dass diese Patienten keinerlei Optikusatrophie gezeigt hätten, wurde nicht beachtet. Seine Befunde wurden mehrfach reproduziert [6, 7], später auch mithilfe von exakten pupillografischen Methoden und aufwendigen bildgebenden Verfahren wie Computertomografie oder MR-Tomografie [1, 14, 16, 27, 28]. Ein Beispiel ist in **Abb. 2** zu sehen. Mit solchen Befunden konnten die Einwände der übersehenen zusätzlichen Läsionen entkräftet werden. Zur Erklärung der Befunde dieser Studien gibt es mehrere Theorien [2, 3, 26, 36].

Es gibt Belege für einen kortikalen Einfluss auf den Pupillenlichtreflex über eine kortiko-prätektale Verbindung [36–38]. Zu beachten ist dazu die Arbeit von Barbur et al. [3], die die Existenz von zwei getrennten pupillomotorischen Kanälen postuliert. Barbur untersuchte mittels Infrarotvideopupillografie die Pupillenreaktion nicht nur auf klassische, sondern auch auf sogenannte spezifische Reize (isoluminante Musterreize, Farbreize oder bewegliche Reize). Er fand, dass Patienten mit Okzipitalläsionen die Pupillenantwort auf spezifische Reize im blinden Halbfeld verloren hatten, die Antwort auf unstrukturierte Lichtreize jedoch erhalten geblieben war, wenn auch gegenüber der gesunden Seite reduziert. Der kleine Lichtpunkt der Pupillenperimetrie würde im Sinne von Barbur das Muster und Farben erkennende System ansprechen. Es besteht also die Vermutung, dass an der Pupillenlichtreaktion 2 Kanäle beteiligt sind: ein „Helligkeitskanal", der die Netzhaut direkt mit der Area praetectalis verbindet und auf übliche Lichtreize reagiert, und ein „Musterkanal", der erst retrogenikulär umgeschaltet wird und die Antworten auf isoluminante spezifische Reize vermittelt. Nach Barbur ist die Pupillenreaktion vorwiegend durch den Helligkeitskanal und nur zum kleineren Anteil durch den schwächeren Musterkanal gesteuert. Die Unterschiede zwischen sehendem und blindem Halbfeld, wie sie bei der Pupillenperimetrie erscheinen, sind aber viel größer als man erwarten würde, wenn allein der Musterkanal ausfiele. Daher muss ein Teil der Helligkeitsantwort ebenfalls über die retrogenikuläre Bahn verschaltet sein. Die Studie von Wilhelm et al. bei Patienten mit beschädigtem dorsalem Mittelhirn (Parinaud's Syndrom) zeigte eine schwache, residuale Pupillenlichtreaktion, eine erhaltene Reaktion auf Muster- und Farbreize und erhaltene Schläfrigkeitsoszillationen der Pupillen. Die Autoren sehen die Ergebnisse als Bestätigung für einen kortikalen Einfluss auf die Pupillenbahn, da die afferente Verbindung zum prätektalen Kern bei diesen Patienten durchtrennt war [36].

Nach den Erkenntnissen zum pupillomotorischen Einfluss der Melanopsin enthaltenden lichtempfindlichen retinalen Ganglienzellen [13, 21] erscheinen diese Überlegungen in einem neuen Licht. Könnte es sein, dass das System dieser Ganglienzellen den einen Kanal und das normale visuelle System den anderen Kanal stellt? Nur letzterer wäre streng retinotop, würde also perimetrisch nachweisbare Ausfälle verursachen, während durch ersteren nur ein RAPD zu erwarten wäre oder vielleicht eine grobe Retinotopie im Sinne von Halbfeldern. Weiteren Aufschluss können nur Studien mit entsprechenden Patientengruppen unter Verwendung von Reizen unterschiedlicher Wellenlänge und Dauer geben.

Nach Barbur [2] würde man die pupillenperimetrischen Befunde bei retrogenikulären Läsionen folgendermaßen erklären. Die Komponente der Pupillenlichtreaktion, die den Pupillendurchmesser unter konstanten Helligkeitsbedingungen reguliert („sustained"), wird vorwiegend durch die subkortikale Pupillenbahn gesteuert. Die zweite – transitorische – Komponente der Pupillenreaktion reagiert auf rasche Änderungen in der Leuchtdichte und kleine Reize. Anscheinend reizen die Lichtreize bei Pupillenperimetrie vorwiegend diese transitorische Komponente.

Wir haben eine ganze Reihe von Patienten mit prä- und postgenikulären Läsionen untersucht und unsere Erfahrungen gerade publiziert [30]. Für unsere Experimente benutzen wir eine eigene, computergesteuerte Methode der Infrarotvideopupillografie, die auch für klinische Zwecke benutzt wird. Erstaunlicherweise lässt sich nach unseren Befunden der Gesichtsfeldausfall mittels Pupillenperimetrie bei postgenikulären Läsionen besser als bei den prägenikulären abbilden. Unsere Studie bringt weitere Belege, dass die postgenikuläre Sehbahn oder die Sehrinde am Pupillenlichtreflex beteiligt sind, zumindest unter bestimmten Stimulusbedingungen.

Schlussfolgerung

Je nach ihrer Lage haben Läsionen der Sehbahn typische Pupillenstörungen zur Folge. Ihre Feststellung kann bei der Topodiagnostik der Läsion sehr hilfreich sein. Umgekehrt aber geben klinische Befunde Anlass zur ausführlichen Pupillenforschung und Kritik des klassischen Modells der Pupillen-

bahn. Die Vorstellung über den Pupillenreflexbogen ist stichhaltiger geworden, Studien sprechen dafür, dass die Pupillenreaktion nicht nur durch subkortikale Zentren gesteuert wird, sondern dass manche ihrer Komponenten durch die Sehrinde beträchtlich beeinflusst sind. Hier eröffnet sich ein interessantes Feld weiterer Forschung.

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Pupillary Disorders in Homonymous Visual Field Defects

7

Karolína Skorkovská, Barbara Wilhelm, and Helmut Wilhelm

Abstract

Classically, the pupil light reflex pathway is considered to be a simple reflex arc consisting of the retinal ganglion cells, intercalated neurons in the midbrain, the oculomotor nerve, and short ciliary nerves. However, there are some specialties in the structure of the afferent pupillary pathway that should be taken into account when interpreting pupillary disorders and that can help in the topodiagnosis of the lesion. Moreover, studies in patients with lesions of the retrogeniculate pathway showed that the pupillary pathway is more complex than previously assumed and the retrogeniculate visual pathway and the visual cortex are also involved in the pupillary light reaction. Clear anatomic evidence is still lacking but pupillographic measurements in patients with various disorders of the visual pathway support the existence of two pupillomotor channels that drive the pupil light reaction – the subcortical (more primitive, luminance channel associated with the intrinsically photosensitive retinal ganglion cells) and the supragenicular (responds to shifts in structured stimuli, is driven by the rods and cones, and receives input from the visual cortex and extrastriate areas). The chapter summarizes possible pupillary findings in patients with homonymous hemianopia.

Keywords

Pupil • Pupil light reflex • Relative afferent pupillary defect • Pupil perimetry • Chromatic pupillography • Swinging flashlight test • Hemihypokinesia • Hemiakinesia • Intrinsically photosensitive retinal ganglion cells • Melanopsin

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7.1 Introduction

The neural pathway of the pupillary light reflex as first described by Wernicke [1, 2] in 1880s consists of four neurons (Fig. 7.1). Afferent fibers of the retinal ganglion cells travel in the optic nerve and undergo hemidecussation at the chiasm before entering the optic tract. In the posterior third of the optic tract, the pupillomotor fibers separate from the sensory fibers, branch medial via the brachium of the superior colliculus to the lateral geniculate nucleus, and synapse in the ipsilateral pretectal nucleus in the dorsal midbrain. Intercalated neurons from each pretectal nucleus then project to both Edinger-Westphal nuclei and parasympathetic fibers from the Edinger-Westphal nuclei innervate the iris pupillary sphincter muscle. According to this model, the suprageniculate visual pathway should have no influence on the pupillary light reflex. However, studies in patients with lesions of the retrogeniculate pathway showed that the pupillary pathway is more complex than previously assumed and the retrogeniculate visual pathway and the visual cortex are also involved in the pupillary light reaction.

Homonymous hemianopia means vision loss on the same side of the visual field in both eyes and is indicative of a lesion involving the visual pathway posterior to the chiasm. Patients with a visual field defect should always have their pupils examined and this applies even more so in the case of homonymous visual field defects. This chapter should summarize possible pupillary findings in patients with homonymous hemianopia.

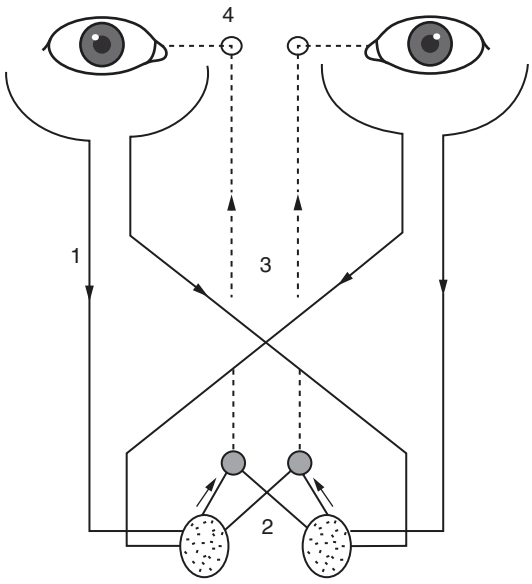


Fig. 7.1 The human pupillary pathway as first described by Wernicke consists of four neurons (excluding photoreceptors and bipolar cells in the retina): retinal ganglion cells (*1*), intercalated neurons in the midbrain (*2*), oculomotor nerve (*3*), and short ciliary nerves (*4*). The simplicity of this model can be no longer accepted (From Wilhelm [2], with permission)

7.2 Examination of Pupils

Examination of the pupils offers objective evaluation of visual function as well as of the vegetative pathways to the eye. Essential information is gathered within a short time. This makes pupillary inspection a valuable part of routine ophthalmological, neurological, and general medical examinations. Due to the proximity of pupillary pathways to various anatomic structures, pupillary dysfunction can be caused by a variety of disorders, some of which may be life threatening. Due to differences in the course of pupillomotor and sensory fibers, pupillary tests can help in the localization of a visual pathway lesion. The ophthalmologist plays a key role in detecting pupillary disorders and in directing further investigations. Therefore, one should have a good knowledge of the diagnostic significance of pupillary function and dysfunction.

There are several ways of how to examine the pupil light reaction. Some methods are based on the asymmetry in the afferent visual pathway, another on the examination of the visual field by means of measuring the pupil light reaction to focal light stimuli or on stimulation methods that are similar to multifocal electroretinography. Recently developed chromatic pupillography can identify pupil light response mediated by the rods, cones, or the intrinsically photosensitive retinal ganglion cells containing melanopsin.

7.2.1 Relative Afferent Pupillary Defect and Swinging Flashlight Test

The most frequently evaluated pupillary parameter in clinical practice is the relative afferent pupillary defect (RAPD). It is typically related to lesions within the anterior visual pathway and is almost always present in unilateral or asymmetric bilateral diseases of the optic nerve, chiasm, or the optic tract. It can be diagnosed by means of the swinging flashlight test and is characterized by diminished pupillary constriction on direct illumination with a normal consensual response to illumination of the contralateral eye.

Swinging flashlight test can be performed as follows: In a darkened room ask the patient to fixate an object in a few meters' distance. Shine with the ophthalmoscope in an angle of 45° from below and from the distance of 20–40 cm into the eyes. Move the light quickly from one eye to the other and observe the direct pupil light reaction of both pupils. Both pupils should be illuminated for the same time (ca. 2 s) and the switch between both eyes should be repeated at least five times. If a relative afferent pupillary defect is present on one side, then at the illumination of this eye both pupils will either enlarge without any previous contraction or this contraction will be smaller and shorter. RAPD can be quantified by means of neutral density filters and expressed in log units: A filter is placed between light source and the "good eye". If there is still a RAPD defect visible, a filter with higher density is chosen until the difference in pupillary constriction between both eyes disappears or even the RAPD switches side. The density of the filter necessary to compensate the side difference is a measure for the RAPD.

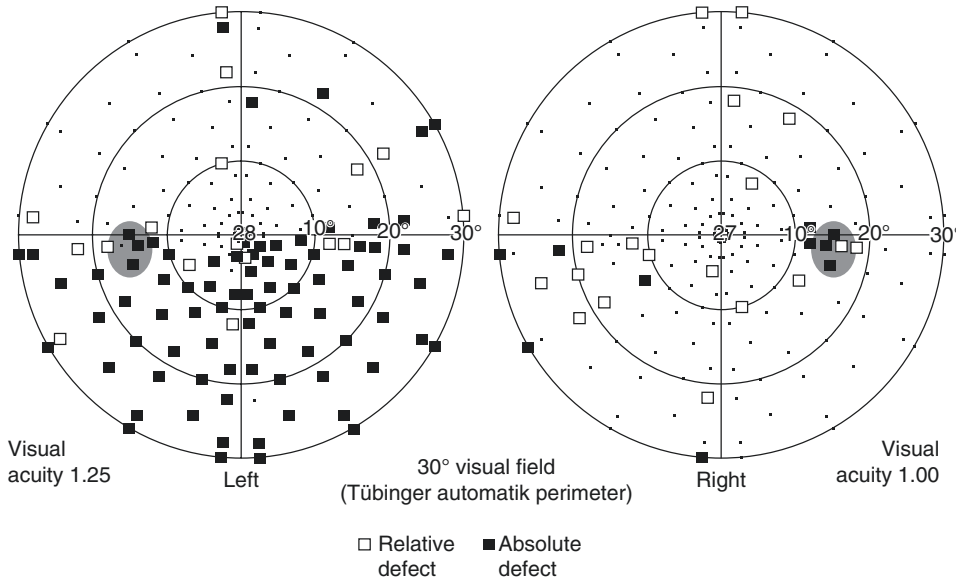
7.2.2 Pupil Perimetry

Pupil perimetry or campimetry is an objective visual field test that measures pupil light reaction (PLR) to focal light stimuli projected onto the retina. Light stimuli are presented at various locations in the visual field, similar as in standard perimetry. However, as the threshold for the pupil light response is higher than the differential light threshold in conventional perimetry, stimuli in pupil perimetry have to be brighter or larger. Brighter stimuli increase straylight, and larger stimuli reduce spatial resolution of pupil perimetry. This is the major problem of all systems applied in pupil perimetry. To overcome this, M-sequence techniques known from multifocal electroretinography have been applied but not yet tested against conventional pupil perimetry.

Visual field defects in pupil perimetry can be recognized by a reduced or absent pupil light reaction within these areas. Studies dealing with clinical applications of pupil perimetry have shown that most diseases affecting the retina and the visual pathway caused pupil field scotomata which match the defects found in standard perimetry (Figs. 7.2, 7.3, and 7.4) [3–5].

Pupil perimetry can be performed either by means of a special pupillographic device or by a modified standard perimeter. However, most of these devices serve for research purposes and only a few machines are available commercially. In our laboratory, the pupillographic device consists of a computer, a 19-inch CRT screen for the stimulus presentation, and a third monitor for continuous monitoring of fixation by observation (Fig. 7.5). Stimuli are displayed on the computer screen at a distance of 20 cm from the subject's eye. A small red spot is presented for fixation. Blinds around the device prevent stray light from the room disturbing the measurement. The pupil reaction is recorded by means of an infrared-sensitive video camera. The pupil edges can be determined by the contrast of the dark fundus and a very light iris infrared reflex. During the test the examiner can observe the quality of fixation, the stimulus sequence, as well as the continuous pupillographic curve. For the stimuli, white light is usually used and different stimulus intensities can be tested with a constant background luminance of 2.7 cd/m^2. The stimulus is usually presented for 200 ms every 2000 ms.

In contrast to standard visual perimetry, pupil perimetry represents a method for objective visual field examination. It can be very useful particularly in patients suspected of stimulation [6] or in patients who do not manage standard perimetry well enough.



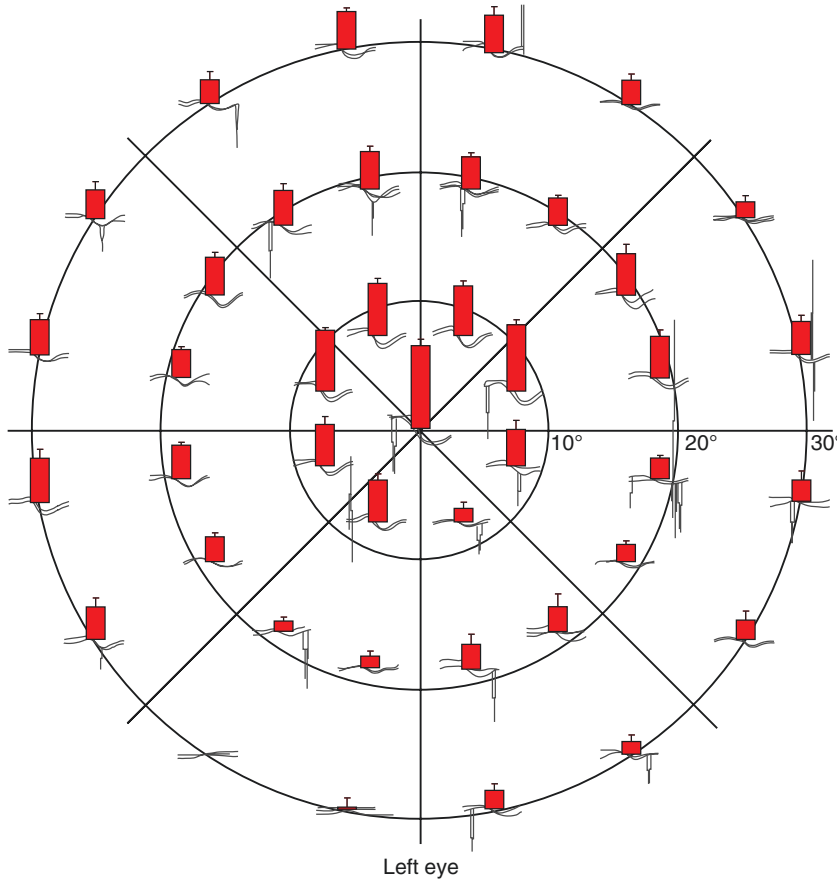
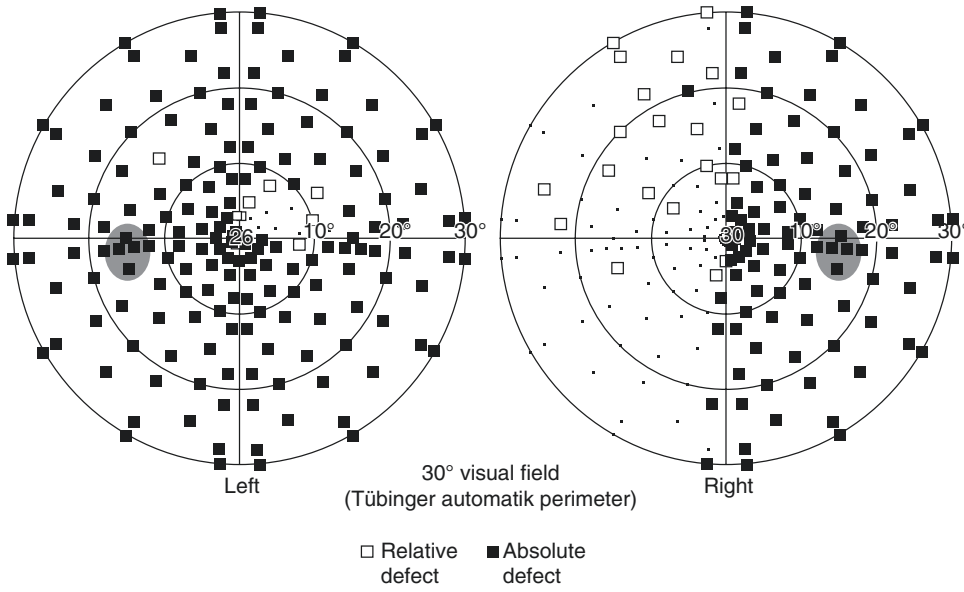


Fig. 7.2 (*Top*) Visual field in a patient with sphenoid wing meningioma causing a lower altitudinal defect in the left eye. (*Bottom*) Pupil field of the left eye as detected by means of pupil perimetry. The column represents the mean value of pupil light response amplitude in millimeters at each tested location in the visual field. Corresponding pupil field defect in the lower hemifield can be recognized by a reduced pupil light reaction in this area



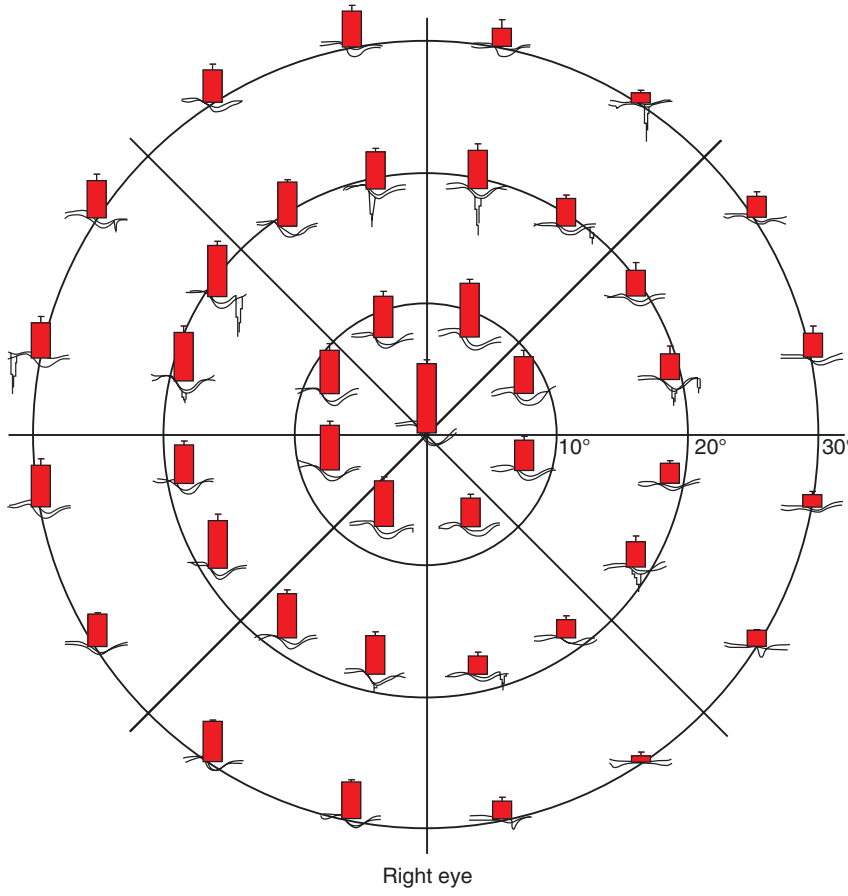


Fig. 7.3 (*Top*) Visual field in a patient with pituitary adenoma affecting the entire visual field of the left eye and the temporal hemifield of the right eye. (*Bottom*) Pupil field of the right eye showing a corresponding pupil field defect in the temporal hemifield

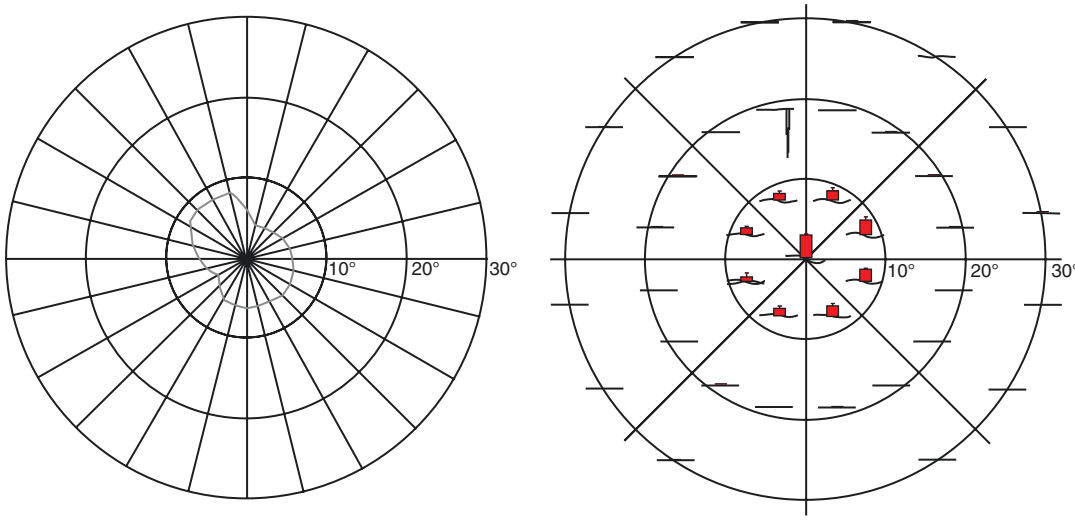


Fig. 7.4 (*Left*) Schematic drawing of advanced concentric visual field loss in a patient with retinitis pigmentosa as detected by kinetic perimetry (Goldmann stimulus V4). (*Right*) Corresponding pupil field with pupil light reaction present only within the preserved visual field (From Skorkovská et al. [4], with permission)

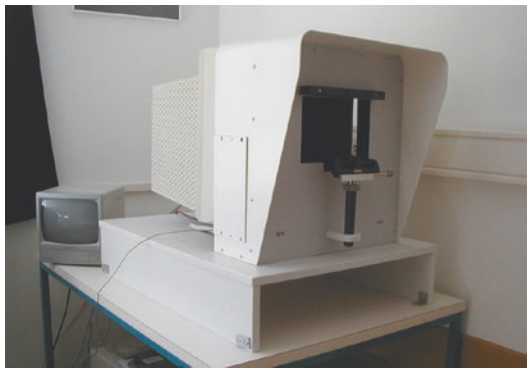


Fig. 7.5 Pupil perimetry (campimetry) in our pupil laboratory. The pupillographic device consists of a computer, a screen for the stimulus presentation, and a third monitor for a continuous monitoring of fixation. The examination is carried out in darkness, separately for each eye

7.2.3 Chromatic Pupillography

Recently it was found that not only the rods and cones, but also other retinal elements – retinal ganglion cells containing melanopsin (ipRGCs) – are intrinsically photosensitive and capable of phototransduction [7–10]. Unlike rods and cones they do not or only marginally contribute to image formation. They serve more as a detector of the surrounding light intensity and are involved in the management of circadian rhythm. In addition to that, axons of the ipRGCs are connected with the pretectal area and can drive pupil light reaction, particularly at high intensities of light (100 cd/m^2). This explains why people who lost sight because of a photoreceptor disease still may have normal pupil light reaction and circadian rhythm [11, 12].

Rods and cones are located in the outer retina, ipRGCs in the inner retinal layer. Each type of photoreceptors has its different wavelength sensitivity. The peak sensitivity of the ipRGCs is in the blue spectrum around 480 nm. By registering the pupil light reaction to light stimuli of different color and intensity, it is possible to separately test the function of different population of retinal photoreceptors, and like this evaluate and monitor the function of outer retina (rods and cones) and inner retina (ipRGC). This method is called chromatic pupillography and appears as a highly sensitive method for objective examination of neuroretinal function that might become a useful complement to electrophysiological tests, at this moment more for research purposes or clinical trials (Figs. 7.6 and 7.7) [13].

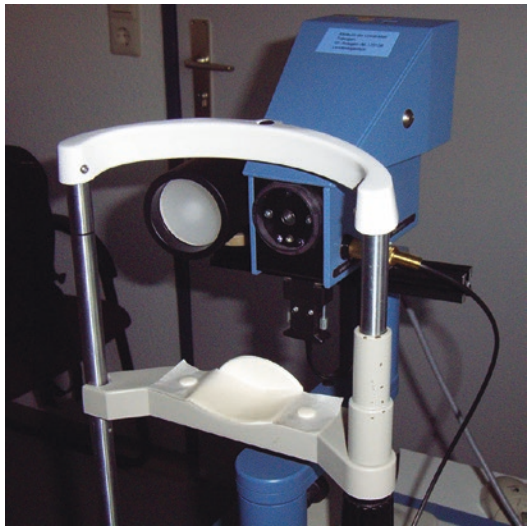


Fig. 7.6 Chromatic pupillography equipment in our laboratory. The stimulus is provided by a mini-Ganzfeld color LED stimulator to one eye and the consensual pupil light reflex of the nonstimulated fellow eye is measured by the compact integrated pupillograph (AMTech GmbH, Dossenheim, Germany)

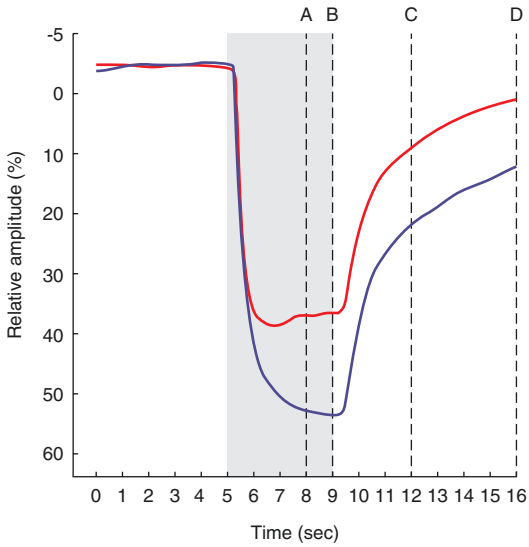


Fig. 7.7 The relative pupil light response amplitude to *red* and *blue light* stimulus in healthy subjects. With *blue light*, the relative amplitude is significantly greater and the time to maximal pupil constriction significantly longer compared to *red light* for all tested time points (*indicated by the vertical lines A–D*). *Blue light* evokes the "sustained" pupil contraction (driven by ipRGCs), while the *red light* rather the "transient" contraction (driven by rods and cones) (From Skorkovská et al. [13], with permission)

7.3 RAPD in Optic Tract Lesions

Optic tract lesions are characterized by homonymous visual field defects, asymmetric bilateral optic disc atrophy (more pronounced contralateral to the lesion), and contralateral RAPD (Fig. 7.8). The closer the lesion is located to the chiasm the more incongruent are the visual field defects. Visual acuity is usually not affected. The suggested causes for this contralateral RAPD in an optic tract lesion are a greater nasal photoreceptor density, a ratio of crossed to uncrossed fibers in the chiasm of 53:47, and a temporal visual field 61–71% larger than the nasal field [14]. A tract lesion disrupts fibers from the contralateral nasal retina and the ipsilateral temporal retina, thus disproportionally diminishing input from the contralateral eye and producing a corresponding RAPD. However, the magnitude of RAPD in patients with an optic tract lesion can range from 0.3 logE to 1.0 logE and this can, probably, be completely explained neither by the rather small asymmetry of crossed to uncrossed fibers nor the difference between temporal and nasal hemifield [15].

Patients with an optic tract lesion represent a unique model for studies of the hemifield organization of the afferent pupillomotor system. A complete tract lesion enables the comparison of the pupil light reaction from temporal and nasal retina without the disturbing influence of stray light because only the intact retinal half can participate in the pupil light reaction. Because of stray light such an estimation of the nerve fiber distribution in the pupillary pathway is not precisely possible in a healthy eye with both retinal halves functioning. By means of pupillography it could be shown that in case of separate light stimulation of either of the retinal halves in optic tract lesions, the pupil light reaction was always greater in the preserved temporal visual field ipsilateral to the site of the tract lesion, compared to the functional contralateral nasal visual field. So, RAPD in optic tract lesions probably reflects the difference in light sensitivity of the intact temporal and nasal visual field [16].

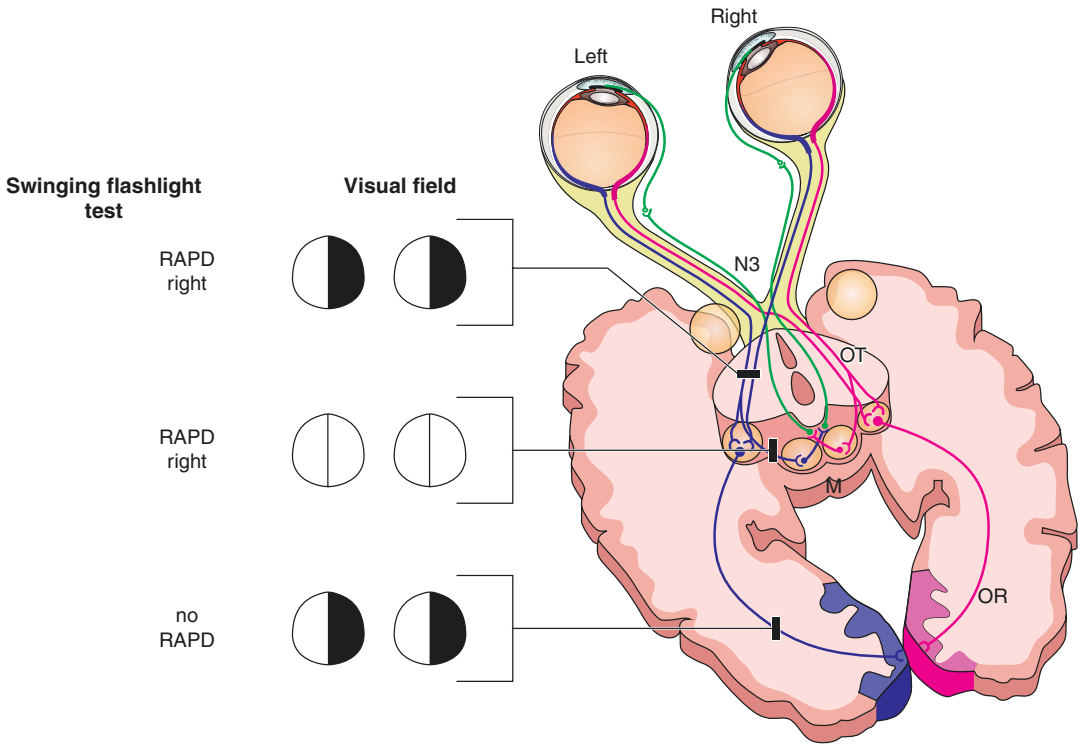


Fig. 7.8 Schematic representation of different findings according to the course of the pupil light reflex pathway (*OT* optic tract, *M* midbrain, *N3* oculomotor nerve, *OR* optic radiation). Lesions of the optic tract result in homonymous hemianopia with contralateral relative afferent pupillary defect (RAPD). Lesions of the brachium of the superior colliculus cause contralateral RAPD but no visual field defect. In suprageniculate lesions with sufficient distance from lateral geniculate body homonymous hemianopia without RAPD develops

7.4 RAPD Without Visual Field Loss

Prior to the termination of retinal ganglion cell axons in LGN, the pupillomotor fibers branch off and travel via the brachium of the superior colliculus to the ipsilateral pretectal nucleus, where they synapse with the next neuron of the pupillomotor pathway. This small region between the optic tract and pretectal area is called pretectal afferent pupillary pathway and is located inside the dorsal midbrain in the brachium of the superior colliculus. A pathology in this area will cause a contralateral RAPD without any visual impairment – that means no decrease in visual acuity, no visual field loss and no optic atrophy (Fig. 7.8). If the lesion was located more proximally (e.g., in optic tract), a visual field defect would be present and on the other hand, if the lesion was more distally (e.g., in Edinger-Westphal nucleus), an anisocoria would be observed.

There are several reports [17–19] in the literature dating back to 1920s that describe patients with a unilateral RAPD without any visual impairment. Most of the patients had a pathology in the dorsal midbrain and all authors considered the cause lesion of the pretectal afferent pupillary pathway in dorsal midbrain. Recently, it was shown by means of pupil perimetry that the pupil field in these patients looked exactly like the visual field in an optic tract lesion [20]. So, the RAPD without visual loss is simply a variant of the RAPD in an optic tract lesion, in which the site of the lesion is moved towards dorsal midbrain and leaves the visual function intact.

7.5 RAPD in Supragenicular Lesions with Homonymous Visual Field Defect

Detection of a RAPD in acute homonymous hemianopias has been commonly used in differentiating infrageniculate from supragenicular lesions, since neither optic atrophy nor a RAPD should occur in acquired affections of the optic radiation or the visual cortex. However, there are exceptions.

For instance, RAPD has been described in patients with congenital occipital hemianopia [21]. The suggested mechanism was transsynaptic optic tract atrophy after intrauterine or perinatal damage to the supragenicular visual pathway, which presumably affected also the afferent pupillary fibers to the pretectal area of the midbrain. This explanation sounds plausible and in accordance with what was written above.

Further, there are numerous studies, reporting disturbances of the PLR in patients with acquired HVFDs due to lesions not involving the optic tract, that are no more compatible with the traditional model of the pupillary pathway: either the presence of pupillary "hemiakinesia" or "hemihypokinesia" in the blind part of the visual field [3–5, 22–27] or RAPD contralateral to the brain lesion, as a response to full-field light stimulation [28, 29]. Results of these studies provide evidence that the pupil light reaction is not a pure subcortical pathway.

Further progress in understanding the underlying anatomic pupillary pathway could be achieved thanks to advances in neuroimaging. Modern methods of analysis enable us to define any lesion very precisely. Like this, clinically relevant RAPD, as a response to full-field light stimulation, could be limited to supragenicular lesions that were found closer than 10 mm to the LGN or involving it, but sparing the optic tract. In lesions located more than 18 mm from the LGN, RAPD did not occur [29]. It was concluded that RAPD was probably not caused by a lesion of the visual pathway itself, but by a lesion of the intercalated neurons between the visual pathway and the pupillomotor centers in the pretectal area of the midbrain, comparable to the lesions that cause RAPD without visual field loss. Further, using a new strategy of lesion analysis by combining subtraction techniques with the stereotaxic probabilistic cytoarchitectonic map it was found that a region in the early course of the optic radiation in the temporal white matter, close to the LGN, seems to be associated with the presence of RAPD. This finding is consistent with the hypothesis that the connection between visual pathway and pretectal area in the dorsal midbrain is probably closely related to the LGN and its involvement in supragenicular homonymous hemianopias can lead to RAPD. So, there seems to be more input from supragenicular neurons and the occipital cortex but the exact anatomy of this connection is still unclear. It may be that the critical area in the early course of the optic radiation near LGN is the site of integration of cortical signals in relation to the PLR into the pupillomotor pathway. Another explanation could be that some afferent pupillomotor fibers of infrageniculate origin bypass the LGN and then travel through this critical area to the mesencephalon.

In summary, the classical view of the pupillary pathway in postchiasmal lesions of the visual pathway is basically true. Infra- and supragenicular lesions can still be distinguished by the presence of RAPD. However, it must be kept in mind that RAPD can develop also in lesions in the surroundings of the pretectal area. And the situation is even more complicated in case of pupillary hemihypokinesia that is to be discussed.

7.6 Pupillary Hemihypokinesia

According to the classic idea of the pupillary pathway, infrageniculate lesions should present with a hypokinesia, supragenicular lesions should not. However, many studies [3–5, 22–27] in patients with retrogeniculate damage and homonymous visual field defects have provided evidence for impairment of pupil responses to small localized stimuli registered by pupillography. Early clinical reports dating back to 1940s were later reproduced by other groups using modern pupillometric techniques in patients well documented by magnetic resonance imaging or computed tomography, and currently there is no doubt that the retrogeniculate visual pathway or

even visual cortex is involved in the pupillary light reaction. In patients with retrogeniculate damage the so-called pupillary hemihypokinesia can be observed which differs from RAPD.

Pupillary hemihypokinesia (or akinesia) means a reduced or absent pupil light reaction to perimetric stimuli in the blind part of the visual field and was observed in all kinds of postchiasmal lesions (Fig. 7.9). The first pupillometric measurements in patients with suprageniculate lesions have been performed already by Harms in 1949 [22] and have challenged the Wernicke's description of the pupil light reflex. Harms found reduced pupil light reaction in war veterans with occipital lobe injuries. At that time, his results were called into question and the findings ascribed to the transsynaptic degeneration or to an overlooked pregeniculate damage. Harm's

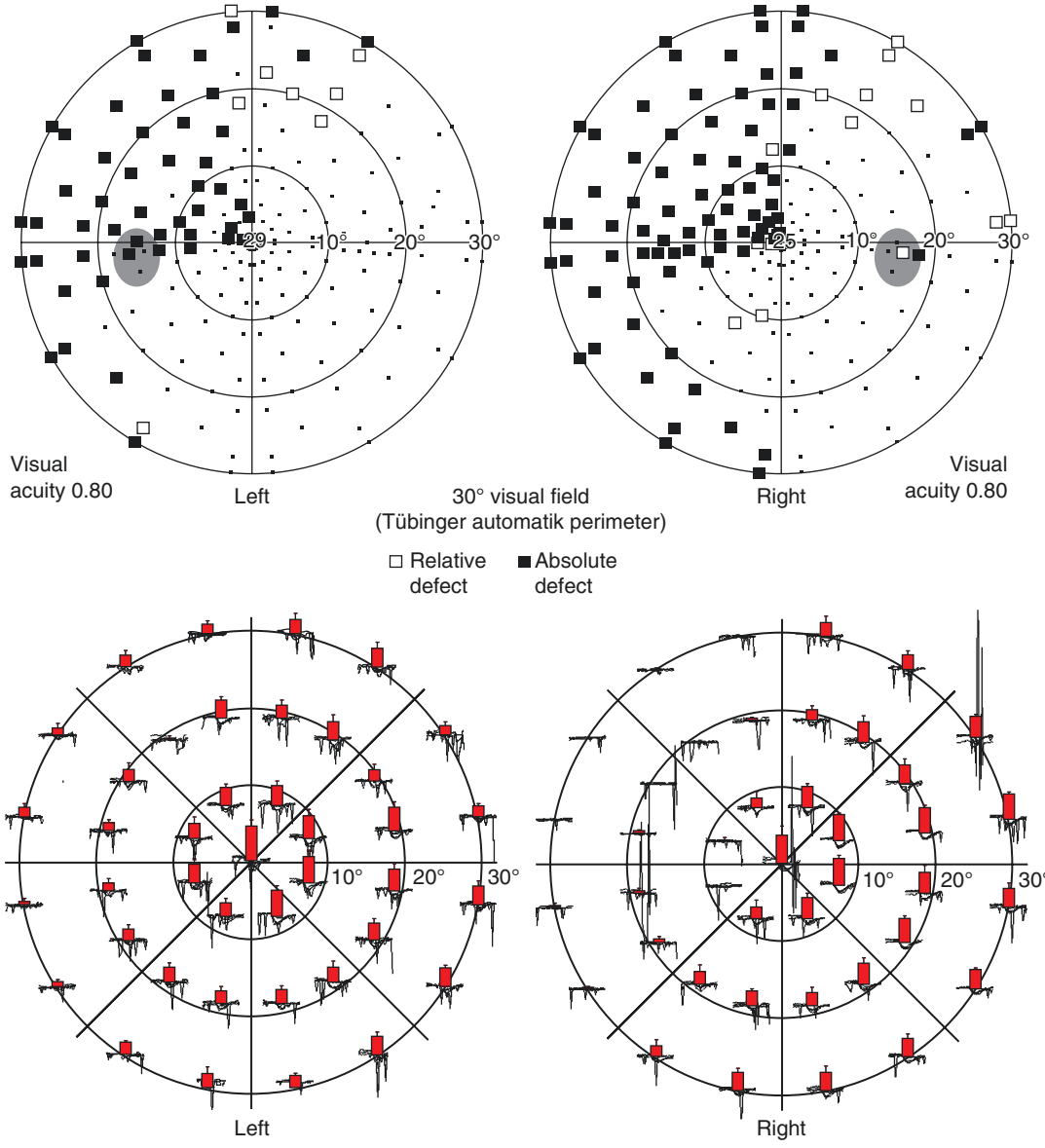


Fig. 7.9 (*Top*) Visual field in a patient with superior left homonymous quadrantanopia due to an ischemia. (*Bottom*) Pupil field of the same patient showing a reduced or absent pupil light reaction in the affected portion of the visual field (From Skorkovská et al. [4], with permission)

findings were eventually many times reproduced, later also with the help of modern pupillographic equipment and sophisticated imaging methods. Still, even today we can only speculate about the underlying cause of this phenomenon.

The findings, for example, can be explained by the view, that in pre- and retrogeniculate lesions different components of the light response may be involved to a different extent. The steady-state component of the pupillary light response regulates the resting pupil diameter depending on the ambient light level; it is characterized by a large spatial summation and a wide dynamic range. This component is represented basically by the subcortical pupillary pathway. The transient component of the pupil light response is responsible for the constriction of the pupil in response to brisk light stimuli. In the presence of this component, the steady-state signal is largely discarded. The transient component reflects merely novel changes in luminance contrast; it is characterized by a "limited spatial summation, band-pass temporal response characteristics, and high contrast gain" [30, 31]. It is obvious that the stimulus characteristics of pupil perimetry predominantly address this transient component. There is strong evidence that – after cortical processing of specific stimulus characteristics – projections from the extrastriate visual cortex contribute considerably to the transient pupil response component.

Indeed, pupillographic measurements with specific stimuli (isoluminant pattern stimuli, chromatic stimuli or moving stimuli) in patients with a retrogeniculate lesion indicate the possible existence of two separate pupillomotor channels: the PLR in the blind hemifield was reduced but not absent. However, all the other specific, "higher" pupil responses to stimulus attributes, like stimulus color, structure, or motion, were completely lost. On the other hand, studies in patients with Parinaud syndrome [32] demonstrated that there was a small, residual PLR and preserved reactions to pattern and color stimuli as well as preserved pupillary sleepiness-related oscillations. Again, the existence of a cortical input to the pupillary pathway was suggested, since the retinal afferent input to the pretectal nuclei had been apparently damaged.

Hence, it is considered that two or more distinct channels could serve the PLR: a more primitive "luminance channel," which connects the retina directly with the pretectal area and responds to diffuse light, and "pattern channel," which is mediated supragenículately and responds to shifts in structured stimuli, like isoluminant grating, motion, and isoluminant color stimuli. The PLR is primarily mediated by the luminance channel and to a smaller extent by the "weaker," supragenículate pattern channel (Fig. 7.10). It seems that the

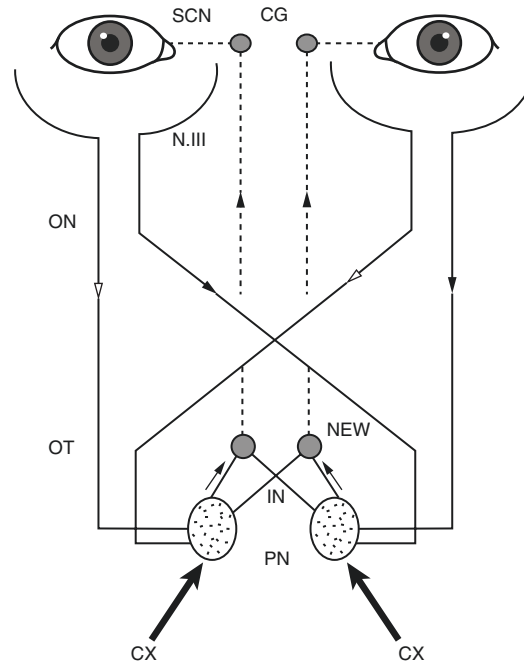


Fig. 7.10 Schematic drawing of the current view of the pupillary light reflex pathway. Afferent pupillomotor fibers travel in the optic nerve and undergo hemidecussation at the chiasm before entering the optic tract. In the posterior third of the optic tract, the pupillomotor fibers branch medial via the brachium of the superior colliculus to the lateral geniculate nucleus (LGN) and synapse in the ipsilateral pretectal nucleus (PN) in the dorsal midbrain. Intercalated neurons from each pretectal nucleus then project to both Edinger-Westphal nuclei. Parasympathetic fibers from the Edinger-Westphal nuclei (NEW) travel with the oculomotor nerve to the ciliary ganglion (CG) and via the short ciliary nerves (SCN) innervate the iris pupillary sphincter muscle. However, there seems to be more input from supragenículate neurons and the visual cortex (CX), although the exact anatomy of this connection is still unclear. It may be that stimuli with different attributes are processed at a different level – subcortically or by supragenículate neurons and the visual cortex. The proposed site of integration of cortical signals to the pupillary response should be located in the early course of the optic radiation near the LGN (From Papageorgiou et al. [29], with permission)

intrinsically photosensitive retinal ganglion cells operate merely on the subcortical level, while the cortical pathway may rely more on ganglion cells that carry predominantly cone inputs. Additionally, it needs to be considered that a pupillary constriction could also be evoked by temporarily canceling the inhibition of the Edinger-Westphal nucleus by the central sympathetic inhibiting system. This might provide a second pathway for pupillary constriction.

Conclusion

Pupillary findings in patients with pregeniculate lesions of the visual pathway are consistent with the subcortical course of the pupil light reflex arc. However, the evidence of pupillary hemihypokinesia in patients with homonymous visual field defects due to retrogeniculate lesions of the visual pathway supports the hypothesis that the afferent pupillary system is not purely a subcortical reflex arc but consists of two pathways: one of these via intrinsically photosensitive retinal ganglion cells (ipRGCs) directly reaching the dorsal midbrain, the other running through the normal RGCs via the visual cortex; although the exact anatomy of this pathway is still unclear. The subcortical pathway accounts for changes in pupil diameter to stimuli of high intensity, whereas the cortical part responds particularly to higher stimulus attributes like color, structure, or motion. Future research will certainly provide further understanding of the problem.

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I. **Skorkovská K, Wilhelm H, Lüdtke H, Wilhelm B.**

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How sensitive is pupil campimetry in hemifield loss?

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Abstract
Background The purpose of our study was to demonstrate the ability of pupil campimetry to reproduce visual field defects caused by pre— and retrogeniculate lesions of the visual pathway.
Methods By means of infrared video pupillography, light responses to perimetric stimuli were recorded. The stimulus pattern consisted of 41 test spots of 4° diameter and 140 cd/m^2 luminance distributed in the central (30°) visual field. Background luminance was 2.7 cd/m^2. Eight patients with pregeniculate lesions and eight patients with retrogeniculate lesions of the visual pathway were examined. Pupil field was evaulated by three skilled visual field interpreters masked to the patients' clinical data including conventional perimetry. The spatial concordance of the visual field and the pupil field was quantitatively assessed by the ratio of intersection area and union area of the observer's result and the visual field defect measured by conventional perimetry. The ratios in the two cohorts were compared by the Wilcoxon rank-sum test.
Results The concordance between pupil and conventional perimetry was better in the group of patients with retrogeniculate lesions. Ratios of the intersection area and the union area in this group were significantly higher than for the group with pregeniculate lesion of the visual pathway ($p<0.05$).
Conclusions According to our results, pupil campimetry demonstrates retrogeniculate visual pathway lesions well in contrast to pregeniculate lesions. This is in contradiction to the classical view of the pupillary pathways, where a retrogeniculate lesion actually should not influence pupillary function, whereas pregeniculate lesions should show pupillary scotomata. The cause might be that different components of the pupillary light reflex are being involved in pre— and retrogeniculate lesions, and the stimulus characteristics of pupil perimetry address better the components represented in the retrogeniculate pathway.

Keywords Pupil · Campimetry · Perimetry · Hemifield loss · Visual field

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Introduction

According to the classical theory [1, 2, 3], the pupillary light reflex is considered to be a simple reflex arc consisting of the retinal ganglion cells, intercalated neurons in the midbrain, the oculomotor nerve and short ciliary nerves. Postgeniculate lesions of the visual pathway should therefore not be detectable by pupil perimetry.

However, many reports in the literature [4–13] provide strong evidence that patients with isolated occipital lesions and homonymous visual field defects show corresponding pupil defects to focal light presented to the same area. The published findings provide compelling evidence for a role of cortical processing of the pupillary light reflex under certain stimulus conditions.

Pupil perimetry (or campimetry) represents an objective method of testing the visual field by examining the pupillary response to focal light stimuli projected onto the retina. Visual field defects in pupil campimetry can be

recognized by a reduced or absent pupil light reaction within these areas. However, the value of pupil field mapping in hemifield loss, both for clinical and scientific purposes, is not yet established, especially not in cases with retrogeniculate lesions. The purpose of this observational study was to show to what extent our method of pupil campimetry is able to reproduce conventional visual field defects caused by pre— and retrogeniculate lesions of the visual pathway, and as such address the issue of understanding of the pupil reflex pathways again, particularly the involvement of retrogeniculate structures. This gives additionally hints on how far pupil perimetry is suited to disprove feigned hemifield defects.

Methods

For this study, eight patients with a pregeniculate lesion (group 1) and eight patients with a retrogeniculate lesion of the visual pathway (group 2) were selected from the patients of our neuro-ophthalmological department. All pregeniculate lesions were caused by tumors of the anterior visual pathway. Retrogeniculate lesions, on the other hand, were mostly due to occipital ischemia. Patients in both groups showed a visual field defect respecting the vertical midline. In all patients, the site and cause of lesion of the visual pathway was confirmed by magnetic resonance imaging or computed tomography.

The study was approved by the local institutional ethics committee and followed the tenets of the Declaration of Helsinki. All participants received written information about the pupillometry and gave their written consent.

All subjects underwent a thorough ophthalmological examination including static perimetry, using Tübingen Automatic Perimeter, or Goldmann 90° kinetic perimetry of both eyes. The computerized infrared (IR) pupil campimetry was performed on the same day as the visual field. In all subjects both eyes were tested consecutively, one eye always being covered with a black eye patch. The pupillographic device consisted of a computer, a 19-inch CRT screen for the stimulus presentation and a third monitor for continuous monitoring of fixation by observation. Stimuli were presented on the computer screen at a distance of 20 cm from the subject's eye (according to conventional terminology, this procedure has to be named campimetry instead of perimetry, because stimuli are not presented in a bowl). Blinds around the device prevented stray light in the room from disturbing the measurement. The pupil reaction was recorded by means of an IR-sensitive video camera. The video signal was processed in the same computer and the pupil diameter was calculated each 40 ms. The stimulus pattern consisted of 41 stimuli presented within the central 30° of the visual field. Stimulus diameter was 4°. White light was used for all stimuli; stimulus intensity was 140 cd/m^2, with a constant background luminance of 2.7 cd/m^2. Each stimulus was presented for 200 ms every 2000 ms. A small red spot was presented constantly as a fixation mark. The perimetry program presented each stimulus at each tested location four times. If the pupil size could not be recorded four times without problems (e.g. blinks), the stimulus was presented more often until four recordings of the pupil size had been done for each stimulus. Afterwards, from these four pupillary responses the average amplitude of the pupillary response in mm for each tested location in the visual field was calculated.

The pupil field loss of one randomly selected eye of each patient was assessed by three skilled visual field interpreters blinded to the patients' data. The observers were asked to draw the pattern of the estimated field defect. The spatial concordance of the visual field and the pupil field as entered by the observers was assessed by the K-Train method. In this method, developed by Schiefer et al. [14], quality of the perimetric examination is quantitatively assessed by the ratio of intersection area and union area of the observer's result and the real visual field defect (Fig. 1). This sub-score reaches a maximum in the case of perfect coincidence, and goes down to zero if the two isopter sets do not have anything in common. Finally, to compare the results in both groups statistically, the ratios in the two cohorts were averaged and compared using the Wilcoxon rank-sum test.

Results

Characteristics of patients in both groups (age, sex, pathology of the visual pathway, visual acuity, pattern of visual field loss, presence of relative afferent pupillary defect) are summarized in Tables 1 and 2.

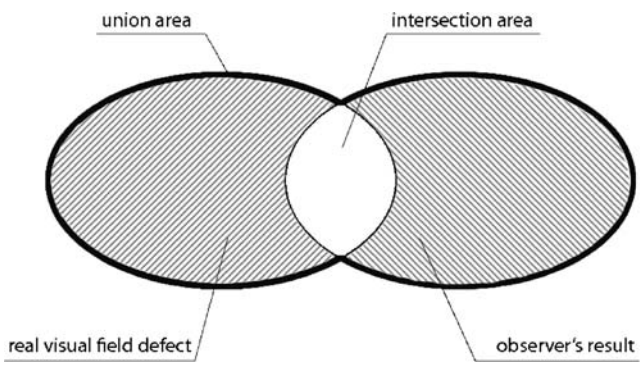
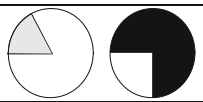
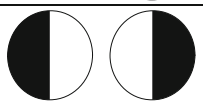
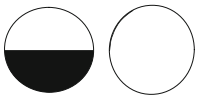


Fig. 1 Concordance between the real visual field defect and the pupil field defined by the observer is quantified by the ratio of the intersection area and the union area of the visual field defect

Table 1 Patients with a pregeniculate lesion of the visual pathway

Pat -ID	Gender Age [yrs.]	Pathogenesis	Eye	VA R	VA L	VFD	RAPD	Ex.1	Ex.2	Ex.3	Avrg Ratio
01	m, 46	Pituitary adenoma	R	0.5	1.5		1.0	0.33	0 (normal)	0.08	0.14
02	w, 55	Optic nerve sheath meningioma	R	1.25	0		-	0.5	0 (normal)	0.6	0.37
03	w, 71	Pituitary adenoma	L	0.9	0.9		no	0 (normal)	0 (normal)	0 (normal)	0
04	m, 37	Craniopharyngioma	L	1.25	1.0		0.6	1.0	0.66	0.57	0.74
05	w, 70	Sphenoid wing meningioma	L	1.0	1.25		1.2	0.75	0.25	0.75	0.58
06	m, 30	Pituitary adenoma	R	1.25	0.25		yes (*)	0.75	0.75	1.0	0.83
07	m, 77	Pituitary adenoma	R	0.8	1.0		yes (*)	0.86	0.93	0.88	0.89
08	m, 64	Pituitary adenoma	R	1.5	0		-	0.75	0.25	1.0	0.67

Patient identification (Pat-ID); gender; age at time of examination; pathogenesis of the brain lesion; eye presented for evaluation; visual acuity of the right (VA_R) and left eye (VA_L); type of visual field defect; presence and magnitude of relative afferent pupillary defect in logarithmic units (RAPD); (*) RAPD in logarithmic units not evaluated; intersection area / union area ratio of observers 1, 2 and 3 (Ex.1, Ex.2, Ex.3); normal - no depression of the pupil light reaction could be observed; average intersection / union area ratio (Avrg ratio)

Mean age of patients in group 1 was 56.3 years. Most lesions of the anterior visual pathway were caused by a tumor in the chiasmal or prechiasmal region. Only one patient (number 4) presented with incongruent left homonymous hemianopia due to the involvement of tractus opticus. Two patients (2 and 8) were blind in one eye at the time of examination. Visual field defects of all patients in this group were large and absolute. In all but one patient, a relative afferent pupillary defect was present.

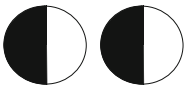
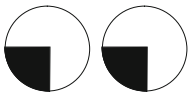
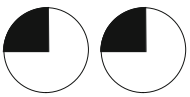
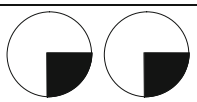
In group 1, all three observers found a relatively good correspondence between perimetric and pupillographic visual field defect in patients 4 to 8 (average intersection/union area ratio>0.5). In patient 3, none of the observers could identify a pupil field loss. Ratio of the intersection area and the union area of each observer in each individual case is listed in Table 1. An example of visual field, pupil field and corresponding intersection/union area ratios of patients 3 and 8 are shown in Fig. 2.

Mean age of patients in group 2 was 66.1 years. In all but one patient (number 4) the lesion of the retrogeniculate pathway was due to occipital infarction or hemorrhage giving rise to a homonymous quadrantanopia or hemianopia. Visual field defects of patients with retrogeniculate lesions were large, absolute and congruent. None of the patients showed a relative afferent pupillary defect, optic discs were all normal.

In group 2, an average intersection/union area ratio>0.5 was reached in all but one patient (number 5). So, in contrast to group 1, a pupil field defect corresponding to the visual field loss could be detected by all observers in seven of eight patients. Ratio of the intersection area and the union area of each observer in each individual case is listed in Table 2. An example of visual field, pupil field and corresponding intersection/union area ratios of patients 5 and 7 are shown in Fig. 3.

The statistical analysis also showed that the intersection/union area ratios were significantly higher in the group of

Table 2 Patients with a retrogeniculate lesion of the visual pathway

Pat -ID	Gender Age [yrs.]	Pathogenesis	Eye	VA R	VA L	VFD	RAPD	Ex.1	Ex.2	Ex.3	Avrg ratio
01	w, 57	Hemorrhage occipital R	R	0.9	1.0		no	0.75	1.0	0.88	0.88
02	m, 75	Ischemia occipital R	L	1.25	0		no	1.0	1.0	0.83	0.94
03	m, 73	Ischemia occipital, R/L, cortical blindness	R	light	light		no	1.0	1.0	1.0	1.00
04	m, 61	Glioblastoma occipital, R	R	0.8	0.8		no	0.8	1.0	1.0	0.93
05	w, 80	Ischemia occipital R	L	1.0	1.0		no	0 (normal)	0 (normal)	1.0	0.33
06	m, 60	Ischemia occipital L	R	1.0	1.0		no	1.0	0.5	1.0	0.83
07	m, 64	Ischemia occipital R	R	1.0	1.0		no	1.0	1.0	1.0	1.00
08	m, 59	Ischemia occipital L	L	1.0	1.0		no	0.5	0.66	1.0	0.72

Patient identification (Pat-ID); gender; age at time of examination; pathogenesis of brain lesion and site of lesion; eye presented for evaluation; visual acuity of the right (VA_R) and left eye (VA_L); type of homonymous visual field defect; presence of relative afferent pupillary defect (RAPD); intersection area / union area ratio of observers 1, 2 and 3 (Ex.1, Ex.2, Ex.3), normal - no depression of the pupil light reaction could be observed; average intersection / union area ratio (Avrg ratio)

patients with retrogeniculate lesion of the visual pathway (p=0.035), confirming a better match between visual and pupil field scotomata in the retrogeniculate lesions.

Discussion

This study compares the agreement between conventional perimetric and pupillometric loss of sensitivity to visual stimuli in patients with pre— and retrogeniculate lesions of the visual pathway. The so-called K-Train method, validated as an appropriate scoring system in the study by Schiefer et al. [14], was used for the comparison of perimetric findings. Intersection/union area ratio closer to 1.0 and a better consensus of pupil field assessment among three observers was reached in retrogeniculate lesions. The observers could very well recognize pupil field defects in cases of retrogeniculate lesions. Pregeniculate lesions, on the other hand, could be identified pupillographically only with difficulty.

Studies in patients with retrogeniculate damage have provided good evidence for an impairment of pupil responses to small localized stimuli registered by pupillography [4–13]. Early clinical reports [4–7] were later reproduced by other groups using modern pupillometric techniques in patients well-documented by magnetic resonance imaging or computed tomography [8–13], and currently there is no doubt that the retrogeniculate visual pathway or even visual cortex is involved in the pupillary light reaction, and our results support those findings. Astonishingly, in our study the retrogeniculate lesions could be better reproduced than pregeniculate by pupil perimetry. In many cases, the pupil reponse in the blind hemifield was not only depressed, but fully absent.

About the underlying cause of this finding we can only speculate. Our findings may, for example, be explained by

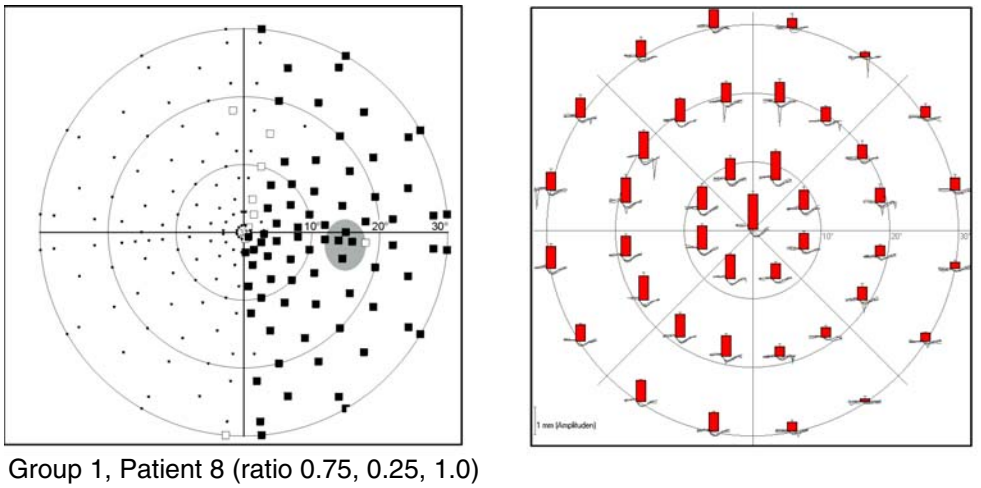


Fig. 2 Visual field, pupil field and intersection/union area ratio of two representative cases from group 1

the view that in pre— and retrogeniculate lesions different components of the light response may be involved to a different extent [15]. The steady-state component of the pupillary light response regulates the resting pupil diameter depending on the ambient light level; it is characterized by a large spatial summation and a wide dynamic range. This component is represented basically by the subcortical pupillary pathway. The transient component of the pupil light response is responsible for the constriction of the pupil in response to brisk light stimuli. In the presence of this component the steady-state signal is largely discarded. The transient component reflects merely novel changes in luminance contrast; according to Barbur [15] it is characterised by a "limited spatial summation, band-pass temporal response characteristics, and high contrast gain". It is obvious that the stimulus characteristics of pupil campimetry predominantly address this transient component. There is strong evidence that (after cortical processing of specific stimulus characteristics) projections from the extrastriate visual cortex contribute considerably to the transient pupil response component.

Furthermore, the difference in the patients groups may play a role in the explanation for our findings: The patients with pregeniculate field defects had mostly compressive, those with retrogeniculate ischemic lesions. Studies dealing with the clinical applications of pupil perimetry have shown that most diseases affecting the retina and the visual pathway cause pupil field scotomata which match the defects found in standard perimetry [7, 12, 13]. However, this is not true for all cases. Some pathologies of the anterior visual pathway (pituitary adenoma, optic neuritis, optic nerve sheath meningeoma) causing a clear defect in standard perimetry did not always show a corresponding pupil field defect [12, 13]. Remarkably, Kardon et al. [12] found that almost all patients with an anterior ischemic neuropathy showed pupillary field defects that closely resembled the visual field threshold loss. In the study by Schmid et al. [13], matching fields were found in eight of 13 patients with retrogeniculate lesions (62%) and in three of seven patients with lesions to the anterior visual pathway (42%). Large and absolute visual field loss was generally the pattern of visual field defect more likely to show up in pupil campimetry.

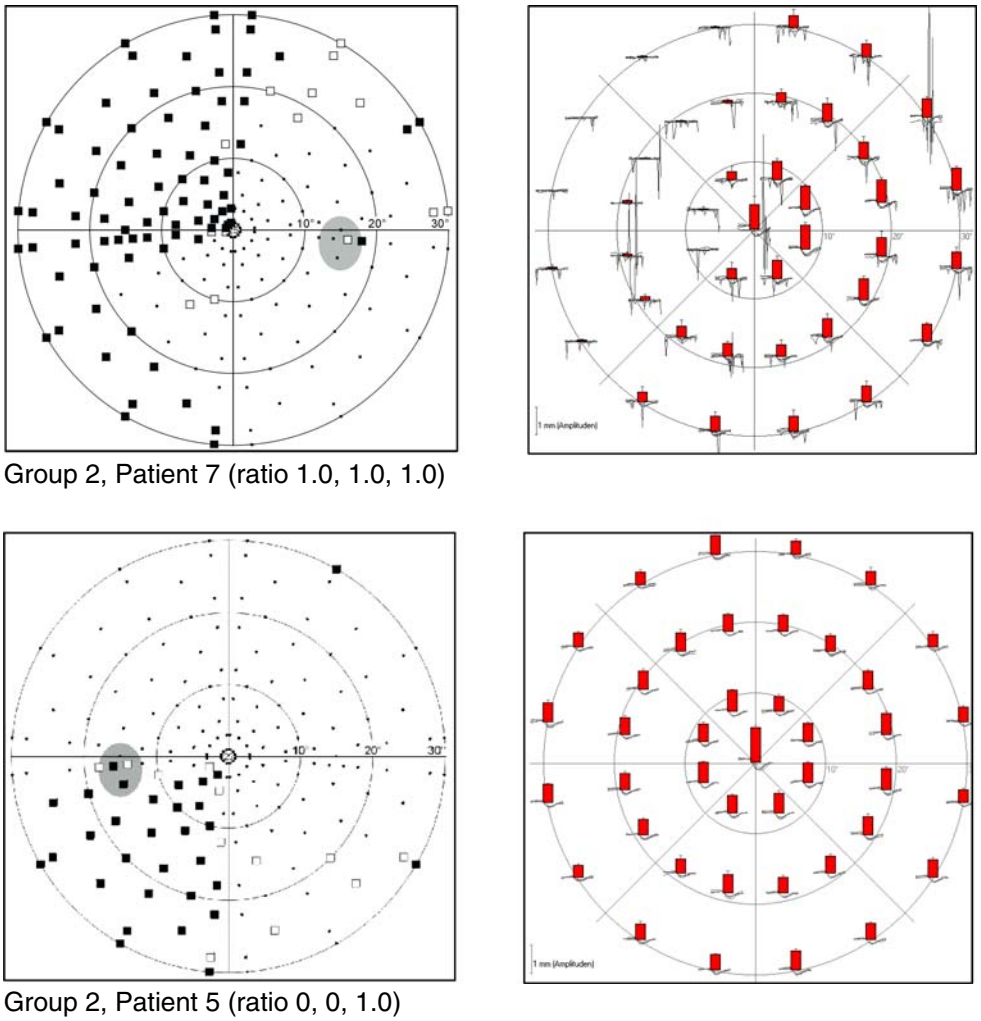


Fig. 3 Visual field, pupil field and intersection/union area ratio of two representative cases from group 2

For an ideal comparison of the closeness of the match between visual and pupil field scotomata in pre— versus postgeniculate lesions, two cohorts with the same etiology at different locations would be required. The problem, however, is that different kinds of disease typically cause either pre— or postgeniculate deficits, and finding two cohorts with the same disease but involving those different sites would be very difficult.

To discuss the discrepancy between conventional and pupil perimetry in any disorder of the visual pathway from methodical points of view, we have to consider differences in sensory and pupillary retinal receptive fields, in the susceptibility of both systems to damage and their recovery rate. Damage to the retina or optic nerve may produce different degrees of deficit at threshold levels of light compared to the brighter light levels used in pupil perimetry. Furthermore, the sensitivity profile across the visual field for visual perception and pupillomotor input may not be equivalent [11, 12].

The ability of pupil campimetry to objectify hemifield defects suggests its use in the examination of patients with suspected functional visual loss. This has been demonstrated in some studies on individual cases, as well [12, 13, 16, 17, 18]. Rajan et al. [18] conducted a study on three patients with presumed functional visual field loss respecting the midlines. They concluded that in cases of functional visual field loss where the pattern is not consistent with retro-chiasmal disease, pupil perimetry can provide objective evidence for normal visual fields. Kardon et al. [12] described a patient with functional inferior altitudinal loss in both eyes, who demonstrated a completely normal pupil field. For clinical practice it would certainly be desirable to know the sensitivity and specificity of pupil perimetry in feigned hemifield loss; however, this is not realistic, as the number of patients with functional visual field loss will never reach the limits needed for a satisfactory statistical analysis, and so we can only draw conclusions from our clinical experience with this method. That retrogeniculate

lesion can be demonstrated by pupil perimetry is of importance for the diagnosis of feigned hemifield loss, because in this situation no other ophthalomogical findings such as optic atrophy or relative afferent pupillary defect can be observed to disprove the presence of a hemifield defect.

According to our results, pupil campimetry does not demonstrate pregeniculate visual pathway lesions with sufficient reliability. In contrast, the sensitivity of pupil campimetry in retrogeniculate lesions is much higher. In those patients, pupil campimetry allows well to demonstrate a visual hemifield loss. Our study provides further evidence that the retrogeniculate visual pathway or even visual cortex is involved in the pupillary light reaction, at least under given stimulus conditions. This is in contradiction to the classical view of the pupillary pathways where a retrogeniculate lesion actually should not influence pupillary function.

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Vnitřně fotosenzitivní gangliové buňky sítnice.

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VNITŘNĚ FOTOSENZITIVNÍ GANGLIOVÉ BUŇKY SÍTNICE

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SOUHRN

Gangliové buňky sítnice s obsahem melanopsinu jsou nově objevenými fotoreceptory sítnice. Díky pigmentu melanopsinu jsou stejně jako tyčinky a čípky schopné vlastní vnitřní fototransdukce. Podílí se na řízení cirkadiánního rytmu a zornicového reflexu, možná mají i doplňkovou úlohu v procesu vidění. Pupilární reakci řízenou gangliovými buňkami s obsahem melanopsinu lze separovat pomocí tzv. chromatické pupilografie. Použití barevných stimulů k odlišení přispění jednotlivých fotoreceptorů k pupilární reakci na osvit může v pokročilých stadiích pigmentové retinopatie přinést detailnější informace o funkci fotoreceptorů než standardní elektroretinografie. Přehled shrnuje současné poznatky o gangliových buňkách sítnice s obsahem melanopsinu s důrazem na jejich význam pro klinickou praxi.
Klíčová slova: gangliové buňky sítnice, melanopsin, pupilografie, pigmentová retinopatie

SUMMARY

INTRINSICALLY PHOTOSENSITIVE RETINAL GANGLION CELLS

Recently discovered intrinsically photosensitive melanopsin-containing retinal ganglion cells contribute to circadian photoentrainment and pupillary constriction; recent works have also brought new evidence for their accessory role in the visual system in humans. Pupil light reaction driven by individual photoreceptors can be isolated by means of the so called chromatic pupillography. The use of chromatic stimuli to elicit different pupillary responses may become an objective clinical pupil test in the detection of retinal diseases and in assessing new therapeutic approaches particularly in hereditary retinal degenerations like retinitis pigmentosa. In advanced stages of disease, the pupil light reaction is even more sensitive than standard electroretinography for detecting residual levels of photoreceptor activity. This review summarizes current knowledge on intrinsically photosensitive retinal cells and highlights its possible implications for clinical practice.
Key words: retinal ganglion cells, melanopsin, pupillography, retinitis pigmentosa

Čes. a slov. Oftal., 71, 2015, No. 3, p. 144–149

Nové fotoreceptory sítnice

Světlo je důležitým regulátorem fyziologických procesů. Kromě vidění ovlivňuje řadu dalších pochodů jako je syntéza melatoninu, cirkadiánní rytmus a spánek. U člověka má navíc světlo vliv na náladu, koncentraci a psychické zdraví. Vidění a světlo nejsou tedy předmětem zkoumání pouze oftalmologie, nýbrž i dalších oborů jako je biologie, psychologie či spánková medicína.

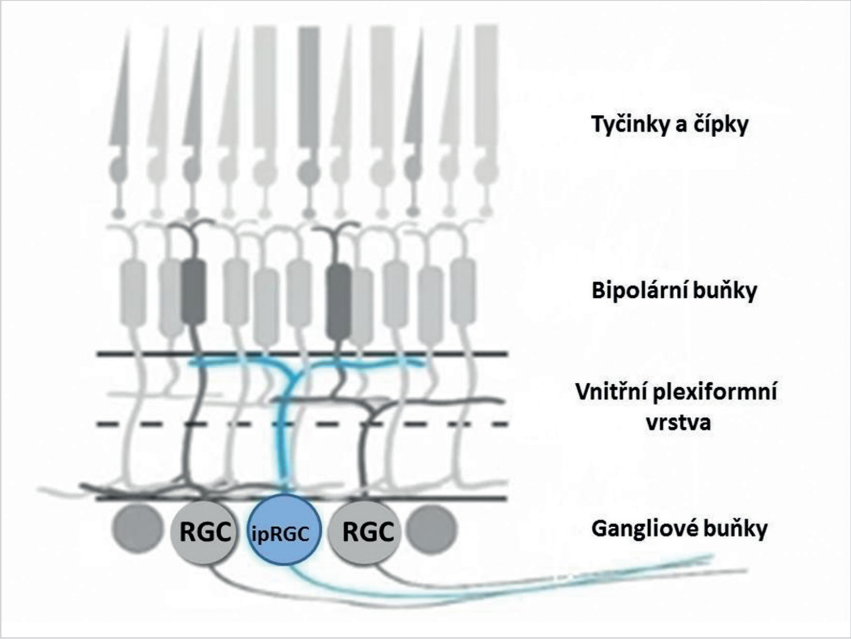
A právě při chronobiologickém výzkumu byly v roce 2002 identifikovány speciální gangliové buňky sítnice, které jsou díky obsahu melanopsinu schopné vlastní vnitřní fototransdukce [1, 9, 18]. Tento objev představoval naprosto senzační nález, vždyť více než sto let byly za jediné fotoreceptory sítnice schopné fototransdukce považovány tyčinky a čípky. Zatímco klasické fotoreceptory se nacházejí v zevní jádrové vrstvě sítnice, leží gangliové buňky s obsahem melanopsinu ve vnitřní jádrové vrstvě sítnice a jejich axony jsou součástí zrakového nervu (obr. 1). Melanopsin funguje jako fotopigment a propůjčuje těmto speciálním buňkám sítnice tzv. vnitřní fotosenzitivitu. K aktivaci vnitřně fotosenzitivních gangliových buněk sítnice (v anglické literatuře ipRGCs – intrinsically photosensitive retinal ganglion cells) může dojít buď po fototransdukci v tyčinkách a čípcích, vlastní vnitřní fototransdukcí za účasti melanopsinu, nebo oběma způsoby najednou [16, 19, 22].

Objevení dalších fotoreceptorů umožnilo vysvětlit některé nejasnosti, které se neshodovaly s tradičním modelem fotorecepce v sítnici, jako například přítomnost zornicového reflexu nebo normálního cirkadiánního rytmu u pacientů, kteří oslepli v důsledku pigmentové retinopatie. V přehledu jsou shrnuty současné poznatky o retinálních gangliových buňkách s obsahem melanopsinu s důrazem na jejich možné využití v klinické praxi.

Morfologické a funkční charakteristiky vnitřně fotosenzitivních gangliových buněk sítnice

U primátů včetně člověka tvoří gangliové buňky sítnice s obsahem melanopsinu 0,2 % všech gangliových buněk sítnice, což je zhruba 3000 buněk na jedno oko [3]. I v rámci takto malé populace vnitřně fotosenzitivních buněk s obsahem melanopsinu lze rozlišit různé podskupiny, z nichž každá má jedinečné morfologické a fyziologické vlastnosti a potenciálně i různé role. V současné době rozlišujeme pět typů vnitřně fotosenzitivních gangliových buněk sítnice (M1 až M5), většinu populace tvoří M1 a M2 buňky (74–90 %) [20]. Původně popsané gangliové buňky sítnice s obsahem melanopsinu přitom odpovídají pouze dnešní podskupině M1. Všechny gangliové buňky s obsahem melanopsinu mají velké tělo a obrovská dendritická pole. Dlouhé dendritické výběžky těchto buněk sahají do vnitřní plexiformní vrstvy sítnice, kde se vzájemně propojují.

K aktivaci fotosenzitivních gangliových buněk sítnice může dojít buď nepřímo ze zevních vrstev sítnice (tedy z tyčinek

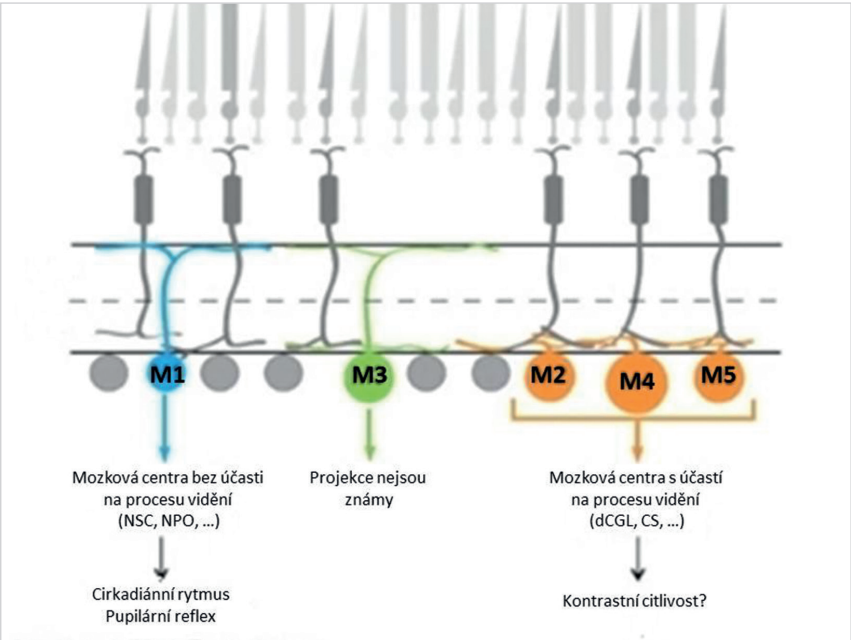


Obr. 1 Schematické znázornění vrstev sítnice a vnitřně fotosenzitivních gangliových buněk sítnice (ipRGC)

a čípků) přes bipolární buňky, přímo jejich vnitřní aktivací, nebo oběma procesy zároveň. K vnitřní aktivaci fotosenzitivních gangliových buněk dochází při působení světla o vyšším jasu, než vyžadují klasické fotoreceptory, udávají se hodnoty kolem 100 cd/m^2. Při vnitřní aktivaci gangliových buněk dochází k jejich depolarizaci a generování akčních potenciálů, jejichž charakter se poněkud liší od odpovědi tyčinek nebo čípků na světlo. Po depolarizaci gangliové buňky s obsahem melanopsinu následuje dlouhá latence k dosažení prvního akčního potenciálu, rychlost výbojů pak pomalu narůstá až do dosažení maxima, které je přímo úměrné jasu stimulu, a poté je rychlost výbojů udržována v konstantním stavu po celou dobu trvání světelného stimulu. Po ukončení stimulu neklesne frekvence výbojů náhle, nýbrž postupně [3]. Naopak při hyperpolarizaci tyčinek a čípků je latence do počáteční depolarizace gangliových buněk sítnice krátká, počáteční výboj ihned dosahuje maxima a následně se frekvence výbojů rychle snižuje, což ukazuje na časnou adaptaci těchto klasických fotoreceptorů.

Spektrální senzitivita vnitřně fotosenzitivních gangliových buněk sítnice je nejvyšší kolem 482 nm (modré světlo), částečně se tedy překrývá se senzitivitou tyčinek (497 nm) a čípků (S-čípky mají absorpční maximum kolem 420 nm, M-čípky kolem 534 nm a L-čípky vykazují nejvyšší senzitivitu při 563 nm) [1]. Schopnost absorbovat světlo je však u gangliových buněk s obsahem melanopsinu oproti tyčinkám a čípkům snížená, proto je pro jejich vnitřní aktivaci potřeba mnohem vyššího jasu [4].

Podle dosavadních poznatků tedy dochází k přímé (vnitřní) aktivaci gangliových buněk s obsahem melanopsinu zejména při stimulaci modrým světlem (cca 482 nm) o velkém jasu (100 cd/m^2) a dlouhém trvání (13 s) [16]. Kromě schop-



Obr. 2 Podskupiny vnitřně fotosenzitivních retinálních gangliových buněk (M1 až M5) a jejich projekce k mozkovým strukturám, které pravděpodobně ovlivňují (NSC – nucleus suprachiasmaticus, NPO – nucleus pretectalis olivaris, dCGL – dorzální část corpus geniculatum laterale, CS – colliculus superior). (Modifikováno podle reference 20)

nosti vlastní vnitřní depolarizace při vhodné světelné stimulaci, mohou být gangliové buňky aktivovány nepřímo z tyčinek a čípků, se kterými jsou trvale propojeny přes bipolární buňky. Tato vnější aktivace vykazuje rychlejší a výraznější depolarizaci a větší citlivost ke světlu než vnitřní fotosenzitivita [19].

Fyziologické funkce vnitřně fotosenzitivních gangliových buněk sítnice

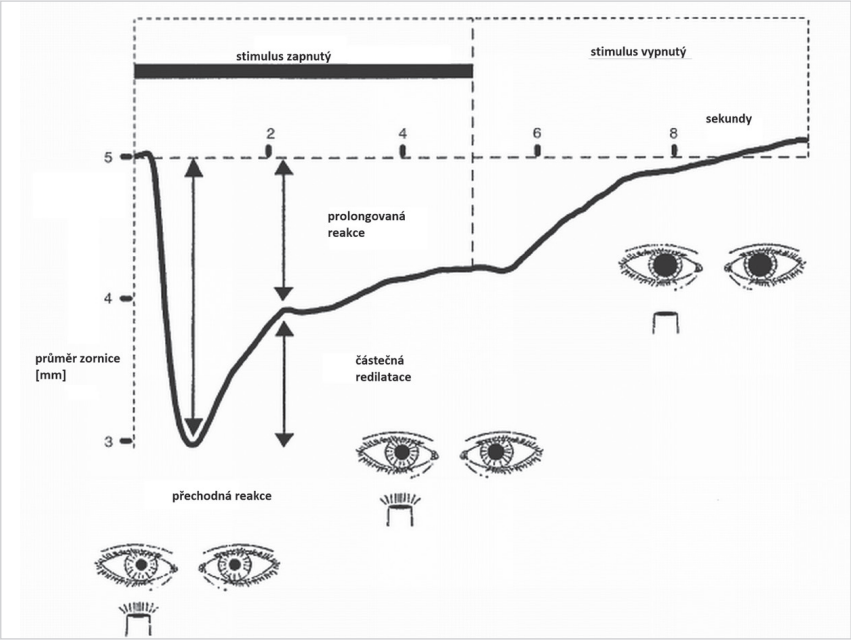
Na rozdíl od tyčinek a čípků přispívají gangliové buňky s obsahem melanopsinu k tvorbě zrakového vjemu pravděpodobně jen okrajově [3, 6]. Fungují spíše jako detektory intenzity okolního osvětlení a podílejí se na řízení cirkadiánního rytmu. Jsou ve spojení s centry pro řízení cirkadiánního rytmu v předním hypothalamu (nucleus suprachiasmaticus, intergenikulární vrstva nucleus geniculatum laterale) a spánku (nucleus preopticus ventrolateralis). Kromě toho vedou axony gangliových buněk s obsahem melanopsinu také do nucleus pretectalis olivaris v dorzálním středním mozku a tvoří tak aferentní část zornicového reflexu (obr. 2). Právě zachování gangliových buněk s obsahem melanopsinu vysvětluje, proč osoby, které osleply v důsledku postižení klasických fotoreceptorů sítnice (tyčinek a čípků u pigmentové retinopatie), mají zachovalý zornicový reflex a normální cirkadiánní rytmus [16, 19, 22]. Tyčinky, čípky a gangliové buňky s obsahem melanopsinu se při řízení cirkadiánního rytmu i pupilárního reflexu vzájemně doplňují. Například tyčinky řídí cirkadiánní rytmus při nízkých intenzitách osvětlení, gangliové buňky s obsahem melanopsinu se zapojují při vyšší světelné intenzitě. Podobně funguje komplementarita fotoreceptorů i při pupilární reakci na osvit.

Pupilární reflex

Podle klasického schématu je pupilární reflexní oblouk tvořen čtyřmi neurony. Aferentní axony retinálních gangliových buněk probíhají nejdříve ve zrakovém nervu. V chiasma opticum přechází axony z nazálních polovin sítnic obou očí do druhostranného tractus opticus, axony z temporálních polovin sítnic probíhají ipsilaterálně. V poslední třetině tractus opticus se oddělí pupilomotorická vlákna od vláken senzorických a postupují dále v brachium colliculi superioris do area pretectalis v dorzálním středním mozku. Odtud vedou interneurony k oběma jádrům Edinger-Westphal, která pomocí parasympatických vláken inervují musculus sphincter pupillae.

Pupilární reflex kontroluje změnou průměru zornice množství světla dopadajícího na sítnici. Až do nedávna byl u člověka spojován pouze s aktivací tyčinek v šeru a čípků při denním osvětlení. Z těchto klasických fotoreceptorů je informace vedena pomocí bipolárních, amakrinních a horizontálních buněk sítnice ke gangliovým buňkám sítnice a dále do mozku. Objev vnitřně fotosenzitivních buněk sítnice však ukázal, že pupilomotorická informace přivedená do středního mozku může pocházet nejen ze zevní vrstvy sítnice (aktivace tyčinek a čípků), nýbrž také z vnitřní vrstvy sítnice (aktivace melanopsinu).

Přesné stanovení vlivu jednotlivých fotoreceptorů na pupilární reakci u člověka je na rozdíl od zvířecích modelů obtížné, jistou pomoc ale nabízí hodnocení průběhu pupilární reakce pomocí pupilografie. Na obr. 3 je zobrazena typická pupilární reakce při osvitu oka jasným světelným stimulem bílé barvy o délce 10 sekund. Během zúžení zornice lze na pupilografické křivce pozorovat dvě fáze. Po zapnutí stimulu dochází k rychlé kontrakci zornice až do dosažení minimálního průměru zornice (maximální konstrikční amplituda). Tato časná, přechodná („transient“) odpověď je rychle následovaná pupilární redilatací (neboli únikem) a přechází v prolongované („sustained“), částečné zúžení zornice, které pokračuje po zbytek trvání stimulu [16, 19]. Až existence gangliových buněk s obsahem melanopsinu umožnila vysvětlit obě fáze pupilární reakce poměrným zapojením klasických fotoreceptorů a vnitřně fotosenzitivních gangliových buněk sítnice do pupilární odpovědi. Zatímco „přechodná“ komponenta pupilárního reflexu je dána časnou adaptací ty-



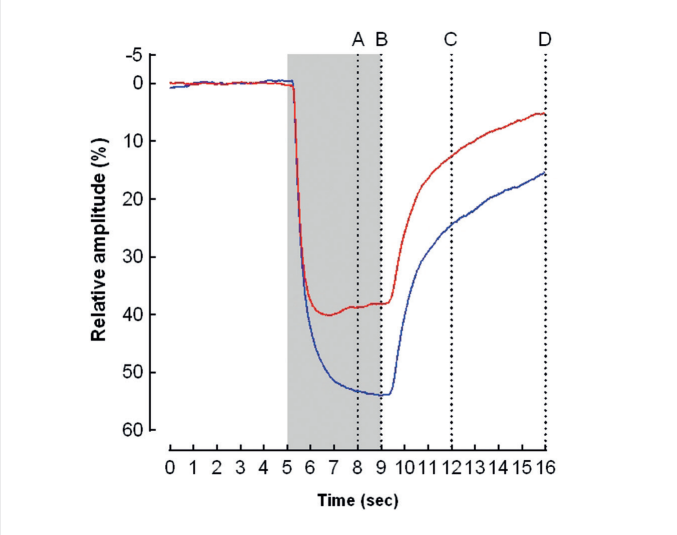
Obr. 3 Pupilografický záznam pupilární reakce na jasný, bílý, světelný stimulus o délce 5 sekund u zdravého člověka. Pupilární reakce se skládá ze dvou fází. Po zapnutí stimulu dochází k rychlé, maximální pupilární konstrikci s krátkou latencí (přechodná fáze pupilární reakce na osvit). Poté se zornice poněkud rozšíří (částečná redilatace) do stadia částečného zúžení zornice, které reprezentuje prolongovanou fázi pupilární reakce na osvit a přetrvává i po vypnutí stimulu. (Modifikováno podle reference 16)

činek a čípků na osvit, je „prolongovaná“ pupilární kontrakce způsobena vnitřní aktivací gangliových buněk s obsahem melanopsinu a souvisí s déletrvající elektrickou aktivitou těchto buněk, jak bylo popsáno výše.

V experimentech na geneticky modifikovaných myších postrádajících buď tyčinky a čípky nebo gen pro melanopsin bylo prokázáno, že ani v jedné skupině zvířat nedošlo k vymizení pupilární reakce na osvit. Tyčinky, čípky i gangliové buňky sítnice s obsahem melanopsinu tedy tvoří aferentní část pupilárního reflexu a navzájem se ve svém fungování doplňují. Poměrné přispění jednotlivých fotoreceptorů ke konstrikci zornice však závisí na parametrech světelné stimulace.

Chromatická pupilografie

Jak již bylo zmíněno, mají jednotlivé typy fotoreceptorů sítnice (tyčinky, čípky i vnitřně fotosenzitivní buňky sítnice s obsahem melanopsinu) jiná absorpční maxima a citlivost na osvit. Bílé světlo, které se při pupilografii nejčastěji používá, zahrnuje široké spektrum vlnových délek, takže dochází k sumaci odpovědí všech fotosenzitivních buněk sítnice. Pomocí světla o různé vlnové délce a jasu lze však selektivně aktivovat jednotlivé receptorové systémy. Podle toho se liší i charakter pupilární reakce a parametry pupilografické křivky. Metoda postavená na tomto principu se nazývá chromatická pupilografie a v současné době jsou v klinických studiích testovány různé protokoly, které by umožnily co nejlépe odděleně stimulovat jednotlivé populace fotoreceptorů sítnice jak u zdravých osob, tak u nemocných s různými očními patologiemi.



Obr. 4 Průměrná relativní amplituda pupilární reakce (osa y) na červený (horní křivka) a modrý stimulus (dolní křivka) u zdravých osob. Šedý sloupec znázorňuje trvání světelného stimulu. Vertikálami jsou vyznačeny body, ve kterých byla stanovena relativní pupilární amplituda, definovaná jako podíl průměru zornice v daný okamžik a jejího výchozího průměru. A – relativní amplituda 3 s po zapnutí stimulu, B – relativní amplituda při vypnutí stimulu, C – relativní amplituda 3 s po vypnutí stimulu, D – relativní amplituda 7 s po vypnutí stimulu. Při osvitu zornice modrým světlem byla relativní amplituda v každém měřeném okamžiku významně větší a latence do maximálního zúžení zornice významně delší než při působení červeného světla. Při působení modrého světla převažovala prodloužená („sustained“) kontrakce zornice, zatímco při působení červeného světla přechodná („transient“) kontrakce zornice

Červené světlo aktivuje zejména čípky, modré světlo o nízkém jasu tyčinky a modré světlo o vysokém jasu gangliové buňky sítnice obsahující melanopsin. Při osvitu zornice modrým světlem je amplituda pupilární reakce významně větší a latence do maximálního zúžení zornice významně delší než při působení červeného světla. Při působení modrého světla převažuje prolongovaná („sustained“) kontrakce zornice, zatímco při působení červeného světla přechodná („transient“) kontrakce zornice (obr. 4). Lze se domnívat, že za navýšením amplitudy a prodloužením pupilární kontrakce při působení modrého světla o vysoké intenzitě stojí vnitřní aktivace gangliových buněk s obsahem melanopsinu [12, 16, 21]. Podobně změny v „přechodné“ reakci zornice na červené světlo a modré světlo o nízkém jasu odráží pravděpodobně postižení tyčinek a čípků, zatímco změny v „prolongované“ pupilární reakci onemocnění gangliových buněk sítnice. Vzhledem k tomu, že se tyčinky a čípky nachází v zevní jádrové vrstvě sítnice a gangliové buňky s obsahem melanopsinu ve vnitřní jádrové vrstvě sítnice, nabízí chromatická pupilografie možnost využití pupilární reakce k objektivnímu vyšetření funkce zevní a vnitřní vrstvy sítnice.

Chromatická pupilografie u pacientů s pigmentovou retinopatií

Pupilární reakce na barevné světelné podněty je zkoumána také u pacientů s různými očními patologiemi, zejména pak u pacientů s pigmentovou retinopatií (RP), kteří jsou díky postižení klasických fotoreceptorů ideálním modelem. U těchto pacientů by se chromatická pupilografie mohla stát pomocnou objektivní metodou při hodnocení funkce zevní vrstvy sítnice nejen při zjišťování progrese onemocnění, ale také například při vyšetření zrakových funkcí po implantaci subretinálního chipu, jehož vývoj a aplikace ve světě úspěšně pokračují.

V řadě studií bylo zjištěno, že u pacientů s pokročilou formou RP je pupilární reakce na modré světlo nízkého a středního jasu (odpověď tyčinek) a reakce na červené světlo (odpověď čípků) ve srovnání se zdravými osobami výrazně snížená [12, 16]. Pupilární odpověď na modré světlo vysokého jasu zprostředkovaná gangliovými buňkami s obsahem melanopsinu byla u některých pacientů s RP normální [12, 14], u jiných snížená [13, 15], přestože by tyto buňky měly teoreticky zůstat intaktní. Tento jev zatím nebyl jednoznačně vysvětlen, nicméně zdá se, že v pokročilých stadiích RP dochází ke snížení počtu a změnám v morfologii také vnitřně fotosenzitivních gangliových buněk, což by mohlo nález vysvětlovat [7]. Důležitým zjištěním řady studií ale bylo, že je pomocí pupilografie možné detekovat aktivitu klasických fotoreceptorů i v pokročilých stadiích onemocnění, kdy je ERG již nevybavné a neměnné [13, 15].

Přestože se tedy občas ve studiích vyskytnou jisté nesrovnalosti, potvrzuje se v zásadě domněnka, že lze pomocí chromatické pupilografie hodnotit funkci zevní vrstvy sítnice u pacientů s RP. Podobně může pupilografie monitorovat případné zlepšení funkce, je-li u pacienta aplikována léčba.

Chromatická pupilografie při onemocnění zrakového nervu

Ve srovnání s červeným stimulem probíhá redilatace zornice po ukončení modrého stimulu o vysokém jasu déle. Tato prolongovaná pupilární konstrikce je v literatuře označovaná jako PIPR (postillumination pupil response) a je důsledkem protrahované elektrické aktivity fotosenzitivních buněk s obsahem melanopsinu při jejich vnitřní aktivaci [10]. Například u pacientů s glaukomem bylo zjištěno, že se s progresí onemocnění parametr PIPR zkracuje, což potvrzuje úbytek gangliových buněk sítnice u tohoto onemocnění [8, 11]. Překvapivě ale u pacientů s dědičnou neuropatií optiku nebyl ve srovnání se zdravými osobami zjištěn rozdíl v parametrech pupilární reakce odrážejících aktivitu gangliových buněk s obsahem melanopsinu [14]. To lze vysvětlit tak, že některé neuropatie optiku (např. glaukom) způsobují difúzní postižení gangliových buněk sítnice včetně buněk obsahujících melanopsin, jiné choroby (např. hereditární neuropatie optiku) právě tyto buňky ušetří, zatímco ostatní gangliové buňky odumírají [17].

Fotoreceptory pro cirkadiánní rytmus

Pro správné fungování cirkadiánního rytmu je nutná synchronizace vnitřních hodin s 24hodinovým cyklem světla a tmy v okolním prostředí. Hlavní biologické hodiny v nucleus suprachiasmaticus dostávají informace o intenzitě okolního osvětlení právě z retinálních gangliových buněk s obsahem melanopsinu. Existence těchto nových fotoreceptorů vysvětluje, proč zůstává i při absenci tyčinek a čípků zachován normální cirkadiánní rytmus. Při geneticky navozeném chybění melanopsinu u myší je cirkadiánní rytmus sice normální (12:12 hodinám), jen při působení modrého světla dochází k jeho fázovému posunu. U myší, kterým oči zcela chybí, však chybí i cirkadiánní rytmus. Pro fungování normálního cirkadiánního rytmu jsou tedy zapotřebí oči, nikoli ale tyčinky a čípky [16, 19, 22].

Výše uvedené rozdíly v postižení gangliových buněk s obsahem melanopsinu u různých neuropatií optiku vysvětlují jejich odlišný dopad na cirkadiánní rytmus a spánek. Například u pacientů s Leberovou hereditární neuropatií optiku, která selektivně šetří gangliové buňky s obsahem melanopsinu, nebývá přes výrazný zrakový hendikep cirkadiánní rytmus postižen [17]. Naopak bylo u zvířat s experimentálně navozeným glaukomem zjištěno, že ve srovnání se zdravými jedinci jim adaptace na posun cyklů světlo – tma trvá významně déle [5]. Pro chronobiologii bylo objevení gangliových buněk s obsahem melanopsinu velmi důležité, odstartovalo celou řadu studií a v blízké době lze jejich klinické výstupy očekávat například v oblasti spánkové medicíny nebo psychiatrie.

Vnitřně fotosenzitivní gangliové buňky sítnice a vidění

Zapojení vnitřně fotosenzitivních gangliových buněk sítnice do procesu vidění je zatím nejasné. Ecker a kol. zjistili, že při absenci tyčinek a čípků byly myši stále schopné rozlišit terčíky s pruhy o vysokém kontrastu a najít cestu z bludiště [6]. Možnou účast gangliových buněk s obsahem melanopsinu při zpracování zrakového vjemu podporují i četné spoje non-M1 buněk k centrálním mozkovým strukturám, které se nepodílí na řízení cirkadiánního rytmu ani pupilárního reflexu [3, 6]. Zda melanopsin nějakým způsobem přispívá k procesu vidění je velmi zajímavá otázka, jejíž zodpovězení může přinést nové šance na restituci vidění u pacientů, kteří oslepli v důsledku onemocnění tyčinek a čípků.

ZÁVĚR

Třetí fotoreceptory sítnice – vnitřně fotosenzitivní gangliové buňky sítnice s obsahem melanopsinu, které byly objeveny původně v rámci chronobiologického výzkumu, zásobují „vnitřní hodiny" informací o světle, významně přispívají k pupilární reakci na osvit a možná i k procesu vidění. Jejich objevení může mít významné důsledky pro řadu oborů včetně oftalmologie. Chromatická pupilografie jistě nemůže nahradit více dostupnou a rozšířenou elektroretinografii, v individuálních případech však může poskytnout detailnější hodnocení funkce zevní vrstvy sítnice než elektroretinografie a uplatnit se ve specializovaných centrech při zavádění nových terapeutických postupů zejména u dědičných dystrofií sítnice. Další studie zabývající se významem vnitřně senzitivních gangliových buněk pro lidský organismus lze jistě očekávat.

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Pupillary response to chromatic stimuli.

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Pupilární reakce na barevné podněty

Pupillary Response to Chromatic Stimuli

Souhrn

Cíl: Porovnat pupilární reakci na barevné světelné stimuly v souboru zdravých osob a zjistit, zda lze tuto metodu aplikovat pro hodnocení funkce zevní a vnitřní vrstvy sítnice. *Soubor a metodika:* Do studovaného souboru bylo zařazeno 17 zdravých osob. Ke stimulaci bylo použito červené (605 ± 20 nm) a modré (420 ± 20 nm) světlo o intenzitě 28 lx, které difuzně osvětlovalo jedno oko po dobu 4 s. Pro druhé oko každé osoby byly hodnoceny následující parametry pupilární reakce: výchozí průměr zornice, latence do maximálního zúžení zornice, relativní pupilární amplituda při maximálním zúžení zornice, tři sekundy po zahájení stimulu, při ukončení stimulu, 3 a 7 s po vypnutí stimulu. Parametry pupilární reakce byly srovnány pro červený a modrý stimulus pomocí párového t-testu. *Výsledky:* S výjimkou výchozího průměru zornice ($p = 0{,}148$) byly rozdíly v parametrech zornicové reakce na červený a modrý stimulus ve všech případech statisticky významné ($p = 0{,}001$). Při osvitu zornice modrým světlem byla relativní amplituda v každém měřeném okamžiku významně větší a latence do maximálního zúžení zornice významně delší než při působení červeného světla. Při působení modrého světla převažovala prolongovaná („sustained") kontrakce zornice, zatímco při působení červeného světla přechodná („transient") kontrakce zornice. *Závěry:* Pomocí našeho vyšetřovacího protokolu bylo možné vysledovat u zdravých osob rozdíly v pupilární reakci na červené a modré světlo, a potvrdit tak zapojení gangliových buněk sítnice s obsahem melanopsinu do pupilárního reflexu zejména při působení modrého světla. Chromatická pupilografie se jeví jako vysoce citlivá metoda, která dokáže objektivně zhodnotit funkci jednotlivých populací fotosenzitivních buněk sítnice.

Abstract

Aim of study: To compare chromatic pupillary responses in a group of healthy subjects and to determine if this method can be used for assessing outer and inner retinal function. *Material and methods:* The study group consisted of 17 healthy subjects. Subjects were tested with a chromatic pupillometer. The parameters of the stimulus were as follows: intensity 28 lx, duration 4 sec, and color blue (420 ± 20 nm) and red (605 ± 20 nm). The examined pupil parameters were baseline pupil diameter, maximal constriction time, relative amplitude at maximal constriction, at 3 sec after stimulus onset, at stimulus offset, at 3 sec after stimulus offset and at 7 sec after stimulus offset. Pupil response parameters to red and blue light were evaluated by paired t-test. *Results:* Except for the baseline pupil diameter ($p = 0.148$), there was a significant difference in all pupil response parameters to red and blue light ($p = 0.001$). With blue light, the relative amplitude was significantly greater and the time to maximal pupil constriction significantly longer compared to red light for all tested time points. Blue light evoked "sustained" pupil contraction, while red light rather induced "transient" contraction. *Conclusions:* Our examination protocol allowed us to unmask differences in pupil response to red and blue light in healthy subjects and to confirm involvement of the melanopsin retinal ganglion cells in the pupil light reflex, particularly with blue light. Chromatic pupillography appears to be a highly sensitive method for objective evaluation of the outer and inner retina function.

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Klíčová slova

pupilární reflex – melanopsin – fotoreceptorové buňky

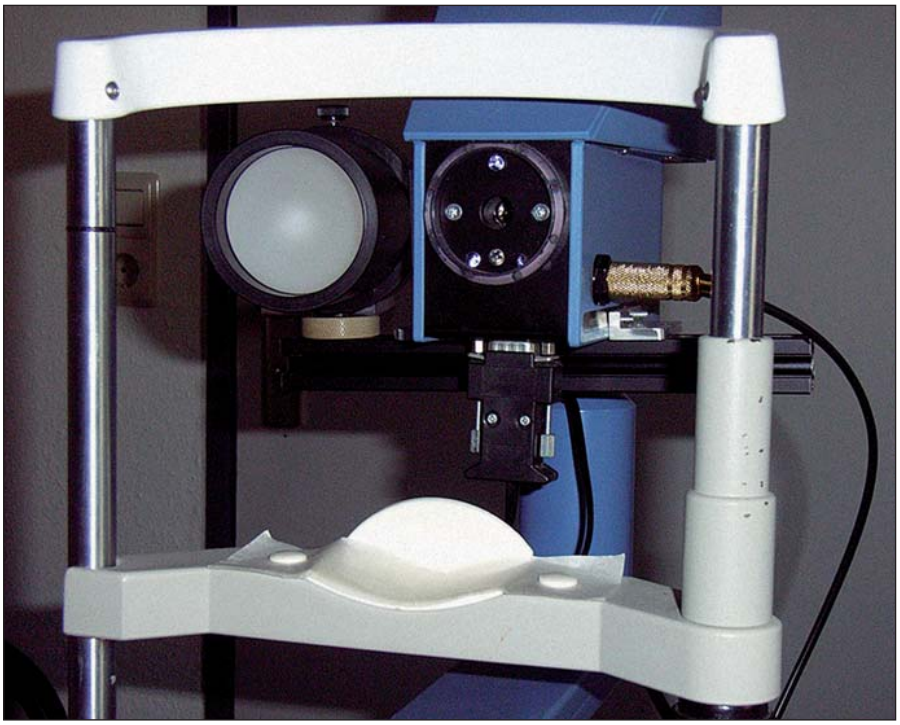
Key words

pupillary reflex – melanopsin – photoreceptor cells

Úvod

Pupilárnímu reflexu a jeho významu při objektivním hodnocení neuroretinální funkce se dostalo nové pozornosti díky nedávnému objevu nových fotoreceptorů sítnice – gangliových buněk obsahujících melanopsin [1–4]. Melanopsin funguje jako fotopigment a propůjčuje těmto speciálním buňkám sítnice tzv. vnitřní fotosenzitivitu. K depolarizaci buněk může dojít buď po fototransdukci v tyčinkách a čípcích, nebo vlastní vnitřní fototransdukcí za účasti melanopsinu, anebo oběma způsoby najednou. Na rozdíl od tyčinek a čípků nepřispívají gangliové buňky s obsahem melanopsinu k tvorbě zrakového vjemu. Fungují spíše jako detektor intenzity okolního osvětlení, a podílejí se tak na řízení cirkadiánního rytmu. Jsou ve spojení s centry pro řízení cirkadiánního rytmu v předním hypothalamu (nucleus suprachiasmaticus, intergenikulární vrstva nucleus geniculatum laterale) a spánku (nucleus praeopticus ventrolateralis). Kromě toho vedou axony gangliových buněk s obsahem melanopsinu také do nucleus pretectalis olivaris v dorzálním středním mozku, a tvoří tak aferentní část zornicového reflexu. Právě zapojení melanopsin-RGCs (Retinal Ganglion Cells) do zornicového reflexu vysvětluje, proč osoby, které osleply v důsledku postižení klasických fotoreceptorů sítnice (tyčinek a čípků), mají zachovalý zornicový reflex a normální cirkadiánní rytmus [5,6].

Tyčinky a čípky se nacházejí v zevní jádrové vrstvě sítnice, gangliové buňky s obsahem melanopsinu leží ve vnitřní jádrové vrstvě sítnice a jejich axony jsou součástí zrakového nervu. Jednotlivé typy fotoreceptorů sítnice mají přitom jiná absorpční maxima a citlivost. Pomocí světla o různé vlnové délce a intenzitě by tedy mělo být možné aktivovat selektivně jednotlivé receptorové systémy. Metoda postavená na tomto principu byla pojmenována chromatická pupilografie. V současné době jsou v klinických studiích testovány různé protokoly, které by pomocí světla o různé vlnové délce a intenzitě umožnily stimulovat jednotlivé populace fotoreceptorů sítnice jak u zdravých osob, tak u nemocných s různými očními patologiemi [7–11]. Takto vypracovaná metodika by pak v klinické praxi mohla pomoci objektivně rozlišit, zda se jedná o onemocnění zrakového nervu nebo fotoreceptorů sítnice, případně lépe kvantifikovat postižení jednotlivých populací fotoreceptorů u degenerativních onemocnění sítnice. Cílem naší práce bylo porovnat pupilární reakci na červený a modrý světelný stimulus ve skupině zdravých osob pomocí vlastního protokolu a dostupného technického vybavení a zjistit, zda a ve kterých parametrech se pupilografické křivky liší, aby bylo v budoucnu možné použít tento postup pro klinické účely.



Obr. 1. Přístroj Compact Integrated Pupillograph.

Soubor a metodika

Studie byla provedena v pupilografické laboratoři na oční klinice v Tübingenu. Do studie byly zařazeny zdravé osoby s normálním oftalmologickým nálezem z řad zaměstnanců oční kliniky a přátel autorů studie. U všech zúčastněných osob bylo před měřením zornicové reakce provedeno běžné oftalmologické vyšetření k vyloučení oční patologie (vyšetření zrakové ostrosti, změření nitroočního tlaku, vyšetření zornicových reakcí, vyšetření předního a zadního očního segmentu na štěrbinové lampě). S výjimkou korekce refrakční vady brýlemi nebo kontaktními čočkami se nikdo z osob ve studovaném souboru s očima neléčil. Studie byla schválena etickou komisí lékařské fakulty na univerzitě v Tübingenu v Německu. Účastníci studie byli podrobně informováni o účelu a průběhu studie a podepsali souhlas se svou účastí ve studii.

K vyšetření zornicové reakce byl použit přístroj Compact Integrated Pupillograph (CIP, výrobce AMTech, Německo, obr. 1). Měření probíhalo v zatemněné místnosti. Při vyšetření bylo vždy jedno oko osvětleno barevným světlem a zornicová reakce byla měřena na druhém oku pomocí infračervené videokamery. Do studie pak bylo u každé osoby zařazeno jen pravé oko. Ke stimulaci bylo použito červené (605 ± 20 nm) nebo modré (420 ± 20 nm) světlo o intenzitě 28 lx, které difuzně osvětlovalo stimulované oko po dobu 4 s. Rozlišení přístroje bylo 0,01 mm a jeho vzorkovací frekvence 250 Hz.

Každý stimulus byl prezentován pětkrát. Z pěti odpovědí zornice byla zjištěna průměrná amplituda pupilární reakce na daný barevný podnět a ta byla použita pro další výpočty. Byly hodnoceny následující parametry pupilární reakce: výchozí průměr zornice, latence do maximálního zúžení zornice, relativní pupilární amplituda při maximálním zúžení zornice (podíl změny průměru zornice po prezentaci stimulu a jejího výchozího průměru), relativní pupilární amplituda 3 s po zahájení stimulu, relativní pupilární amplituda při ukončení stimulu, 3 s po vypnutí stimulu a 7 s po vypnutí stimulu. Relativní pupi-

lární amplituda byla ve všech případech definována jako podíl průměru zornice v daný okamžik a jejího výchozího průměru. Všechny zjišťované parametry pupilární reakce byly ve studovaném souboru následně srovnány pro červený a modrý stimulus pomocí párového t-testu.

Výsledky

Do studovaného souboru bylo zařazeno 17 očí 17 zdravých osob. Průměrný věk osob ve studovaném souboru byl 55,6 ± 11,7 let. V tab. 1 jsou uvedeny průměrné hodnoty všech měřených parametrů zornicové reakce pro červený a modrý stimulus a jejich standardní odchylka. V posledním sloupci tabulky je statistická významnost „p" rozdílu obou hodnot po vyhodnocení t-testem. S výjimkou výchozího průměru zornice (p = 0,148) byly rozdíly v parametrech zornicové reakce na červený a modrý stimulus ve všech případech statisticky významné (p = 0,001).

Na grafu 1 je prezentována průměrná zornicová reakce na červený a modrý podnět ve studovaném souboru. Rozdíl v průběhu zornicové reakce na červený a modrý podnět je jasně patrný. Při osvitu zornice modrým světlem byla relativní amplituda významně větší a latence pupilární reakce významně delší než při působení červeného světla. Při působení modrého světla převažovala prolongovaná („sustained") kontrakce zornice, zatímco při působení červeného světla přechodná („transient") kontrakce zornice.

Tab. 1. Průměrné hodnoty jednotlivých parametrů pupilární reakce měřených ve studovaném souboru během prezentace modrého nebo červeného stimulu. Tučně zvýrazněné hodnoty „p" ukazují na statisticky významné rozdíly mezi zjištěnými hodnotami.

	Modré světlo	Červené světlo	p
Výchozí průměr zornice (mm)	5,43 ± 1,11	5,49 ± 1,18	0,148
Latence do max. zúžení zornice (s)	3,51 ± 0,82	2,11 ± 1,11	**0,001**
Relativní amplituda			
• při maximálním zúžení zornice (%)	54,7 ± 6,0	42,1 ± 6,0	**0,001**
• 3s po zapnutí stimulu (%)	53,1 ± 6,1	38,6 ± 6,2	**0,001**
• při vypnutí stimulu (%)	54,0 ± 5,8	38,1 ± 6,4	**0,001**
• 3 s po vypnutí stimulu (%)	24,3 ± 7,0	12,5 ± 5,2	**0,001**
• 7 s po vypnutí stimulu (%)	15,3 ± 6,4	5,0 ± 4,2	**0,001**

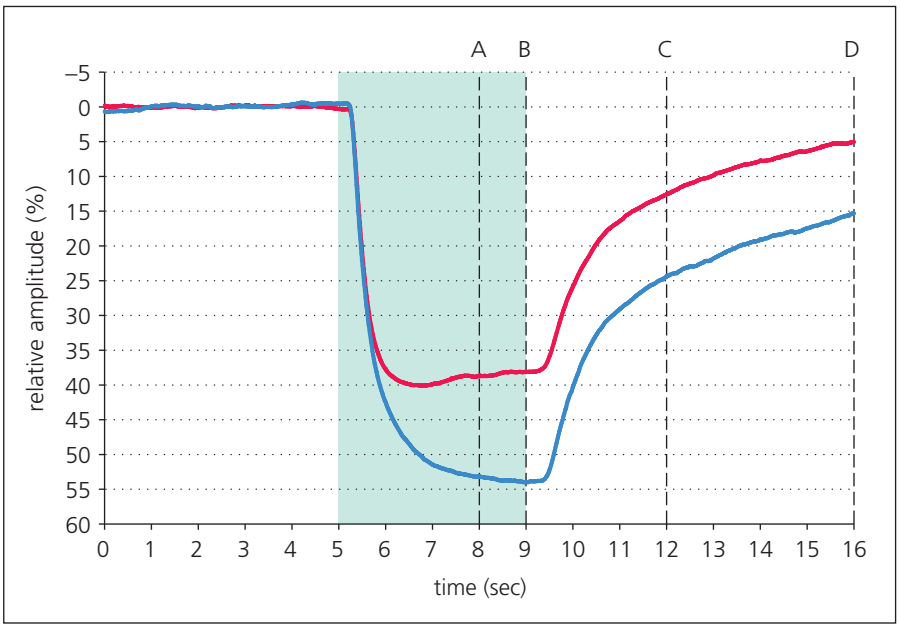
Diskuze

Pupilární reflex kontroluje změnou průměru zornice množství světla dopadajícího na sítnici. Pupilární reflex byl u člověka spojován pouze s aktivací tyčinek v šeru a čípků při denním osvětlení. Z těchto klasických fotoreceptorů byla informace vedena pomocí bipolárních, amakrinních a horizontálních buněk sítnice ke gangliovým buňkám sítnice a jejich axony dále do mozku. Před 10 lety však Lucas et al prokázali, že u pokusných myší postrádajících tyčinky i čípky byla pupilární reakce na osvit sice snížená, nicméně však přítomná. Zároveň byl u těchto zvířat zachován normální cirkadiánní rytmus [12]. Krátce nato se podařilo identifikovat podskupinu vnitřně fotosenzitivních gangliových buněk sítnice obsahujících melanopsin [2,13], které se na rozdíl od tyčinek a čípku neúčastní tvorby zrakového vjemu, nýbrž se podílejí na zajištění cirkadiánního rytmu a zornicového reflexu [3,4,14]. Axony těchto buněk vedou do oblasti dorzálního středního mozku (centrum pupilárního reflexu) a do hypothalamu (centrum pro cirkadiánní rytmus).

Pupilární reakce na osvit je tedy kombinací aktivity tyčinek, čípků a gangliových buněk sítnice obsahujících melanopsin. Nejčastěji se při pupilometrii používá bílé světlo. Bílé světlo však zahrnuje široké spektrum vlnových délek, takže dochází k sumaci odpovědí všech fotosenzitivních buněk sítnice účastnících se pupilární reakce. Chromatická pupilografie naopak umožňuje odlišit jednotlivé populace buněk, které k této sumaci přispívají. V naší studii jsme se zabývali srovnáním pupilární reakce na červené a modré světelné stimuly v souboru zdravých osob. Červené světlo má dlouhou vlnovou délku a aktivuje zejména čípky. Modré světlo reprezentuje krátkou vlnovou délku, na kterou reagují při nízkých intenzitách tyčinky, s rostoucí intenzitou osvětlení se přidávají gangliové buňky sítnice obsahující melanopsin a částečně také čípky. Podle dosavadních poznatků dochází k přímé (vnitřní) aktivaci gangliových buněk s obsahem melanopsinu zejména při stimulaci světelnými podněty o krátké vlnové délce (cca 482 nm), velké intenzitě (100 cd/m^2) a dlouhém trvání (13 s) [5].

Při osvitu zornice modrým světlem byla v naší studii relativní pupilární amplituda významně větší a latence do maximálního zúžení zornice významně delší než při působení červeného světla. Lze se tedy domnívat, že za navýšením amplitudy při působení modrého světla stojí zapojení gangliových buněk s obsahem melanopsinu do pupilární odpovědi. Delší latence pupilární reakce na modrý stimulus rovněž podporuje dosavadní poznatky o chování gangliových buněk obsahujících melanopsin. Elektrofyziologická studie Daceyho et al, kteří měřili akční potenciály z jediné gangliové buňky s obsahem melanopsinu izolované in vitro ze sítnice opice makaka, totiž ukázala, že po přímé depolarizaci této gangliové buňky následuje dlouhá latence k dosažení prvního akčního potenciálu. Rychlost výbojů pak pomalu narůstá až do dosažení maxima, které je přímo úměrné světelné intenzitě, a poté je rychlost výbojů udržována v konstantním stavu po celou dobu trvání světelného stimulu. Po ukončení osvitu neklesne frekvence výbojů náhle, nýbrž postupně. Naopak při hyperpolarizaci tyčinek a čípků je latence do počáteční depolarizace gangliových buněk sítnice krátká, počáteční výboj ihned dosahuje maxima a následně se frekvence výbojů rychle snižuje, což ukazuje na časnou adaptaci těchto klasických fotoreceptorů [15].

Zmíněným elektrofyziologickým charakteristikám sítnicových fotoreceptorů odpovídají dvě fáze pupilární reakce během zúžení zornice. Když se rozsvítí světelný stimulus, nastává rychlé a okamžité zúžení zornice do dosažení maxima neboli tzv. maximální konstrikční amplitudy. Tato časná, přechodná („transient") odpověď je následována rychlou pupilární redilatací neboli únikem („escape"), který přejde v postupnou, prolongovanou



Graf 1. Průměrná zornicová reakce na červený a modrý podnět ve studovaném souboru.

(„sustained") pupilární konstrikci. Ta pokračuje po zbytek trvání stimulu. „Přechodná" a „prolongovaná" komponenta pupilárního reflexu může být vysvětlena rozdílným přispěním tyčinek, čípků a gangliových buněk sítnice s obsahem melanopsinu při zpracování světla [5]. V naší studii při působení modrého světla převažovala prolongovaná („sustained") kontrakce zornice, zatímco při působení červeného světla přechodná („transient") kontrakce zornice. Prolongovaná pupilární kontrakce při prezentaci modrého stimulu dokumentuje déletrvající elektrické výboje gangliových buněk s obsahem melanopsinu. Při stimulaci červeným světlem nebyla prolongovaná kontrakce zornice patrná.

Využití chromatické pupilografie u onemocnění sítnice je zatím ve fázi klinických studií. Různé vyšetřovací protokoly jsou testovány zejména u pacientů s dysfunkcí tyčinek a čípků. Všechny protokoly vychází z předpokladu, že tyčinky (absorpční maximum 498 nm) reagují nejlépe na modré světlo o nízké intenzitě a gangliové buňky s obsahem melanopsinu jsou citlivé na modré světlo o mnohem vyšší intenzitě. S-čípky (čípky s absorpčním maximem při 460 nm, tedy při krátkých vlnových délkách) přispívají k pupilární reakci při hodnotách světelnosti asi o 3 log více, než je dostačující pro tyčinky. L/M čípky (čípky se spektrální citlivostí ke středním (530 nm) a dlouhým (560 nm) vlnovým délkám) mohou být naopak samostatně stimulovány při vlnových délkách nad 620 nm, při kterých tyčinky, gangliové buňky a S-čípky nereagují [16,17]. Kardon et al při vývoji jejich protokolu chromatické pupilografie vyšetřili i pacienta s retinitis pigmentosa, což je hereditární dystrofie sítnice postihující tyčinky a čípky. Pupilární odpověď na modré světlo nízké a střední intenzity byla ve srovnání se zdravými osobami výrazně snížená (v důsledku převažujícího postižení tyčinek) a odpověď na červené světlo byla mírně snížená (v důsledku postižení čípků). Pupilární reakce na intenzivní modré světlo však snížená nebyla, pravděpodobně díky zachované vnitřní aktivaci gangliových buněk s obsahem melanopsinu, které u retinitis pigmentosa nejsou postiženy [7]. Rovněž ve své další studii hodnotili Kardon et al pupilární reakci na barevné podněty, tentokrát u větší skupiny pacientů s retinitis pigmentosa. Byly nalezeny významné rozdíly mezi pacienty s retinitis pigmentosa a zdravými osobami při testovacích podmínkách, které měly zdůraznit přispění tyčinek (1 cd/m^2, modré světlo) nebo čípků (100 cd/m^2, červené světlo). V obou případech byla pupilární odpověď u pacientů s retinitis pigmentosa ve srovnání se zdravými osobami významně snížená, nicméně přítomná i u pacientů s vyhaslým elektroretinogramem (ERG). Navzdory slibným výsledkům byla však u dvou pacientů ve studii pupilární odpověď i přes abnormální ERG srovnatelná se zdravými osobami. Autoři proto konstatují, že jejich současný testovací protokol ještě není dostatečně selektivní pro aktivaci jednotlivých populací fotoreceptorů [9]. Kawasaki et al srovnávali pomocí pupilární reakce funkci tyčinek, čípků a gangliových buněk s obsahem melanopsinu u devíti pacientů s autozomálně dominantně dědičnou formou retinitis pigmentosa a 12 zdravých osob. Pupilární odpověď na modré světlo nízké intenzity po adaptaci na tmu byla u pacientů s retinitis pigmentosa snížená, což pravděpodobně reflektovalo sníženou funkci tyčinek, a dále se s progresí onemocnění snižovala. Pupilární reakce na červené světlo se u nemocných očí adaptovaných na světlo naopak nelišila od pupilární reakce zdravých osob. Překvapivě ale byla u pacientů s retinitis pigmentosa významně snížená i pupilární odpověď zprostředkovaná gangliovými buňkami s obsahem melanopsinu. Autoři studie zdůrazňují, že s ohledem na korelaci amplitudy pupilární reakce a progrese onemocnění lze chromatickou pupilografii využít pro detailnější monitorování degenerace fotoreceptorů, než nabízí klasická elektroretinografie [11].

Dalším parametrem, který lze sledovat při hodnocení příspěvku gangliových buněk sítnice s obsahem melanopsinu k pupilárnímu reflexu, je protrahovaná kontrakce zornice po vypnutí stimulu (Postillumination Pupil Response, PIRP). Ve srovnání s jasným, červeným stimulem probíhá redilatace zornice po ukončení modrého stimulu o vysoké intenzitě opožděně v důsledku protrahované elektrické aktivity gangliových buněk sítnice obsahujících melanopsin [18]. Bylo prokázáno, že u pacientů s glaukomem se s progresí onemocnění parametr PIRP zkracuje, což potvrzuje úbytek gangliových buněk sítnice u tohoto onemocnění [19,20].

Současné vyšetřovací metody, které hodnotí zrakové funkce, jsou převážně metody subjektivní. Vyžadují dobrou spolupráci pacienta a nelze vyloučit fluktuaci výsledků. Naopak pupilometrie je metoda objektivní, protože pupilární reflex závisí na aktivních nervových spojeních mezi sítnicí a mozkovým kmenem a ty nemohou být pacientem ovlivněny. Na základě dosavadních výsledků se chromatická pupilografie jeví jako vysoce citlivá metoda, jež

dokáže objektivně zhodnotit funkci jednotlivých populací fotosenzitivních buněk sítnice. To může být velmi výhodné při hodnocení progrese onemocnění nebo přínosu léčby. Jako přínosné se jeví zejména její využití při vyšetřování pacientů s degenerativním onemocněním sítnice či při kvantifikaci přínosu nových léčebných postupů u pacientů zařazených do experimentálních studií. Pomocí našeho vyšetřovacího protokolu bylo možné vysledovat u zdravých osob rozdíly v parametrech pupilární reakce na červené a modré světlo, a potvrdit tak podíl gangliových buněk sítnice s obsahem melanopsinu na pupilární reakci. V další studii plánujeme aplikovat náš protokol pro srovnání parametrů pupilární reakce mezi souborem zdravých osob a pacienty s onemocněním sítnice a zrakové dráhy.

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