Ocular pulse amplitude is reduced in patients with advanced retinitis pigmentosa

Karl-Georg Schmidt, Lutz E Pillunat, Konrad Kohler, Josef Flammer

Abstract

Background/aims—The choroid, a low resistance vascular structure carrying 85% of the ocular blood flow, provides nourishment to and removal of potential toxic waste products from the adjacent non-vascularised outer layers of the retina, macula, and optic disc regions. Choroidal perfusion may be reduced in retinitis pigmentosa (RP) and might contribute to retinal pigment epithelium (RPE) degeneration. The aim of this study was to determine whether choroidal perfusion is reduced in RP and whether this is correlated with the stage of disease.

Methods—Ocular pulse amplitude (OPA) evaluated with the ocular blood flow (OBF) system, applanation intraocular pressure (IOP), visual fields, blood pressure (BP), and heart rate (HR) were measured in 75 RP patients having stage RP-I (stage I: visual field size: 7.85–14.67 cm²; n = 22), stage RP-II (stage II: visual field size: 2.83–7.84 cm²; n = 29), or stage RP-III (stage III: visual field size: 0.52–2.82 cm²; n = 24) were compared with matched healthy controls and each other.

Results—Neither IOP nor systemic perfusion parameters were significantly (p >0.1) altered, but OPA (mm Hg) in RP patients beginning with stage RP-II (1.6 (0.1), 27.3%, p<0.0001), and RP-III (1.2 (0.1), 45.5%, p<0.0001) was significantly reduced when compared with matched subgroups from a pool of healthy controls (2.2 (0.1), n = 94).

Conclusions—OPA can be used neither for early clinical detection of RP nor to follow the natural course of the disease. However, our data show that in advanced stages of RP not only the retina but also the choroidal circulation is affected.

Retinitis pigmentosa (RP) comprises a group of progressive degenerative retinal diseases caused by genetic defects localised on different chromosomes affecting approximately 1.5 million people worldwide. In the majority of cases, RP leads to blindness at around the age of 60 years.¹

Whereas retinal perfusion is reduced in RP;² possibly related to a difference in the electrophysiological properties of retinal capillary pericytes;³ a review of the literature shows contradictory results regarding the role of the choroidal vasculature in this genetic aberration. Histological examination showed a normal choroid in two donor eyes,⁴ while Henkind and Gartner observed absence of the choriocapillaris.⁵ Ulrich et al using perfusion pressure videoangiography showed atrophy of the choroid capillary network.⁶ Langham and Kramer noted an overall 48% reduction of the mean ocular pulse amplitude in 13 RP patients with varying degrees of disease when compared with healthy volunteers.⁷

The choroid is a low resistance vascular structure which maintains a constant thermal environment for the retina,⁸,⁹ as well as supplying 80% of the total retinal oxygen,¹⁰ all the retinal glucose,¹⁰ and 100% of the nutrients to the macula and optic disc region.¹¹ It is also responsible for the removal of potential toxic waste products from the retina. Nutrition and clearance of the retina by diffusion necessitate an extremely high blood flow in the choroid (800–1200 ml/100 g/min,¹² which reflects 85% of the total ocular blood flow).¹³ Reduced blood flow is correlated with hypoxia in an extreme situation resulting in, for example, myocardial or cerebral tissue infarctions. Similar cell death mechanisms might also exist in ocular pathology, such as glaucoma and RP. Results from clinical studies show reduced choroidal perfusion in normal tension glaucoma (NTG) patients and increased choroidal perfusion in ocular hypertensive volunteers pointing at a protective mechanism or adaptive change to prevent hypoxia of neural tissue because reduced blood flow might result in functional (visual field defects) and morphological (nerve fibre layer loss) damage.¹⁴⁻¹⁶

Vasoactive drugs increase choroidal perfusion in NTG¹⁷,¹⁸ and high tension glaucoma (HTG) patients,¹⁷,¹⁸ and improve visual fields.¹⁹ Improved ocular haemodynamics and a beneficial effect on the remaining visual field area on breathing carbon dioxide, a strong vasodilator, has already been demonstrated in RP patients.²⁰

This study was designed to evaluate ocular pulse amplitude (OPA), a measure for choroidal blood flow in RP, and to correlate these data with visual field size.

Materials and methods

Included in the investigation were 75 RP patients with no known systemic or ocular disease other than the category for which they were selected. Patients and healthy controls were on no ocular or systemic therapy.

The RP patients chosen had a history of pre-treatment IOPs <21 mm Hg, typical concentric visual field loss as determined by standard Goldmann perimetry (III, 4e) and electroretinographic findings (diminished or extinguished b-wave amplitude), and showed typical fundus appearance.
Visual field size of all patients and controls was determined by the same well trained and highly motivated and experienced perimetrist along different radii in a random and rhythmic pattern using standard Goldmann perimetry (III, 4e, stimulus movement at 2° per second) scanning the visual fields into a 166 MHz computer (Fujitsu America Inc, San Jose, CA, USA) and calculating the area within the III, 4 margin using the Autocad R 12 program (Autodesk Systems Inc, San Rafael, CA, USA); visual field size reduction was expressed in percentages when compared with our standard of a healthy visual field (15.10 (0.06) cm², 0% visual field size reduction, n = 94, age 23.3 (2.2) years).

The RP patients were staged according to visual field size related to patient self-assessment: RP-I (stage I: visual field size: 7.85–14.67 cm², respective visual field size reduction 2.9–48.0%; n = 22, male = 12, female = 10, age: 25.1 (2.2) years), RP-II (stage II: visual field size: 2.83–7.84 cm², respective visual field size reduction: 48.1–81.2%; n = 29, male = 17, female = 12, age: 33.3 (2.8) years), and RP-III (stage III: visual field size: 0.52–2.82 cm², respective visual field size reduction: 81.3–96.6%; n = 24, male = 14, female = 10, age: 47.7 (3.9) years).

Patient groups were compared with matched control subgroups selected from a pool of 94 healthy volunteers with no known ocular or systemic disease, who showed no visual field defects and/or disc alterations and had IOPs < 21 mm Hg matched for age (SD 3 years), sex, IOP (SD 2 mm Hg), and refraction (SD 1.5 diopters spherical equivalent). The study has been approved by the appropriate institutional review board, and informed consent was obtained from each patient/volunteer following complete explanation of the procedure.

OPA is an indirect measure of choroidal perfusion. A bolus of blood entering the eye corresponding to the cardiac pulse represents a change in IOP as a function of time reflecting the pulsatile component (approximately 70%) of intraocular blood flow, and 85% of which is choroidal.

The technology of the ocular blood flow (OBF) system (OBF Labs Ltd, Wilts) and its relation to choroidal blood flow has been described in detail elsewhere. In addition to pneumotonometric values, IOP was measured by Goldmann applanation tonometry. Brachial artery pressures were measured non-invasively (Riva-Rocci) using a blood pressure cuff and a stethoscope. Heart rate (HR) was measured manually using a stopwatch. Applanation IOP, systolic (BP syst) and diastolic (BP diast) blood pressures (BP) and HR were taken before OPA measurements.

**Statistics**

All data represent arithmetic mean (SEM); Student’s unpaired two tailed t test and linear regression analysis were used for statistical analysis; correlation (r) and regression (q) coefficients were calculated. Measurements were performed on both eyes of each subject. The level of significance was 5%. RP groups were compared with matched subgroups from a pool of healthy volunteers and with each other.

**Results**

When compared with matched subgroups from a pool of healthy controls (n = 94), neither IOP (Fig 1, Table 1) nor systemic perfusion parameters (Table 1) were significantly (p > 0.1) altered in any of the three RP groups investigated.

OPA (mm Hg; Fig 2, Tables 1 and 2) in RP-I (2.2 (0.1)) was within the same range as the controls (2.2 (0.2)). However, in all other RP groups, OPA was highly significantly reduced. At stage II (1.6 (0.1)) the reduction was 27.3% (p < 0.0001) further declining—corresponding to the severity of the disease—to a 45.5% reduction (p < 0.0001) at stage RP-III (1.2 (0.1)).

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**Table 1 Comparison of perfusion parameters (mean (SEM)) of retinitis pigmentosa (RP) patients stages I (n = 22), II (n = 29), and III (n = 24), each compared with a matched control subgroup from a pool of healthy volunteers (n = 94)**

<table>
<thead>
<tr>
<th></th>
<th>OPA (mm Hg)</th>
<th>IOP (mm Hg)</th>
<th>Blood pressure (systolic, mm Hg)</th>
<th>Blood pressure (diastolic, mm Hg)</th>
<th>Heart rate (pulse, beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.2 (0.1)</td>
<td>15.0 (0.3)</td>
<td>124.8 (1.6)</td>
<td>77.1 (1.3)</td>
<td>76.8 (1.6)</td>
</tr>
<tr>
<td>RP-I</td>
<td>2.2 (0.1)</td>
<td>16.1 (0.5)</td>
<td>121.0 (4.2)</td>
<td>76.2 (2.3)</td>
<td>76.2 (4.2)</td>
</tr>
<tr>
<td>Matched control</td>
<td>2.2 (0.2)</td>
<td>14.9 (0.8)</td>
<td>123.4 (5.9)</td>
<td>76.8 (1.9)</td>
<td>78.0 (5.0)</td>
</tr>
<tr>
<td>RP-II</td>
<td>1.6 (0.1)*</td>
<td>14.7 (0.4)</td>
<td>123.3 (2.7)</td>
<td>77.2 (1.5)</td>
<td>80.0 (1.9)</td>
</tr>
<tr>
<td>Matched control</td>
<td>2.2 (0.1)</td>
<td>15.0 (0.6)</td>
<td>127.1 (4.2)</td>
<td>75.7 (2.0)</td>
<td>76.3 (2.5)</td>
</tr>
<tr>
<td>RP-III</td>
<td>1.2 (0.1)*</td>
<td>14.7 (0.3)</td>
<td>127.6 (4.1)</td>
<td>79.8 (3.1)</td>
<td>80.7 (4.0)</td>
</tr>
<tr>
<td>Matched control</td>
<td>2.3 (0.1)</td>
<td>15.1 (0.4)</td>
<td>124.5 (3.7)</td>
<td>76.4 (2.6)</td>
<td>76.7 (3.2)</td>
</tr>
</tbody>
</table>

*Represents p < 0.05 using Student’s unpaired two tailed t test.
Since nitric oxide (NO), a potent vasodilator produced in the retina,39 RPE,37 as well as ophthalmic and ciliary arteries,31 is involved in the regulation of choroidal vascular tone,30 a destruction of the RPE and retina may lead to an impeded production of this metabolite, resulting in vasoconstriction and even obliteration of choroidal and retinal vessels as a secondary phenomenon due to the RP disease process in the RPE and retina.

A consequence from our data may be to use vasodilators in RP in order to quantify their influence on ocular perfusion and visual field size and to correlate both parameters in a long term double blind randomised crossover placebo controlled study. Before starting in humans, the OPA alteration found in RP patients should be proved in an RP animal model—for example, in the RCS rat. This will allow us to follow the course of OPA in parallel to progression of the disease and to correlate OPA measurements with histological changes in the RPE, retina, and choroid. In a future series of experiments vasodilators should be investigated.

This may also help to clarify whether choroidal ischaemia contributes as a primary factor to progression of RP or is (as discussed above) caused secondly as a result of mediators released in the RPE and/or retina. In either case dilating choroidal vessels should increase OPA in advanced RP and thus—as demonstrated with a carbon dioxide provocation test34—possibly improve visual field size.

Care must be taken in choosing the vasodilator suited best for such a study since vasodilators in general do not necessarily increase ocular perfusion.

Nitrates, such as isosorbide dinitrate (ISDN), cause vasodilatation, especially in the veins. Nitrate induced peripheral venous pooling reducing cardiac preload is well investigated.32 This and the direct spasmylytic effect on coronary arteries33 are the basis for the wide use of nitrates in coronary artery disease.32 33 Frayser and Hickam34 noted arterial and venous dilatation in retinal vessels following application of nitrates. Surprisingly, oxygen saturation was reduced in the retinal vessels, and the arteriovenous oxygen difference was increased, interpreted by the authors as a reduction in retinal perfusion. This finding might be explained by local vasoconstriction due to oxygen35 and/or the drop in systolic ophthalmic artery pressure, systolic ocular perfusion pressure and OPA, passively reflecting the drop in systemic blood pressure.36

Nifedipine and nimodipine are dihydropyridine based calcium channel blockers with different tissue selectivities for vascular smooth muscle cells. Nifedipine acts primarily on coronary and peripheral vessels and is used in coronary artery disease.32 33 Nifedipine is applied in patients with NTG, reducing reduced choroidal perfusion16 and
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Conclusion

OPA, a haemodynamic parameter reflecting mainly choroidal perfusion, is reduced in RP patients beginning at stage II, which differs from another observation reporting on an overall reduction of OPA without correlating it to stage of disease.

Because OPA is also reduced in other pathologies, 15–27 and reduction is not significant up to stage II, it can be used neither as a specific measure for clinical detection of RP nor to follow the natural course of this disease. However, the data show that in advanced stages of RP not only the RPE and retina but also the choroid are affected by this genetic aberration.

The apparent decrease of choroidal capacity in RP suggests a vasodilatory approach to the choroid, avoiding a “steal” effect. Thus, a long term nitrate therapy cannot be enhanced by ophthalmocirculatory aspects. A negative effect on progression of retinal degeneration in RP patients who are also on nitrates for other disorders is conceivable. In contrast with nitrates, nifedipine and other primarily arterial vasodilators might increase ocular, mainly choroidal, perfusion and thus improve nourishment to and removal of potential toxic waste products from the RPE and the adjacent non-vascularised outer layers of the retina, macula, and optic disc regions in RP patients.

Future controlled studies on vasoactive drugs will elucidate the effect of increased ocular perfusion on progression of this disease.


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