Retinal Oxygen Saturation in Retinitis Pigmentosa and Macular Dystrophies in Asian-Indian Eyes

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Purpose. To study the oxygen-saturation profiles in RP and macular dystrophies and compare them with age-matched healthy controls.

Methods. In a cross-sectional prospective study, 62 subjects with RP, 23 with macular dystrophies, and 78 controls were enrolled, and retinal oximetry was performed with the Oxymap T1 retinal oximeter. The images were analyzed for oxygen saturation and diameter of retinal vessels.

Results. All parameters showed a significant difference among the three groups. Patients with RP showed significantly lower diameters (98.4 μm and 136.9 μm arteriolar and venous) (P < 0.001), higher saturations (102.3% and 59.1%) (P < 0.001; 0.06), and higher arterio-venous saturation difference (AVSD) (43%) (P < 0.001) compared with the other two groups. Macular dystrophies showed higher global arteriolar values (96.7%) and AVSD (41.6%) but comparable venous values (54.9%) to the control group (90.6%, 57.4%, and 33.3%).

Conclusions. Oximetry is sensitive in quantifying hemodynamic changes in retinal dystrophies. It is still unclear whether these hemodynamic changes are a cause or a result of the disease process.

Keywords: retinitis pigmentosa, retinal oxygen saturation, oximetry, cone dystrophies

Retinitis pigmentosa (RP) encompasses a large group of hereditary diseases of the posterior segment of the eye characterized by degeneration, atrophy, and finally loss of photoreceptors and RPE, leading to progressive visual loss.1 The prevalence of RP is estimated to be 1 in 4000 individuals, with a total of approximately 2 million affected persons worldwide.2,3 The prevalence has been reported to be higher in the Indian population.4 Hereditary macular disorders are characterized by defects of the cone photoreceptors or RPE underlying the macula, and include Stargardt disease, cone dystrophy, cone-rod dystrophy, and other maculopathies.5 Many genes affecting the photoreceptors have been implicated in the pathogenesis of these diseases.1,5 Although the exact mechanism of cell death in RP is not known, oxidative stress is known to play a major role.6

Disturbed ocular blood flow has been described as another potential causative factor in RP.1 This is an interesting hypothesis, as reduced ocular blood flow can occur either as a primary event and cause ischemia and tissue loss, or as a physiological secondary response to reduced tissue and demand. Konieczka et al.1 suggested that reduction in ocular blood flow in RP patients could be a primary event.

An early ocular hemodynamic finding in patients with RP is increased arterio-venous (AV) transit time and reduced blood flow velocity, which have been observed before any clinically detectable ocular pathology.7 Doppler imaging has demonstrated that peak systolic flow velocities are decreased in both ophthalmic arteries and posterior ciliary arteries.9 Interestingly, this decrease in blood flow velocity was not confined to the ocular circulation. Systemic findings like reduced flow in the cutaneous capillaries of the finger and longer recovery time after cold provocation have been observed in RP patients.8

There is evidence that in RP patients, ocular blood flow is reduced beyond what is attributable to reduction secondary to retinal atrophy. Konieczka et al.1 hypothesize that the primary ocular blood flow is reduced in RP patients due to peripheral vascular dysregulation syndrome (PVD). Cellini et al.8 further demonstrated a disturbance in peripheral blood flow in addition to that in the eye in RP patients. Reduced blood flow in the retina and an increase in the AV transit time have been observed before the appearance of any ophthalmoscopic signs.7 In summary, the observation of an association with PVD syndrome and peripheral vascular abnormalities and the increased AV transit time occurring early in the disease argue strongly in favor of vascular disturbances being a primary event.

Apart from blood flow velocity and vascular diameters, it is possible to measure the saturation of oxygen in the hemoglobin contained in the ocular vessels. A photospectrometric device measures oxygen saturation in a noninvasive manner.9 An increase in venous saturations and a resultant decrease in AV saturation difference (AVSD) in eyes with RP have been reported.10–12

A large majority of genes associated with cone dystrophies are yet to be discovered; this hints toward the existence of unknown cone-specific or cone-sensitive processes.5 No established evidence exists to implicate ocular blood flow abnormalities in the pathogenesis of cone dystrophies. It would therefore be interesting to study the ocular blood flow and oxygen saturations in cone dystrophies.

We aimed to study and compare the oxygen-saturation profiles and vascular diameters in RP and macular dystrophies and compare them with age-matched controls.
Materials and Methods

A total of 114 consecutive patients presenting to the retina department at Narayana Nethralaya, Bangalore, diagnosed with RP, cone dystrophy, or Stargardt disease were enrolled in the study. The diagnosis of these conditions was made based on the presentation, clinical features, and electrophysiological examination. A detailed history was taken for every patient and patients with any cardiovascular disease, diabetes, hypertension, or history of migraine or using any ocular or systemic medications were excluded. The study followed the tenets of the Declaration of Helsinki. The ethics committee and institutional review board of Narayana Nethralaya approved the study. All patients provided written consent for the study.

All patients underwent a complete ophthalmic examination. These included measurement of the best-corrected visual acuity, anterior segment examination, measurement of the IOPs, and a fundus examination. All underwent fundus photography, spectral-domain optical coherence tomography (SD-OCT), and full-field ERG. Patients younger than 18 years, smokers, and those with a previous history of trauma, nystagmus, and poor media clarity were excluded from the study.

This article summarizes the oximetry findings; the SD-OCT and ERG findings were used only for confirmation of diagnosis. They have not been included, as it would confound the reader with too much information.

Image Acquisition

Following dilation with 1% tropicamide and 10% phenylephrine, all patients underwent dual-wavelength photospectroscopic oximetry (Oxymap T1 retinal oximeter; Oxymap, Reykjavik, Iceland).

The initial images were obtained after the patients were allowed to rest for 5 minutes to eliminate exercise-induced fluctuations in readings. Resting blood pressure and pulse oximetry (HE; Silicon Labs, Chennai, India) readings were measured in all patients. None of the subjects had consumed caffeine within 2 hours of the examination. The aiming light was set at the lowest setting, flash intensity was 50W, small aperture and large pupil settings were applied to the Topcon TRC 50DX Fundus camera (Topcon, Tokyo, Japan).

One experienced photographer obtained standardized images for all the subjects. We obtained two images per eye of 50° field that were disc-centered in all subjects (Fig.). We ensured that all the images analyzed were in sharp focus. To achieve this, we chose the best quality image between the two eyes in bilateral cases, which not only ensured quality, but also ensured that we take only one reading per patient, eliminating duplication of data. In unilateral cases or cases with only one available image, the best quality image was taken. If no image appeared satisfactory, or if the eye had measurable vessels in only one quadrant, that patient was excluded from the study (n = 29). A circle was drawn concentric to the optic disc, leaving 50 pixels from the disc margin. A second concentric circle was drawn twice the diameter of the first one. Vessel segments were analyzed between these two concentric circles to ensure that retinal eccentricity was uniform. Retinal eccentricity and cell density may have an impact on measured retinal capillary density. The compensation by the software is similar to that suggested by Geirsdottir et al. Analyzable vessels were defined as vessels larger than 8 pixels (74 µm) in width. This value was chosen as a cutoff because of the possibility of inaccurate results for very thin vessels. Global averages were obtained by simple averaging of the values of the quadrants.

Statistical Analysis

Statistical analysis was done using IBM SPSS v22.0 (IBM SPSS Statistics; IBM Corporation, Chicago, IL, USA). All parameters were tested for normality using the Shapiro-Wilk test. Parametric data were analyzed using the one-way ANOVA with the Tukey test for post hoc analysis. Nonparametric data were compared using the Kruskal-Wallis test and the Mann-Whitney U test for the post hoc analysis.

Results

There were a total of 23 eyes with macular dystrophies, 62 eyes with RP, and 78 controls.

Nonmeasurable Vessels

Analyzable vessels were present in all quadrants in the macular and control groups. The RP group had 14 eyes without measurable arterioles in both the superonasal and inferonasal quadrants, 15 eyes without inferonasal arterioles only, 5 eyes without superonasal arterioles only, 1 eye without superonasal venules, and 3 eyes without inferonasal venules. In all quadrants in which the venules were not measurable, the corresponding arterioles were definitely not measurable, although the reverse was not true. In 32 eyes, the arterioles were not measurable but the venules were measurable. In all, 34 (54.8%) of 62 eyes had nonmeasurable vessels in the nasal hemifield.

In our study, we found that the nasal vessels attenuated earlier compared with the temporal ones. In those eyes without measurable temporal vessels, the nasal ones were also not measurable. This accounted for 7 of the 29 eyes that we had to exclude because both the temporal and nasal vessels were not measurable.

Demographics

The average age in the macular dystrophy group was 20.8 ± 11.5 years, in RP group was 30.4 ± 16.7 years, and in the control group was 32.4 ± 9.4 years. Age-matched nonsmoking controls were chosen according to the RP group, as the numbers were larger in that group. The age distribution in the macular group was significantly different from the other two groups. No significant differences were found in the sex distribution. None of the patients had any refractive error beyond ± 0.50 diopter. The IOP for both the RP group (mean 14.5, range, 10–18) and the macular dystrophy group (mean 14.4, range, 9–18) was within normal ranges. The results are summarized in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Macular, n = 23</th>
<th>RP, n = 62</th>
<th>Controls, n = 78</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20.8 ± 11.5 (15.8–25.8)</td>
<td>30.4 ± 16.6 (26.2–34.7)</td>
<td>32.4 ± 9.4 (30.3–34.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>16:7</td>
<td>38:24</td>
<td>36:42</td>
<td>0.066†</td>
</tr>
</tbody>
</table>

* Kruskal-Wallis test to compare the age distribution of three groups. Mann-Whitney U post hoc test Macular versus RP P = 0.005; Macular versus Controls, P < 0.001.
† χ² test to compare difference in sex.
Arteriolar saturation, % 96.7
<
Arteriolar diameter, μm 116.5
(110.1–122.7)
Venous saturation, % 54.9
Venous diameter, m 158.4
(149.8–167.1)
AV difference, % 41.6
AV ratio‡ 0.74
(0.70–0.78)

Global Saturations and Diameters

The global saturations and diameters are summarized in Table 2. All parameters showed a significant difference between the three groups. The RP group showed significantly higher saturations, lower diameters, higher AVSD, and lower AV ratios compared with both groups. Macular dystrophies showed higher global arteriolar values and AVSD but comparable venous values to the control group. Macular and RP groups also showed statistically significant differences in the global arteriolar and venous saturations and diameters.

Quadrant Saturations and Diameters

The RP group had the highest saturations and lowest diameters in all the quadrants. The values are summarized in Table 3.

### Table 3. Summarizing the Quadrantwise Arteriolar Saturations and Diameters for the Three Groups

<table>
<thead>
<tr>
<th>Quadrant</th>
<th>Parameter, n</th>
<th>Macular, n = 23</th>
<th>RP, n = 62</th>
<th>Controls, n = 78</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST</td>
<td>Arteriolar saturation, % 99.9 102.9 106.9</td>
<td>92.3–109.9</td>
<td>102.0</td>
<td>99.6</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td></td>
<td>Arteriolar diameter, μm 127.7 132.7 138.7</td>
<td>127.3</td>
<td>132.9</td>
<td>139.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Venous saturation, % 57.6 60.8 64.0</td>
<td>53.5</td>
<td>60.8</td>
<td>61.0</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Venous diameter, μm 151.8 160.0 168.2</td>
<td>170.7</td>
<td>161.5</td>
<td>170.5</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td></td>
<td>AVSD, % 43 51.0 59.0</td>
<td>36.1</td>
<td>32.1</td>
<td>35.0</td>
<td>0.001</td>
</tr>
<tr>
<td>SN</td>
<td>Arteriolar saturation, % 97.5 100.7 104.9</td>
<td>99.4</td>
<td>102.9</td>
<td>110.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Arteriolar diameter, μm 109.5 114.0 118.0</td>
<td>107.9</td>
<td>110.3</td>
<td>114.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Venous saturation, % 58.0 61.0 63.0</td>
<td>57.7</td>
<td>60.6</td>
<td>60.6</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>Venous diameter, μm 120.0 124.0 128.0</td>
<td>141.9</td>
<td>144.7</td>
<td>144.7</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>AVSD, % 43 51.0 59.0</td>
<td>42.0</td>
<td>35.8</td>
<td>40.0</td>
<td>0.001</td>
</tr>
<tr>
<td>IN</td>
<td>Arteriolar saturation, % 97.5 100.7 104.9</td>
<td>99.9</td>
<td>102.9</td>
<td>103.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Arteriolar diameter, μm 109.5 114.0 118.0</td>
<td>102.7</td>
<td>111.0</td>
<td>111.0</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Venous saturation, % 58.0 61.0 63.0</td>
<td>57.6</td>
<td>60.7</td>
<td>60.7</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>Venous diameter, μm 120.0 124.0 128.0</td>
<td>139.0</td>
<td>144.4</td>
<td>144.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>AVSD, % 43 51.0 59.0</td>
<td>42.3</td>
<td>32.5</td>
<td>42.3</td>
<td>0.001</td>
</tr>
<tr>
<td>IT</td>
<td>Arteriolar saturation, % 97.5 100.7 104.9</td>
<td>97.8</td>
<td>102.2</td>
<td>103.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Arteriolar diameter, μm 109.5 114.0 118.0</td>
<td>127.2</td>
<td>106.9</td>
<td>134.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Venous saturation, % 51.0 56.0 59.0</td>
<td>51.1</td>
<td>51.9</td>
<td>51.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Venous diameter, μm 159.5 165.0 171.0</td>
<td>181.4</td>
<td>181.0</td>
<td>181.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>AVSD, % 45.0 48.0 51.0</td>
<td>46.6</td>
<td>34.6</td>
<td>46.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Kruskal-Wallis test used to obtain significance for nonparametric data.
† RP versus Controls P < 0.001; Macular versus Controls P = 0.005.
‡ RP versus Controls P = 0.004.
§ RP versus Controls P = 0.004.
|| RP versus Controls P < 0.001; Macular versus Controls P < 0.001.
¶ AV ratio implies the ratio of the diameters.

Number of quadrants analyzed for each parameter are given in the header row. Where the number differs from the number in the header, it has been indicated in the parameter box in italics. ST, supero-temporal; SN, supero-nasal; IN, infero-nasal; IT, infero-temporal.

"Kruskal-Wallis test used to obtain significance for nonparametric data."
Retinal Oximetry in RP and Macular Dystrophies

DISCUSSION

This study represents one of the largest descriptions of oxygen-saturation profiles in eyes with RP, and the first description in macular dystrophies and its comparison with RP.

A decrease in vascular diameters, and an increase in arteriolar (104.1%) and venous saturations (60.0%) and AVSD (44.1%) in the RP group in comparison with macular and control groups were observed in the study. Türksever et al.,11 Eysteinsson et al.,10 and Ueda-Consolvo et al.12 equivocally confirm the decrease in vascular diameter. Türksever et al.11 reported an increase in arteriolar saturation with a mean of 99.3%, whereas Eysteinsson et al.10 found no change in RP with a mean of 91.7%. Venous saturation was increased in all three studies (58.0%-66.8%). Our study was equivocal in the venous saturation increase, but found an opposite trend in the AVSD. Türksever et al.11 mentioned that the AVSD correlated positively with the central macular thickness and hence attributed its decrease to the progression of retinal atrophy. Eysteinsson et al.10 on the other hand have stated that both AVSD and retinal blood flow decrease in RP, and coupled with the decrease in choroidal blood flow results in decreased oxygen delivery from the retinal circulation. Both groups indicate that the effects are secondary to the degeneration rather than primary. The alterations observed in the saturations and diameters could be a primary and resulting in the dystrophy or could be secondary to the disease process. We may hypothesize that findings that occur early in the disease are more likely primary and ones that are seen in advanced disease may most likely be an effect of the disease process.

Macular dystrophies differed from both RP and control groups in the global arteriolar saturations, with the arteriolar saturations being highest in the RP group. Venous saturations differed from the RP group but not from controls.

Several theories have been postulated to explain the arteriolar attenuation seen in RP. One such hypothesis is that the photoreceptor atrophy and death causes less oxygen utilization, which results in higher oxygen partial pressures in the inner retina. This would then result in a reflex constriction and reduction in ocular blood flow, thus indicating that the vascular changes are secondary to localized disease process. On the contrary, Konieczka et al.3 stated that there is a high prevalence of PVD syndrome in RP patients, which causes alteration early in the disease. Patients with PVD syndrome react differently to stimuli such as coldness, or physical or emotional stress. There is dysregulation of vessels with vasospasm. Hence a system-wide vascular spasm that also manifests in the eye could be one explanation, whereas tissue loss,1 atrophy, and thus a decreased demand could be the other hypothesis. The above theories may probably explain why as many as 54.8% of eyes in the RP group lacked measurable vessels in the nasal hemifield. Expectedly, there was no significant difference in the vascular diameters between the macular and control groups.

There exists a capillary free zone around larger vessels that derive oxygen directly from them.14 It has been shown that translocated cells of the RPE can deposit a thick layer of extracellular matrix around retinal vessels.15 This can effectively block oxygen diffusion out of the vessels and explain the high saturation seen in the arterioles but the unknown effect of these cells and the proximity of the measured segments to the optic disc throw enough doubt on this theory.

The thickness of the retinal nerve fiber layer (RNFL) is known to be decreased in RP.16,17 In our own study (Mohan A, Dabir S, Kummeli M, Shetty R, Kumar RS, unpublished observations, 2014), we found an inverse correlation between vascular saturation and perivascular RNFL thickness in normative Asian-Indian eyes. This could explain our observation of increasing arteriolar and venous saturation.

In a normal eye, arteriolar saturations can be expected to increase when there is more demand and less oxygen tension in the inner retinal tissue. This phenomenon, though, will have to be accompanied by a corresponding increase in vascular diameters because that is the only established way the inner retina can increase oxygen delivery by physiological hyperemia.14 The arteriolar attenuation that we observed in the RP group makes this response unlikely.

An increase in arteriolar saturation can hypothetically cause a corresponding increase in venous saturation. The venous saturation also can increase due to less utilization secondary to tissue atrophy in RP. This possibly explains the increase in venous saturation seen in our patients and is similar to that noted in the other studies.

Oxygen utilization by tissue is the product of AVSD and blood flow.14 Blood flow is heavily dependent on the vascular diameters. It is known that the AV transit time is increased and vascular diameters are decreased in RP, thus resulting in very low volume of blood flow. Hence, for a given amount of oxygen extraction, the AVSD would increase if the blood flow decreases. This is accompanied by a decreased choroidal blood flow in RP.8 We could possibly imply that even though tissue atrophy and death would cause lower oxygen demand, in view of the fall in blood flow, AVSD would have to increase to adequately meet the demands of the residual functioning retina. In addition, hypoxic tissue would extract more oxygen per unit volume of blood.10 This could possibly explain the increased AVSD seen in the RP group in our study.

An alteration in oxygen-saturation profiles was seen in all quadrants in the RP group but mainly in the infero-temporal quadrant in the macular group. The lower saturations in the infero-temporal venules in normative individuals has been attributed to its anatomic location in relationship to the optic disc.18 In macular dystrophies, it stands to reason that the macular blood supply is the most affected compared with...
those with RP, thus contributing to the altered oxygen-saturation profiles that we noted in the infero-temporal quadrant.

Our study is limited by the relatively small sample size we had in the macular dystrophy group. Another limitation was that blood pressure was not measured, but it is assumed that there was no difference in blood pressure between those with retinal degeneration and age-matched controls, given the relatively young age of the subjects included in the study. The current approach of our study excludes vessels narrower than 8 pixels or 74 μm, hence we cannot comment on vessels that were narrower than this cutoff and therefore not measurable. A correlation of oxygen-saturation profiles with RNFL thickness could throw further light on the reasons for our observations. A correlation with electro-retinographic findings can in the future help us obtain a better correlation between oximetry values and disease severity.

This study represents the largest so far reported on retinal dystrophies and establishes the increase in arteriolar, venous saturations, and AVSD increase. It is important to ascertain whether the hemodynamic observations are primary or secondary. If they are secondary, they will only help us establish severity; if primary, they have a multitude of therapeutic implications. It also has been shown that the central defects progress slower with nilvadipine, which is a calcium channel blocker. Magnesium, omega-3 fatty acids, and fluordrocortisone have all been hypothesized to help in the above methods prove to be effective, retinal oximetry can be used as a noninvasive tool to identify potential patients who might benefit and subsequently monitor response to treatment.

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References