Retinal oximetry in normal and amblyopic children

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Retinal oximetry in normal and amblyopic children: a pilot study

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ABSTRACT.
Purpose: **To study the retinal vascular oxygen saturation in amblyopic eyes and compare them to unaffected fellow eyes and eyes of normal subjects.**
Methods: **A total of 32 amblyopic, 24 normal and 13 fellow eyes of patients below age of 18 were enrolled in this prospective observation study. Retinal oximetry was performed using the Oxymap T1 retinal oximeter. Retinal vascular oxygen saturations and diameters were compared between amblyopic eyes, normal eyes and unaffected fellow eyes.**
Results: **The average age was 8.6 years in the amblyopia group (M:F 16:16) and 10.9 years in the normal group (M:F 7:5; p = 0.024). Median corrected distance visual acuity in the amblyopia group was 20/50; it was 20/20 in the other groups (p < 0.001). The average arteriolar and venous saturation in the amblyopia, normal and fellow group was 84.5% (95% CI: 82.6–86.4), 83.2% (95% CI: 80.7–85.6) and 80.8% (95% CI: 78.6–82.9) and 51.9% (95% CI: 50.4–53.4), 50.8% (95% CI: 48.2–53.4) and 49.3% (95% CI: 45.7–52.9). There was no statistically significant difference between the saturation values of the amblyopia group and the controls, however, significantly higher values were found in the amblyopia group compared to the fellow group for arteriolar and venous saturations (p = 0.013; p = 0.005). Arteriolar and venous diameters showed no significant difference between groups.**
Conclusion: **Amblyopic eyes showed higher mean oxygen saturations than the fellow eyes. This observation could be due to altered neuronal activity or could be due to a measurement artefact due to alterations in retinal reflectivity.**

Key words: amblyopia – retinal oximetry

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Introduction

Amblyopia has been traditionally defined as decreased vision in one or both eyes caused by abnormal binocular interaction and/or pattern vision deprivation which in some cases can be corrected by treatment (Burian & Von Noorden 1985). Amblyopia results from degradation of the retinal image during a sensitive period of visual development. The degradation of the image, and subsequent central suppression that leads to amblyopia, results from one of three causal processes, namely – strabismus, anisometropia and/or stimulus deprivation. Hence, the disorder (amblyopia) is not the cause but it is the effect of an underlying pathological process (Holmes & Clarke 2006).

Although amblyopia has been defined as low visual acuity in one or both the eyes with a structurally normal globe, there are many studies that show that the amblyopic eye may have some structural anomalies including changes in retinal ganglion cells, the retinal nerve fibre layer (RNFL) and the optic nerve (Lempert 2000; Baddini-Caramelli et al. 2001; Yen et al. 2004; Repka et al. 2006; Wu & Hunter 2006; Dickmann et al. 2009; Huynh et al. 2009; Pineles & Demer 2009; Wu et al. 2013), but there are also studies which have found no significant differences in the RNFL in amblyopic and normal eyes (Delint et al. 1998; Altintas et al. 2005; Kee et al. 2006; Repka et al. 2006; Miki et al. 2010; Al-Haddad et al. 2011).

Retinal oximetry is a new tool which helps in measuring the oxygen saturation of haemoglobin in the blood vessels of the retina. A number of retinal diseases have been studied and significant differences have been found from normal (Hardarson & Stefánsson 2011; Hardarson & Stefansson 2012; Hardarson et al. 2012; Geirsdottir et al. 2013; Olafsdottir et al. 2014; Vandewalle et al. 2014; Battu et al. 2015). Since it is believed that in amblyopia, there is a structurally normal globe and it is mainly the visual function which is decreased, it would be interesting to see if there is a change in a quantitative functional parameter like retinal vessel oximetry.

Aim of the study

- To compare the retinal vessel oxygen saturation between amblyopic eyes and healthy control eyes of children.
- To compare the interocular difference in retinal vessel oxygen saturation in children with unilateral amblyopia between the amblyopic and nonamblyopic fellow eye
- To compare the retinal vessel oxygen saturation between healthy fellow eyes of unilateral amblyopic patients and healthy control eyes.

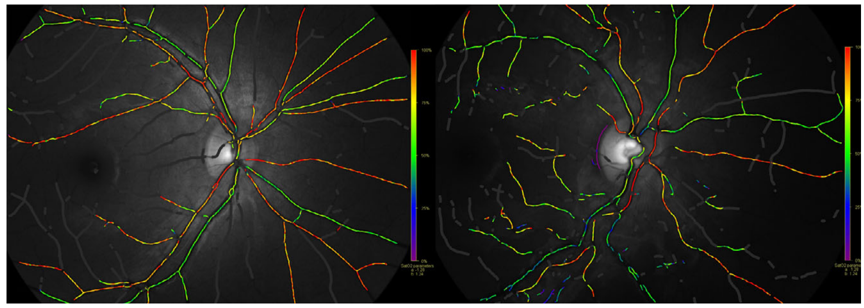

Fig 1. Retinal oximetry pseudocolor map showing a comparison between a normal (left) and amblyopic (right) eye.

Materials and Methods

Children and adolescents (<18 years of age) presenting to the outpatient department of a tertiary eye care centre (Bangalore, India), were enrolled in the study with their written consent. The study follows the tenets of Helsinki. The Institutional Review Board and Ethics Committee approved the study. This was a comparative observational cross-sectional noninterventional study.

Inclusion and exclusion criteria

Subjects diagnosed clinically to have treatment naive amblyopia (ametropic, anisometropic or strabismic) were included in the amblyopia group; subjects with bilateral amblyopia had the worse eye included. Clinically, amblyopia was defined as a corrected distance visual acuity (CDVA) of ≤20/30 or a difference in the CDVA between the two eyes of at least two Snellen chart lines in the absence of any clinically detectable ocular pathology. The control group comprised of children who presented for a routine annual check-up with normal ophthalmic exam and CDVA of 20/30–20/20 and their right eye was included. The fellow eyes of subjects with unilateral amblyopia were analysed separately in the fellow group. Patients with significant cataract or any identifiable ocular pathology were excluded from the study.

Image acquisition and segment selection

All patients underwent dilation with 1% tropicamide and 10% phenylephrine and subsequent retinal imaging (Fig. 1) with the oximetry using the Oxymap T1 retinal oximeter (Oxymap hf., Reykjavik, Iceland) running the software version 2.5.1. They were allowed to rest for 5 min before the images were captured. This was done to eliminate exercise-induced fluctuations in readings. None of the subjects had consumed caffeine within 2 hr of the examination.

The aiming light was set at the lowest setting, flash intensity was 50Ws, small aperture and large pupil settings were applied to the TRC 50DX (Topcon, Oakland, NJ, Japan) Fundus camera.

One experienced photographer obtained standardized images for all the subjects which were 50° disc centred. The right eyes of all patients were imaged first and then the left eye; two images were taken per eye and the one with the better image quality was selected. If both the images had inadequate image quality then the eye was excluded. Image quality was decided based on the automatic objective image quality score with cut-off of 7.

Segments were selected as described in our previous study (Mohan et al. 2015). We analysed global arteriolar and venous saturation and diameter and arterio-venous saturation difference (AVSD) and compared them between the amblyopic and control (normal and fellow eyes) arms.

Statistical analysis

Statistical analysis was done using the IBM Armonk, NY, United States SPSS v22 software. All continuous variables were tested for normality using the Shapiro–Wilk test. The difference between means was tested using independent *t*-test for normally distributed data and the Mann–Whitney *U* test (unpaired) or the Wilcoxon signed rank test (paired) for non-parametric data. For normally distributed data the Pearson's correlation was used, for non-parametric data the Spearman's correlation was used. The level of significance was $p < 0.05$.

When significant differences in age were found between groups, a multivariate analysis was done keeping the saturations as the dependent variable and the age and the group as the independent variable to correct for age.

Results

There were a total of 32 amblyopic eyes, 24 normal eyes and 13 fellow eyes of patients with unilateral amblyopia. The image quality of the groups were comparable ($p = 0.192$) with the mean quality being 7.6 ± 0.27, 7.8 ± 0.52 and 7.9 ± 0.48 in the amblyopic, normal and fellow eyes, respectively.

Amblyopic eyes versus healthy controls

In the amblyopia group, the average age was 8.6 years (95% CI: 7.2–9.9) with a male–female ratio of 16:16 (Table 1). The normal group had an average age of 10.9 (95% CI: 9.3–12.4) and a male–female ratio of 7:5. Age distribution showed a significant difference between amblyopic and normal groups ($p = 0.024$); no differences were found in the sex distribution. Twenty-five eyes were right sided while seven were left sided in the amblyopia group; all eyes were right sided in the control group.

The CDVA was lower in the amblyopia group with a median of 20/50 (range: 20/200–20/30) on Snellen's chart; all subjects in the normal group had a CDVA of 20/20 ($p < 0.001$). The spherical equivalent in normals varied from −1.0 to +1.75 D; in the amblyopia group it varied from (−7.8 to +10.1 D).

Table 1. Demographics, oxygen saturation and diameter values of the amblyopia and normal groups.

	Amblyopia (n = 32)	Normal (n = 24)	p value*
Age	8.6 (7.2–9.9)	10.9 (9.3–12.4)	**0.024**
Sex (M:F)	16:16	14:10	0.6
Corrected distance visual acuity (median and range)	20/50 (20/30–20/200)	6/6 (all)	**< 0.001**
Spherical equivalent	−7.9 to +10.1	−1.0 to +1.5	0.32
Arteriolar saturation	84.5 (82.6–86.4)	83.2 (80.7–85.6)	0.39
Arteriolar diameter	125.7 (121.5–130.0)	128.2 (124.4–132.0)	0.37
Venous saturation	51.9 (50.4–53.4)	50.8 (48.2–53.4)	0.47
Venous diameter	164.2 (157.8–170.5)	160.5 (154.6–166.4)	0.39
Arterio-venous saturation difference	32.7 (30.6–34.7)	32.4 (29.9–34.8)	0.86

Values in bold indicate statistical significance.
* Independent t-test for continuous variables; Chi-Square test for nominal data.

The average arteriolar saturation in the amblyopia and normal group were 84.5% and 83.2% (p = 0.393). The venous saturations were, respectively, 51.9% and 50.8% (p = 0.465) while the AVSD was 32.7% and 32.4% (p = 0.857). None of the parameters showed a significant difference between the groups.

There were no significant correlations between the saturation and diameter parameters with the age, group, CDVA or spherical equivalent.

Amblyopic eyes versus healthy fellow eyes

The average age of the amblyopic subjects that also had fellow eye measured (N = 13) was 10.4 (95% CI: 8.1–12.7; Table 2). Their male–female ratio was 6:7. Eight of the amblyopic eyes were right sided and five were left sided, being of course the reverse for the fellow eyes.

The CDVA was lower in the amblyopia eyes with a median of 20/50 (range: 20/200–20/30) on Snellen's chart. All fellow eyes had a CDVA of 20/20 (p < 0.001). The spherical equivalent varied from +1 to +8 D in amblyopic eyes and from −0.38 to +6.25 D in fellow eyes (p = 0.003).

Both arteriolar and venous saturation were significantly higher in the amblyopic eyes compared to the fellow eyes (85.4% and 80.8%, p = 0.013, and 53.4% and 49.3%, p = 0.005, respectively). The AVSD were 32.2% and 31.5% (p = 0.259), respectively, with no differences seen between the eyes.

Healthy fellow versus normal eyes

We found no differences between the normal fellow eyes and eyes in the normal group, also after correcting for age.

Discussion

This to the best of our knowledge is the first study of retinal oximetry in amblyopic eyes and one of the few studies (Liu et al. 2017) to report oximetry values in subjects below the age of 18 years. We found no differences between the amblyopia group and the control group or the fellow eye and the control group, however, the saturations in the amblyopia group were significantly higher than those in the fellow eyes.

Wiesel & Hubel (1963) put forth an interesting theory by studying cortical changes in amblyopic eyes of kittens. They said that binocularly driven cells no longer respond to stimuli from the deprived eye and undergo a change in function, becoming monocularly driven by stimuli from the sound eye. There is no change in the number of monocularly driven cells responding to stimuli from the deprived eye but the reduction in the total cell population driven by this eye provides electrophysiological evidence of cortical changes occurring in amblyopia. This can be a possible explanation for the significant difference seen between the amblyopia and the fellow group, however, the limitation of the small sample size must be kept in mind before interpreting results.

Amblyopia is a condition where we find decreased visual acuity in a structurally normal globe. We had also studied the vascular diameters of the vessels that were used for oximetry. Comparison between the groups showed no differences. The comparable vascular diameters in the three groups conform with this theory. This data were not included in the results because the preferred way to study the vascular diameters would be to use the method described by Knudtson et al. (2003).

A decrease in thickness can alter the measured light intensities as seen in the study by Mohan et al. (2016) and thus alter the final calculated optical density ratio. Also as postulated in the study a thinner RNFL may imply a smaller capillary-free zone and thus higher measured saturations due to decreased oxygen consumption. It thus needs to be kept in mind that the above observations could be due to a change in functional metabolism or could be due to an optical artefact. As stated earlier, in the introduction, the literature on RNFL changes in amblyopia does not yield a conclusive trend; hence, it is difficult to hypothesize an explanation for our findings based on structural changes.

One limitation of our study was that we did not have corresponding Optical Coherence Tomography (OCT) measurements to see if our findings were

Table 2. Demographics, oxygen saturation and diameter values of the amblyopia and fellow groups.

	Amblyopia (n = 13)	Fellow (n = 13)	p value*
Corrected distance visual acuity (median)	20/80 (range: 6/9–6/60)	20/20 (all)	**< 0.001**
Spherical equivalent	+1 to +8	−0.38 to +6.25	**0.003**
Arteriolar saturation	85.4 (83.0–87.8)	80.8 (78.6–82.9)	**0.013**
Arteriolar diameter	125.7 (119.5–131.9)	126.7 (118.2–135.2)	0.75
Venous saturation	53.4 (51.1–55.7)	49.3 (45.7–52.9)	**0.005**
Venous diameter	166.2 (158.5–173.9)	156.7 (147.1–166.3)	0.20
Arterio-venous saturation difference	32.2 (29.0–35.5)	31.5 (27.9–35.0)	0.26

Values in bold indicate statistical significance.
* Wilcoxon signed rank test.

artefactual or true. In future, we will follow up patients under treatment for amblyopia and see if oximetry values return to normal in eyes that respond and remain elevated in nonresponsive eyes. A higher number of unaffected fellow eyes also would help us confirm the findings of a compensatory increase in function of fellow eyes.

Another limitation of the study was that the amblyopic group was significantly younger than the normal group. Probably, children in the amblyopia group presented earlier to the paediatric clinic due to decreased vision compared to otherwise normal children presenting for a general check-up. In our normative database (Mohan et al. 2015) on adults of the same population age showed a positive correlation with measured saturations; however, in this study, age did not show any correlation with the oxygen saturation values. The spherical equivalent was very variable ranging from −7.8 to +10.1 in the amblyopia group and this could possibly result in artefactual alterations however previous studies on normal adults (Jani et al. 2014; Mohan et al. 2015) show no significant association.

Conclusion

In conclusion, we find higher measured saturations in amblyopic eyes versus the fellow eyes. This observation could be due to altered neuronal activity or could be due to a measurement artefact due to alterations in retinal reflectivity.

References

Al-Haddad CE, Mollayess GMEL, Cherfan CG, Jaafar DF & Bashshur ZF (2011): Retinal nerve fibre layer and macular thickness in amblyopia as measured by spectral-domain optical coherence tomography. Br J Ophthalmol **95**: 1696–1699.

Altintas O, Yüksel N, Ozkan B & Caglar Y (2005): Thickness of the retinal nerve fiber layer, macular thickness, and macular volume in patients with strabismic amblyopia. J Pediatr Ophthalmol Strabismus **42**: 216–221.

Baddini-Caramelli C, Hatanaka M, Polati M, Umino AT & Susanna R (2001): Thickness of the retinal nerve fiber layer in amblyopic and normal eyes: a scanning laser polarimetry study. J AAPOS **5**: 82–84.

Battu R, Mohan A, Khanna A, Kumar A & Shetty R (2015): Retinal oxygen saturation in retinitis pigmentosa and macular dystrophies in Asian-Indian eyes. Invest Ophthalmol Vis Sci **56**: 1–5.

Burian HM & Von Noorden GK (1985): Burian-von Noorden's binocular vision and ocular motility. St. Louis: MO: C.V. Mosby.

Delint PJ, Welssenbruch C, Berendschot TTJM & Van Norren D (1998): Photoreceptor function in unilateral amblyopia. Vision Res **38**: 613–617.

Dickmann A, Petroni S, Salerni A, Dell'Omo R & Balestrazzi E (2009): Unilateral amblyopia: an optical coherence tomography study. J AAPOS **13**: 148–150.

Geirsdottir A, Hardarson SH, Olafsdottir OB & Stefánsson E (2013): Retinal oxygen metabolism in exudative age-related macular degeneration. Acta Ophthalmol **92**: 27–33.

Hardarson SH & Stefansson E (2012): Retinal oxygen saturation is altered in diabetic retinopathy. Br J Ophthalmol **96**: 560–563.

Hardarson SH & Stefánsson E (2011): Oxygen saturation in branch retinal vein occlusion. Acta Ophthalmol **90**: 466–470.

Hardarson SH, Elfarsson A, Agnarsson BA & Stefánsson E (2012): Retinal oximetry in central retinal artery occlusion. Acta Ophthalmol **91**: 189–190.

Holmes JM & Clarke MP (2006): Amblyopia. Lancet **367**: 1343–1351.

Huynh SC, Samarawickrama C, Wang XY, Rochtchina E, Wong TY, Gole GA, Rose KA & Mitchell P (2009): Macular and nerve fiber layer thickness in amblyopia: the Sydney Childhood Eye Study. Ophthalmology **116**: 1604–1609.

Jani PD, Mwanza J-C, Billow KB, Waters AM, Moyer S & Garg S (2014): Normative values and predictors of retinal oxygen saturation. Retina (Philadelphia, Pa) **34**: 394–401.

Kee S-Y, Lee S-Y & Lee Y-C (2006): Thicknesses of the fovea and retinal nerve fiber layer in amblyopic and normal eyes in children. Korean J Ophthalmol **20**: 177–181.

Knudtson MD, Lee KE, Hubbard LD, Wong TY, Klein R & Klein BEK (2003): Revised formulas for summarizing retinal vessel diameters. Curr Eye Res **27**: 143–149.

Lempert P (2000): Optic nerve hypoplasia and small eyes in presumed amblyopia. J AAPOS **4**: 258–266.

Liu X, Wang S, Liu Y, Liu LJ, Lv YY, Tang P, Jonas JB & Xu L (2017): Retinal oxygen saturation in Chinese adolescents. Acta Ophthalmol **95**: e54–e61.

Miki A, Shirakashi M, Yaoeda K, Kabasawa Y, Ueki S, Takagi M & Abe H (2010): Retinal nerve fiber layer thickness in recovered and persistent amblyopia. Clin Ophthalmol **4**: 1061–1064.

Mohan A, Dabir S, Yadav NK, Kummelil M, Kumar RS & Shetty R (2015): Normative database of retinal oximetry in Asian Indian eyes (Bui BV, Ed.). PLoS ONE **10**: e0126179.

Mohan A, Dabir S, Kurian M, Shetty R, Chidambara L & Kumar RS (2016): Perivascular and quadrant nerve fiber layer thickness and its relationship with oxygen saturation. Curr Eye Res **41**: 1223–1228.

Olafsdottir OB, Vandewalle E, Abegão Pinto L et al. (2014): Retinal oxygen metabolism in healthy subjects and glaucoma patients. Br J Ophthalmol **98**: 329–333.

Pineles SL & Demer JL (2009): Bilateral abnormalities of optic nerve size and eye shape in unilateral amblyopia. Am J Ophthalmol **148**: 551–557.e2.

Repka MX, Goldenberg-Cohen N & Edwards AR (2006): Retinal nerve fiber layer thickness in amblyopic eyes. Am J Ophthalmol **142**: 247–251.

Vandewalle E, Abegão Pinto L, Olafsdottir OB et al. (2014): Oximetry in glaucoma: correlation of metabolic change with structural and functional damage. Acta Ophthalmol **92**: 105–110.

Wiesel TN & Hubel DH (1963): Single-cell responses in striate cortex of kittens deprived of vision in one eye. J Neurophysiol **26**: 1003–1017.

Wu C & Hunter DG (2006): Amblyopia: diagnostic and therapeutic options. Am J Ophthalmol **141**: 175–184.

Wu S-Q, Zhu L-W, Xu Q-B, Xu J-L & Zhang Y (2013): Macular and peripapillary retinal nerve fiber layer thickness in children with hyperopic anisometropic amblyopia. Int J Ophthalmol **6**: 85–89.

Yen M-Y, Cheng C-Y & Wang A-G (2004): Retinal nerve fiber layer thickness in unilateral amblyopia. Invest Ophthalmol Vis Sci **45**: 2224–2230.

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