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ORIGINAL RESEARCH

Variations in Retinal Oxygen Saturation in a Diverse Healthy Population

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Purpose: Local retinal oxygen saturation is a research technique, which has the potential as a biomarker for diabetes. However, normative data has not been established. This study examined differences in oxygen saturation around the macula and characterizes the relationship between age, race, refractive error (RE), sex, blood pressure (BP), prediabetic status and oxygen saturation.

Methods: Fifty-nine subjects aged 22–69 (38.8 ± 14.7 years) were included who were racially diverse and with equal gender distribution. None had eye disease. Oxygen saturation was taken with the Zilia Ocular in 4 locations around the macula 3.1 degrees from the fovea and they were also averaged. BP, RE, and HbA1c were noted. Regression analyses for oximetry and other factors were completed as were *t*-tests with multiple comparison corrections.

Results: There were significant variations in oximetry measures by race, with higher pigmentation levels associated with lower oximetry values ($p < 0.01$). There was no relationship between oximetry and sex ($p = 0.34$), RE ($p = 0.67$), BP (systolic $p = 0.61$, diastolic $p = 0.71$) nor prediabetic status ($p = 0.87$). Oximetry was associated with age when controlling for race ($P < 0.002$). Nasal-temporal variations showed nasal oximetry to higher than temporal measures ($P < 0.01$).

Conclusion: This study revealed race/pigmentation is an important influence on oximetry measures. Retinal location also caused variations, likely due to proximity to larger vessels nasally. No differences in sex, RE nor BP were observed to alter local oxygen saturation. However, age was correlated when considered with race. This study will inform our future work in different disease states and is an important first step in evaluating this technology.

Plain Language Summary: This study evaluates a new research instrument (Zilia Ocular) which measures how much oxygen is in the very small blood vessels of the retina. Our group wanted to evaluate healthy people to find out if the measurements the instrument takes are different in different sexes, ages, races, glasses prescriptions and blood pressures. We also looked at if they were changed in people with prediabetes and if it is different in different locations on the retina. We found that the measures are different in different races and ages. The measures also change with location in the eye. The other factors did not change the measurements of oxygen saturation on this instrument. We need to know this information because we want to detect changes in the retina in diabetes in diverse patient groups; however, we need to know about normal variations to better understand and collect that data.

Keywords: oximetry, oxygen saturation, prediabetes, refractive error, blood pressure

Introduction

Oxygenation of retinal tissue is an important factor in the progression of vascular diseases such as diabetes, while the lack of oxygen in the retina is a contributing cause of proliferative diabetic retinopathy.[1,2] As diabetic retinopathy is the leading cause of preventable blindness in working-aged Americans, any measures that could detect early diabetic eye disease could be beneficial for public health. In addition, there are millions of people worldwide with prediabetes.[3] Since about 10% of the patients with prediabetes convert to type 2 diabetes each year, studying possible retinal changes before type 2 diabetes onset could be beneficial as well.[4] Many adults with diabetes and prediabetes do not know they have the disease and are not being treated. Those with prediabetes are typically included in control groups of research studies and are not separately studied. Overall, prediabetes are understudied in the eye, but it is known that prediabetes can cause

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alterations to retinal health, causing changes in color vision, retinal function and thinning of the retinal nerve fiber layer in studies done by our group and others.[5–7] To date, it is unknown if the changes seen are a result of glucose, insulin, or other health factors.

Studies of oxygen saturation in the retina in controls to date have been done in large vessel retinal oximetry. The values for oxygen saturation in the larger retinal vessels average 92% for arteries and 55% for veins.[8–10] Jani et al found differences in large vessel oxygen saturation with age and hypertension.[9] More recently, Kirsch et al noted differences in large vessel oxygen saturation measures of both arterioles and venules are related to retinal and iris pigmentation.[11] Studies have also shown differences in oxygen saturation with diseases such as diabetes. From those studies, observed retinal vessel oxygen saturation increases in subjects with diabetes, although the amount of change depends on the severity of the disease.[12–14] In addition, these studies did not include subjects with prediabetes as their own group.

Local retinal oxygen saturation in the capillaries rather than the peripapillary of larger vessels is a relatively new research technique, which has potential as a biomarker for diseases, such as diabetes, which affect the capillary network. However, little is known about what influences local retinal oxygen saturation measures have on healthy individuals or those with prediabetes. Evaluation in healthier subjects needs to be examined before the technique can be applied to diabetes. A newer retinal oximeter, the Zilia Ocular (Quebec, Canada), takes local measurements of oxygen saturation in capillaries rather than large vessels. Previous studies with this instrument arise largely from our group and find the instrument to have good repeatability, as well as high sensitivity to circadian rhythms in control populations.[15,16] The detailed principles of how this technology works are described in other publications. These papers also illustrate how the depth of the oximeter is known to typically include the retina up to the RPE.[17–21] In brief, to compute oxygen saturation within the capillary beds of the tissue, this instrument uses diffuse reflectance spectroscopy that detects oxygenated and deoxygenated hemoglobin, producing oxygen saturation measures collectively across the retinal tissue. This will include the superficial, middle, and deep capillary beds and possibly even the anterior choroid.

In this study, we evaluate normal variations in retinal oxygen saturation in areas around the macula. The macula is the most important area for vision, thus changes to macular health are especially important. No data has been published on how macular tissue oximetry is affected by age, race, sex, blood pressure or refractive error. As many ocular findings are associated with these demographic and health factors, we hypothesized that they could also alter retinal oxygen saturation. These variables must be known to use this instrument in a diverse population. Understanding natural variations with this instrument is an important first step towards quantifying pathological differences as compared to controls within future studies for our research group and others.

Materials and Methods

Subjects

Fifty-nine previously acquired control subjects between the ages of 22–69 were included in this retrospective study. Of the 59 subjects, 47 were controls with normal glucose function and 12 were undiagnosed prediabetics per a single HbA1c reading. Prediabetes in this study was an HbA1c of between 5.7% and 6.4% following the criterion of the American Diabetes Association.[22] None of the 12 prediabetics knew of their prediabetes status on presentation or were being treated. Exclusion criteria included subjects with eye diseases affecting the anterior and posterior segment health, including significant lens changes and/or cataracts. Subjects who were previously diagnosed with prediabetes, Type 1 diabetes, Type 2 diabetes, or had a HbA1c greater than 6.4% were also excluded. This study's data collection was approved by and in accordance with regulations set by the Institutional Review Board of the University of Houston and complied with the Declaration of Helsinki. Subjects were recruited from the University of Houston and the University Eye Institute at the University of Houston College of Optometry into studies, which included data collection either immediately following their eye exam or upon a scheduled appointment in our lab. All subjects who had the full needed data set and met the inclusion criterion above were included.

Eye Exam Data Collected

Subjects were asked to self-report medical and ocular history, current knowledge of diabetic status, current medical conditions, and current medications. Demographic information including race, age, and sex was collected by self-report. Blood pressure was taken at the time of the study with an Omron (Hoffman Estates, IL) 3 series upper arm blood pressure monitor if not completed during their recent eye exam. Non-cycloplegic refractive error was gathered through chart review and recorded or via autorefraction (Nidek, San Jose, CA) if needed. Spherical equivalents were calculated by investigators. The subject's best corrected visual acuity was taken to ensure all acuities were 20/30 or better, and anterior segment health was examined using slit lamp examination. Van Herick estimation of the anterior chamber was conducted before dilation of the right eye with one drop of 1% tropicamide and one drop of 2.5% phenylephrine. Posterior segment health was determined by fundus photography post-dilation. All subjects had healthy retinas free of optic nerve and retinal disease per photography examined by a masked optometrist.

Blood Testing

The subject's third or fourth finger was pricked with a standard commercial diabetes lancing device and <1.0 mL of blood was collected. Blood samples were used to quantify blood glucose and HbA1c on all subjects (Siemens DCA HbA1c analyzer, Munich, Germany). HbA1c was used to classify subjects as control or prediabetic. The participants were not required to fast to participate.

Retinal Oximetry Acquisition and Technique

The protocol for recording oxygen saturation levels is our standard method first described in Williams et al.[15] Only the right eye was included. Data was gathered using an oximeter/fundus camera (Zilia Ocular, Zilia Inc, Quebec, Canada) after the instrument was calibrated for each subject. Measurements (1.5 degree acquisition spot size) were acquired in 10-second intervals to capture an average of 20 readings, which are averaged together by the instrument producing a value. The indicated acquisition spot size is a nominal value considering an eye without refractive error and having an average adult axial length. It is calculated assuming a flat planar acquisition region, given its small dimensions. A mechanism is integrated in the device to optically compensate for the refractive error and the axial length (integrated in the focus of the fundus, which can be fine-tuned by the examiner) which accounts for a range of −9.5D to +17.5D. Acquisitions were taken around the macula at four locations, 3.1 degrees from the fovea at the superior/temporal, inferior/temporal, superior/nasal, and inferior/nasal locations by placing the target at specified locations on a grid superimposed on the fundus image while avoiding acquisition over medium or large-sized vessels. Figure 1 shows the fundus grid and where the measures were taken for reference. Subjects were instructed to fixate on an internal central blue fixation spot to

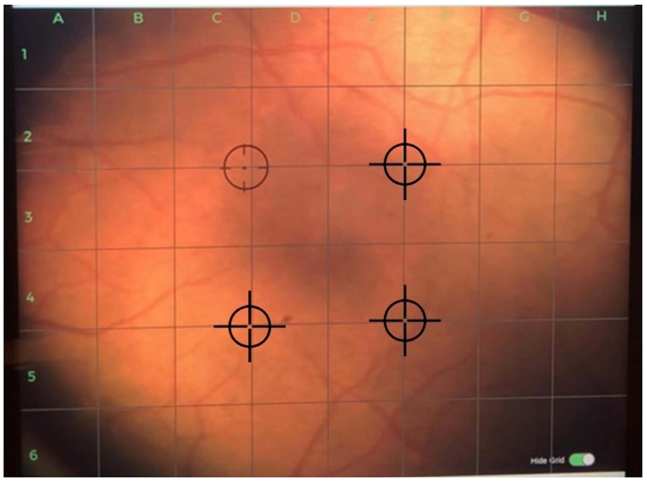

Figure 1 Grid Overlay on Fundus with Measurement Points Noted. This shows the display on the Zilia Ocular highlighting the measurement locations. The measures were taken at the 4 locations indicated and then averaged to calculate a macular oximetry value.

minimize eye movements. Data points where eye movements are greater than the radius of the acquisition spot size were discarded by the instrument. Oxygen saturation measures included in this study were all taken and then analyzed by the same examiner for consistency. If a subject had had more than one value for retinal oximetry taken, their last data point was selected for inclusion.

To compute oxygen saturation within the capillary beds of the macular and adjacent tissues, this instrument uses diffuse reflectance spectroscopy. White light emitting diodes emits light that enters the eye, are collected within a small movable target, and are reflected from the fundus back to the spectrometer. The instrument's proprietary algorithms analyze the absorption spectra of oxygenated or deoxygenated hemoglobin and report a mean value, which includes all hemoglobin in the retina until the pigmented tissue of the RPE is reached. Oxygen saturation measurements are then displayed between the range of 0 −100%.[19–21] The reported oxygen saturation is the percent of hemoglobin in this tissue that is currently bound to oxygen within the capillary area measured.

Statistical Analysis

Regression analysis was used to evaluate the relationship between retinal oxygen saturation and race, age, sex, refractive error, and blood pressure. Multivariate regression was used to evaluate multiple variables together. T-tests were used for sex and prediabetes analysis and ANOVA with post hoc analysis were used to evaluate regions and races.

Results

Subjects

Subject information can be found in Table 1. There were 59 total Subjects between the ages of 20 and 70 (average age 38.8 ± 14.7 years) available for analysis. The 20–29-year-old group was the largest group. Overall, there were 31 women and 28 men were included. This study consisted of 14 subjects who reported their race as Black, 14 as Asian, 12 as Other (which included those who reported that they were Hispanic or multiracial), and 19 as White. Subjects with and without prediabetes were included in all data analyses.

Table 1 Subject Group Information

	Average (Ranges)	**P-values**
Race	14 Black, 14 Asian, 12 Other, 19 White	p < 0.0001
Average Blood Pressure (mmHg)	123.98 ± 14.74 (90 to 176) 81.51 ± 10.47 (55 to 110)	p = 0.60 p = 0.71
HbA1c (%)	5.3 ± 0.41% (4.5 to 6.3)	
Prediabetes (n)	12 (average HbA1c = 5.9%) (5.8 to 6.3)	p = 0.87
Average refractive error	−0.92 ± 2.5D (28 myopes, 17 emmetropes and 14 hyperopes) (−7.52 to +5.87)	p = 0.67
Age Group numbers (n)	20–29 −25 30–39 −10 40–49 −6 50–59 −11 60–69 −7	p = 0.43 p < 0.002 when race is controlled
Sex	31 Female, 28 Male	p = 0.34

Differences in Oxygen Saturation with Race or Pigment Differences

There was a strong correlation between increased skin pigmentation as a proxy for retinal pigment and decreased oximetry (ANOVA, $p < 0.0001$). Figure 2 shows the distribution of the average oxygen saturation percentage in all regions measured. For the Black subject group, which had the darkest skin and retinal pigment, average oxygen saturation was 48.07 ± 8.81%. The next highest pigmented retinas were found in the Asian subject group with an average oxygen saturation 53.12 ± 4.55%. For the Other race subject group (third in pigment), average oxygen saturation was 55.47 ± 7.59%. For the White subject group with the lightest skin and retinal pigment, the average oxygen saturation was 59.53 ± 6.78%.

Oxygen Saturation and Age

Ages ranged between 22 and 69 (mean 38.8 ± 14.7 years). No significant relationship was observed between age and oxygen saturation in univariate analysis ($p = 0.43$) (Figure 3). However, when race was controlled for our multivariate

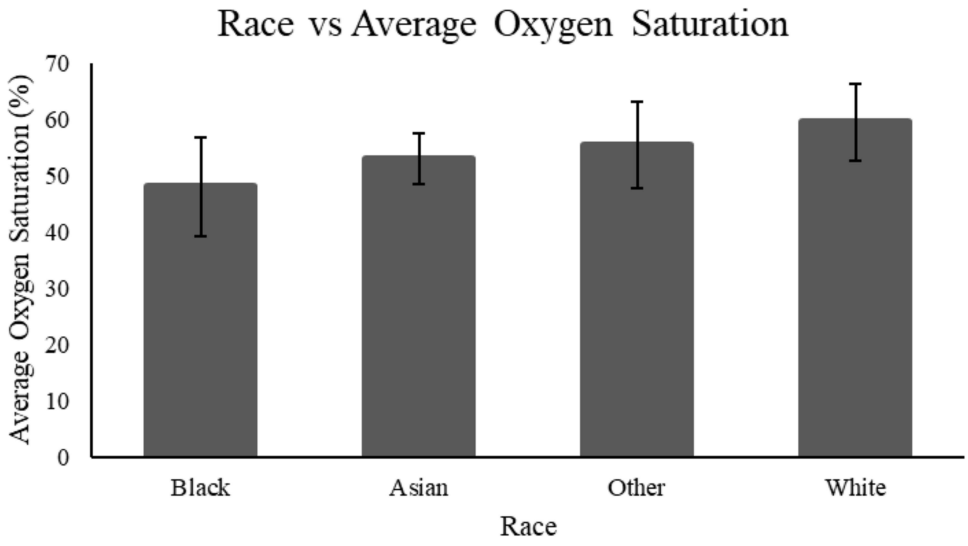

Figure 2 Race versus Average Oxygen Saturation (%). Races were grouped into Black, Asian, Other, and White with an increasing saturation trend following less pigmented fundi races. Standard deviations bars are shown. ($p<0.0001$).

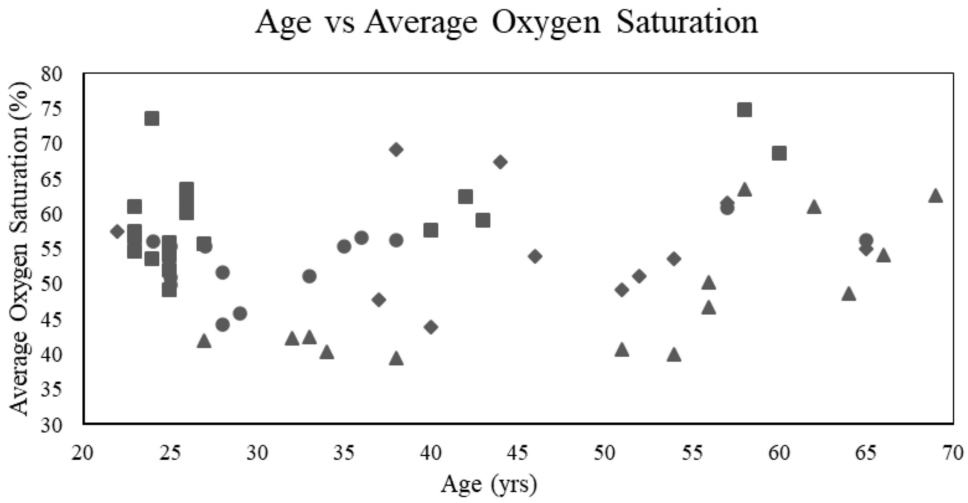

Figure 3 Age versus Average Oxygen Saturation (%). Distribution of subject age and respective average oxygen saturation is plotted. No discernable pattern is noted ($p=0.43$). Age and Oxygen Saturation are related, however, if race is controlled for in a multivariate model ($p<0.002$). Black = triangle, Other = diamond, Asian = circle, White = square.

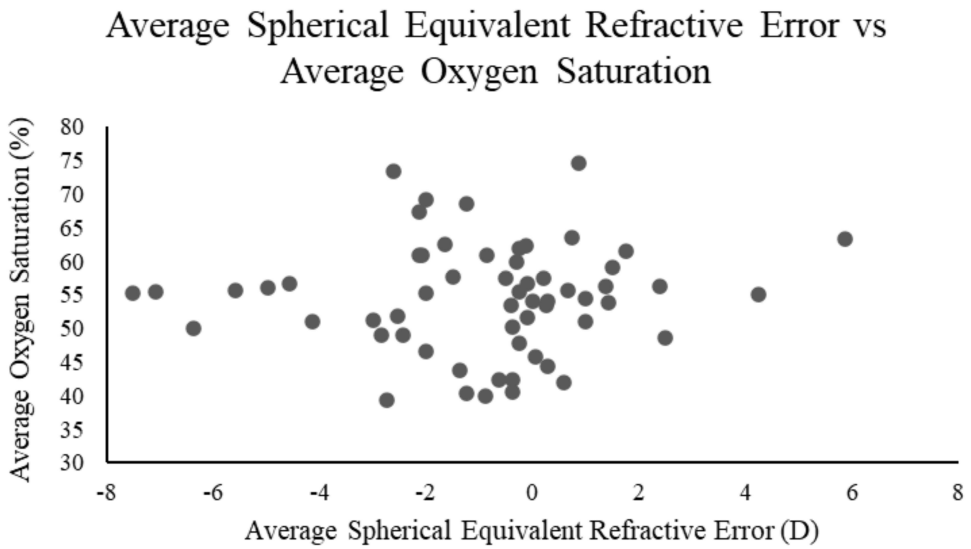

Figure 4 Average Spherical Equivalent Refractive Error versus Average Oxygen Saturation (%). Subject average spherical equivalent refractive error was plotted against their respective average oxygen saturation percentage. No discernable pattern was noted (p = 0.67).

model, an age effect was seen ($p < 0.002$), where oxygen saturation increased with age when race is held constant. The multivariate analysis of the relationship between oxygen saturation with race and age has an R^2 of 0.39. The race has a coefficient of 4.68 ($p < 0.0001$) and Age has a coefficient of 0.20 ($p = 0.002$). No other factors were found to be significantly associated with retinal oximetry in a multivariate analysis.

Oxygen Saturation Relationship with Sex, Refractive Error and Blood Pressure

There was no relationship between retinal oxygen saturation and sex, refractive error nor blood pressure. There were 31 female and 28 male subjects with an average oxygen saturation of 55.43% and 53.39%, respectively. No statistical difference between sex was found ($p = 0.34$). Figure 4 shows subjects' refractive error ranged between + 5.87 D and −7.52 D. No statistical significance was found with refractive error and retinal oxygenation saturation ($p = 0.67$). Axial length data was not gathered. Blood pressure (systolic and diastolic) also had no influence on the oximetry measures ($p = 0.60$, $p = 0.71$, respectively, with regression analysis).

Retinal Location

There were significant differences noted in oxygen saturation at different locations around the macula. Table 2 highlights the oxygen saturation differences in the locations. The temporal values (%) were lower than the nasal values (%). It was found that the inferior nasal quadrant had the highest average oxygen saturation at 57.74%, while superior temporal had the lowest at 50.56%. There was a statistical difference between the nasal and temporal regions by ANOVA ($p < 0.001$).

Effect of Prediabetes

Overall, there was no difference in averaged oxygen saturation between those subjects with and without prediabetes. The control subjects had an average oxygen saturation of 54.38 ± 8.56%, and the prediabetes patients had an average oxygen saturation of 54.77 ± 6.47% ($p = 0.87$). We included subjects with prediabetes in the other analyses in this study as part of the control groups.

Table 2 Regional Data for Oximetry Measures

Superior temporal: 50.56 ±10.83	Superior Nasal: 56.83 ± 10.95
Inferior temporal: 52.35 ± 9.33	Inferior Nasal: 57.74 ± 9.62

Discussion

The goal of this study was to evaluate normal control data from a diverse population to determine which demographic factors could influence macular retinal oximetry measures. This information improves our future research and that of other groups who may use the same technique. We did find factors, which influence these measures in normal data that should be considered when gathering data in disease populations. Overall, we also found that retinal oximetry is extremely variable in the normal population, ranging from 40% to 75%.

Race variations were observed in our control data set, with more pigmented skin and fundi having lower saturation measures. We believe those with more pigmented skin often have more fundus pigmentation. The authors also believe this is likely a result of the measurement technique not being robust against different fundus pigmentations and not a true value difference in fundus oxygen saturation between groups. One possibility for this finding is that the instrument picking up more oxygen saturation data from the underlying choroid in subjects with lighter pigmented retinas, which do not absorb as much light. Choroidal saturation is higher than in retinal capillaries, so even a small influence from the choroid could be influential.[23] The data from large vessel oximetry evaluating pigment differences have provided mixed results to date. Some studies found no statistical differences between oxygen saturation and race, unless both race and sex are considered together.[9,10] However, one study did find a similar correlation of more pigmented eyes having lower saturation measures.[11] The technique here is not the same as large vessel oximetry, and pigmentation may play a larger role around smaller vessels. It is also noteworthy that there are race and sex differences in oximeters measuring saturation in other tissues such as pulse oximetry measures through the skin.[24,25] Studies on these instruments have noted they can be biased and less accurate as pigment increases, calling for caution in interpreting these measures. It is clear that the data here show a need to race or pigment match retinal oximetry data when possible for the most accurate comparisons.

As the authors work in an area that has a great deal of racial and ethnic diversity (Houston TX USA), going forward we plan to account for differences observed in this data by grading fundus pigmentation (regardless of race or ethnicity) and creating and using a fundus pigmentation score in addition to age, to match control and disease cohorts. This score will include fundus appearance and take into account reported race and ethnicity. There is no widely accepted score of fundus pigmentation to date that we are aware that will work for our research. Fundus pigmentation does correlate to skin and iris pigmentation, but there can be variations.[11] In follow-up to this work, we plan to create the needed scale, which will use retinal photos, race, iris and fundus pigment information to create a data scale for comparisons. Our work contains a much greater diversity of races and ethnicities than other studies, which report on this data.

We expected to see age differences, as there are known age differences in other tests of ocular structure and function like optical coherence tomography, electroretinography, and contrast sensitivity.[26–28] Jani et al also found age-related differences in oxygen saturation in larger vessels.[9] We did see a statistical relationship between age and oxygen saturation, but only after controlling for race differences. While we did eliminate those with cataracts, this age difference could arise from differences in media or from changes in retinal vessel health. This indicates that for retinal oxygen saturation studies going forward, race/pigmentation is the strongest confounding factor for oximetry data, but age is also important. Thus, both age and race matched data are necessary for retinal oximetry in the population. It is worth noting that our data set had more 20–29 year participants than other age groups. A clearer age effect may be seen if we gather more control data in older subjects and those less than 20 years. In this data set, we did not include patients with any retinal pathology or lens changes. This subject recruitment exclusion criteria made gathering retinal oximetry measures on older control subjects more difficult.

We also expected refractive error to influence oximetry as there are data that shows that with increased axial length (higher myopia), the retina stretches and vessels spread more.[29,30] As such, oxygen saturation levels could be lower in those that have myopia. The instrument controls for retinal magnification from refractive error, however it does not control for differences in blood flow that could result from refractive error. However, we did not find a statistical relationship with refractive error and oxygen saturation. Our results also show no statistical relationship with oxygen saturation and systolic or diastolic blood pressure. This result is different than Jani et al who found a relationship between larger vessel oxygen saturation and hypertension.[9] However, capillary beds do not have the same regulation response as larger vessels.

This study also demonstrated measurement location influences on retinal oxygen saturation with a statistical difference between nasal and temporal regions. As the vessels traverse the retina and branch from the optic nerve, there are more vessels concentrated nasally as the optic nerve is positioned more nasally within the retina. This leads to nasal temporal variations in many clinical tests of structure and function (eg OCT, mfERG). Thus, we expected there to be nasal-temporal oxygen saturation differences, with nasal vasculature having higher oxygen saturation levels due to perfusion from both larger caliber and more densely populated vessels nearby. This is in agreement with other large vessel ocular oximeters, which find the same result.[31] Furthermore, this area is also inside the area of macular pigment. While we do not anticipate that macular pigment would have an impact on retinal oximetry measures as it comes from vessel measures only, we did not measure the macular pigment nor do we know the effect variations in macular pigment may have on the penetration of the signal. The area we are measuring in is not the highest concentration of pigment so may be more variable. It is also known that macular pigment can change with age.[32]

Lastly, we evaluated undiagnosed prediabetes as a factor in our data. We specifically wanted to look at those who did not know they have prediabetes as it is a silent disease in which they could have subclinical retinal changes. However, our results showed no differences between subjects with undiagnosed prediabetes and healthy subjects in this sample. This suggests that small groups of patients with undiagnosed vascular diseases such as prediabetes are not likely to have a significant impact on oxygen saturation control data gathered in eye clinics. However, given the small sample of prediabetes included, the unknown duration of prediabetes, and the fact they were grouped based on a single HbA1c measure and not repeated data over time, lends to the need for additional longitudinal studies to discern if prediabetes could have subtle influence on oxygen saturation values.

Retinal oximetry has promise in research studies on vascular disease, however there are location and demographic factors, which must be controlled for in studies which use this technique to evaluate differences in populations. Overall, we find that oxygen saturation within the healthy population is highly variable from person to person, indicating that longitudinal studies may prove more useful for this technology. This study provides a basis for the evaluation of macular oxygen saturation studies in our lab and others moving forward.

Ethics Approvals

The subjects were control groups in studies 962, 2674, or 3080 that were approved by the University of Houston IRB. All subjects provided written informed consent after questions were answered.

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Disclosure

The authors report no conflicts of interest in this work.

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