DIFFERENCES IN OCULAR BLOOD FLOW BETWEEN PEOPLE OF AFRICAN AND EUROPEAN DESCENT WITH HEALTHY EYES

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ABSTRACT

Purpose: To investigate differences in ocular blood flow between people of African (AD) and European descent (ED) with healthy eyes.

Methods: Retrobulbar and retinal capillary blood flow was assessed in one eye of 58 participants (24 AD, 34 ED) with healthy eyes with systemic blood pressure lower than 140/90. Retrobulbar blood flow was measured in the ophthalmic artery (OA), central retinal artery (CRA), nasal (NPCA) and temporal posterior ciliary arteries (TPCA). Peak systolic velocity (PSV), end diastolic velocity (EDV) and resistive index (RI) were assessed. Retinal capillary blood flow was assessed using mean retinal flow and avascular space defined as the percent of area measured with no blood flow. Groups were compared using t-tests and Pearson correlations were compared using Fisher r-to-z transformation.

Results: Compared to people of ED, people of AD had significantly lower EDV in the NPCA (p=0.01), and higher RI in the CRA (p=0.04) and TPCA (p=0.01). No significant differences were observed in mean retinal capillary flow or avascular area. In the CRA, a significant positive correlation was observed between pattern standard deviation (PSD) and PSV (p=0.02) and this correlation was significantly different from that observed in the ED group (p=0.01). A significant correlation was also observed between PSD and EDV (0.04) in the AD group.

Conclusion: This study suggests that retrobulbar blood flow is lower in healthy eyes in persons of AD compared to ED. This may provide a mechanism through which people of AD are at increased risk for ophthalmic diseases such as glaucoma.

Key Words: glaucoma; ocular blood flow; visual function; racial difference

INTRODUCTION

Primary open-angle glaucoma (POAG) is a progressive optic neuropathy in which damage to the retinal ganglion cells results in loss of visual function.[1] POAG is the most common form of glaucoma,[2] and people of African descent (AD) are disproportionately affected by this disease compared to people of European descent (ED).[3,4] In the United States, higher prevalence and incidence of POAG have been reported for people of AD.[5] In similar age groups, African Americans have been reported to be up to six times more likely to have POAG compared to white Americans, and POAG is the leading cause of irreversible blindness in the African American population.[6]

The reasons underlying the well-documented susceptibility of people of AD to POAG remain unclear. POAG is a multifactorial disease, and differences between people of AD and ED could be due to a single factor or to a combination of factors. Several differences have been reported between people of AD and ED with healthy eyes. Specifically, people of AD have been shown to have on average larger optic discs, larger cup-to-disc ratios, thicker retinal nerve fiber layer, and thinner corneas.[7-10] People of AD have also been shown to have slightly worse visual function.[11] Racial differences associated with some of the risk factors for glaucoma have also been reported. For example, people of AD have been reported to have a higher prevalence of diabetes[12] and systemic hypertension.[13]

Vascular factors may also play a role in the racial differences observed in POAG. Several studies have shown a relationship between POAG and both ocular blood flow and ocular perfusion pressure (OPP).[14-16] Differences in retinal,[17] choroidal,[18] and retrobulbar[19-22] blood flow have been shown in patients with POAG. Additionally, ocular

vascular markers have been shown to correlate with visual field loss.[17,23-25] POAG is also associated with other vascular conditions including systemic hypertension,[25] nocturnal arterial hypotension,[26] and optic disc haemorrhages.[27] Large population-based studies have shown a relationship between OPP and the prevalence, incidence and progression of glaucoma.[14,16,28,29]

Within the AD population, vascular factors may have a greater impact compared to people of ED. For example, people of AD have higher rates of cardiovascular disease[30] and AD patients with POAG have been reported to have significantly lower blood flow values in all retrobulbar blood vessels compared to POAG patients of ED.[31] Finally, racial differences were observed in a longitudinal study of ocular blood flow in POAG. Patients of AD, but not ED, showed a significant and positive association between change in retinal capillary blood flow and ONH parameters over a 3-year follow-up period.[32] To the best of our knowledge, racial differences in ocular blood flow have not been assessed in healthy eyes. The purpose of this study was to determine whether differences in ocular blood flow exist between AD and ED individuals with healthy eyes.

MATERIALS AND METHODS

Fifty-eight eyes from 58 participants with healthy eyes were enrolled in the study. Of these, 24 were of AD and 34 were of ED. One eye was randomly selected and tested for each participant. Participants were recruited into the study through advertisements, from family members of patients, or were referred to the study from primary eye care clinics. Informed consent was obtained from all participants in the study. All methodology were approved by the Indiana University School of Medicine institutional review board. This study was performed in compliance with the Health Insurance Portability and Accountability Act (HIPAA) as well as the tenets of the Declaration of Helsinki.

Inclusion Criteria

Both eyes of each participant were healthy based on a complete dilated ocular examination. Healthy eyes were defined as having open angles, best-corrected visual acuity of 20/40 or better, spherical refraction within ±5 diopters, cylinder correction within ±3 diopters, symmetric optic discs defined as an asymmetry in the vertical cup-to-disc ratio ≤ 0.2, no hemorrhages or retinal nerve fiber layer defects, and a normal appearance of the optic disc. All participants also had IOP of less than 22 mmHg and no repeatable abnormalities on static automated perimetry (definition of normal results provided in the Visual Function section below). Participants with a family history of glaucoma were included.

Exclusion Criteria

Participants were excluded if they had a history of intraocular surgery (except for uncomplicated cataract surgery) or if they showed evidence of other ocular diseases including diabetic retinopathy. Participants were also excluded if they had diseases affecting the visual field such as demyelinating diseases, diabetes, HIV positive or diagnosed with AIDS, or pituitary lesions. In addition participants were excluded if they were taking medications known to affect visual field sensitivity or vision color. Participants with controlled systemic blood pressure exceeding 140/90 were excluded from the study. Finally, participants who did not identify as being of either of AD or of ED by self-report were excluded from the study.

General methodology

Participants were seen on three different visits, each performed at least one day apart. On average, all visits were performed over a short time frame to ensure that eyes remained healthy throughout the study (mean of 42 ± 33 days; range of 3 to 200 days). At baseline, participants underwent a complete ocular examination and took two practice visual field tests. The visual field and blood pressure measurements included in the analyses were performed on the second and third visit. Ocular blood flow was measured on the third visit. Participants were asked to avoid caffeine, smoking and alcohol prior to the third visit on which ocular blood flow measurements were taken. IOP (average of two consecutive measurements) was obtained using Goldmann applanation tonometry and central corneal thickness (average of three consecutive measurements) was obtained using the Pachette 2 ultrasonic pachymeter (DGH Technologies, Exton, Pennsylvania, USA). Brachial systolic and diastolic blood pressures and pulse were measured after a five-minute rest period using a calibrated automated sphygmomanometer. Mean arterial pressure (MAP) was calculated as 2/3 diastolic blood pressure + 1/3 systolic blood pressure. OPP was assessed and defined as 2/3 MAP – IOP.

Ocular Blood Flow

Ocular blood flow (OBF) was measured in the retrobulbar vessels using Color Doppler Imaging (CDI) and in the retinal capillaries using the Heidelberg Retinal Flowmeter (HRF), which are described in more details in the next sections. All measurements were obtained by, or under the direct supervision, of one of the authors (B.S.) who has over fifteen years of experience in obtaining ocular blood flow measurements.

Retrobulbar blood flow

Retrobulbar blood flow was assessed using CDI with the Philips HDI 5000 SonoCT Ultrasound System with the microvascular small parts clinical option (Philips Medical Systems, Bothell, Washington, USA) using a 7.5 MHz linear probe. To ensure the quality of the measurements, the average of at least three EKG waves was used and angle correction was applied when needed.[33] CDI measurements were taken in the ophthalmic artery (OA), central retinal artery (CRA), and nasal and temporal posterior ciliary arteries (NPCA and TPCA, respectively). In each vessel, peak systolic (PSV) and end diastolic (EDV) velocities were determined and the Pourcelot vascular resistive index (RI) was calculated. RI was defined as [RI=(PSV – EDV)/PSV]. These measurements have been previously shown to be reproducible.[34]

Retinal capillary blood flow

Retinal capillary blood flow was measured with confocal scanning laser Doppler flowmetry using the HRF (Heidelberg Engineering, Heidelberg, Germany). HRF uses an infrared laser to scan the retina and optic disc to measure vascular perfusion, and has been show to be reproducible.[35,36] Areas of perfused tissue are differentiated from avascular tissue, allowing for a quantification of the degree of vascularity of the fundus. To ensure quality, all measurements had a DC value (brightness sensitivity setting) between 100 and 200.[37,38] A detailed description of this method is available elsewhere.[38,39] We estimated the mean retinal flow and avascular areas defined as the percent area with no blood flow (% zero flow pixels) in the superior and inferior hemifields.

Visual Function

Visual function was assessed using standard automated perimetry (SAP) on the Humphrey Field Analyzer II using the 24-2 program and the Swedish Interactive Thresholding Algorithm (SITA) version 4.2 (Carl Zeiss Meditec, Dublin, CA). SAP uses a small (0.43° of visual angle) flash of white light presented on a dim background (31.5 apostilbs) for 200 milliseconds. This test is non-selective in that all types of retinal ganglion cells can detect the stimuli. All participants were provided with appropriate corrections for viewing distance, had a pupil size of at least 3 millimeters and were asked to press a response button whenever they saw a stimulus while fixating on a central target.

Participants included in this study underwent a total of four visual field tests. Two tests were performed at the first study visit (practice tests) and two tests were performed at the third visit. To minimize the impact of learning effects, whenever possible, the last two visual field tests were averaged and used for analysis. In cases where one or both of the last two visual field tests were unreliable, we used the tests performed on the first visit. When only one reliable test was available, we used the results of that one test without averaging the results (this occurred only for 2 participants of ED and both had normal results). Reliability was defined as less than ≤20% false positive and false negative errors, as well as less than ≤20% fixation losses. Visual fields were further reviewed to ensure that the visual fields were free of artifacts.[11]

Definition of visual field abnormality. In order to meet the visual field inclusion criteria, participant had to have normal visual fields, defined as no repeatable visual field defect. An abnormal visual field was defined as having either a mean deviation (MD) triggered at 5% or worse, a pattern standard deviation (PSD) triggered at 5% or worse, or an

outcome other than “within normal limits” or “borderline” on the glaucoma hemifield test (GHT). When two visual field tests were available, the results had to be abnormal on both visual field tests of a given eye for the results to be considered abnormal because confirmation of visual field defects has been shown previously to improve the specificity of the results.

Racial difference in visual function. Racette et al[11] previously reported the presence of differences in SAP between people of AD and ED with healthy eyes with normal visual field results. In this study, we therefore compared the AD and ED groups on the following parameters: MD, PSD, and the number of points triggered at 5% or worse (<5%, <2%, <1%, or <0.5%) and at 1% or worse (<1% or <0.5%) on the total deviation (TD) and pattern deviation (PD) plots. When averaging the number of abnormal points, the level of abnormality (<5%, <2%, <1%, and <0.5%) and the location of the points were not considered.

Statistical Analysis

Participant-specific categorical variables were compared using the Fisher exact test, and continuous variables were compared using the 2-tailed, unpaired t-tests. Correlations between OBF and visual field parameters in the AD and ED groups were obtained using the Pearson correlation coefficient. Differences in these correlations were assessed using the Fisher r-to-z transformation using the VassarStats (http://vassarstats.net). All other statistical analyses were performed in JMP statistical software (version 9.0.2; SAS Institute Inc, Cary, North Carolina). $P<0.05$ was considered statistically significant. Multiple testing corrections were not applied.

RESULTS

Table 1 shows the demographics and general health data of the participants of AD and ED. No significant differences in age were observed between the two groups, with a mean of 52.8 ± 7.7 years of age in the AD group compared to 53.2 ± 8.7 years in the ED group (p=0.88). Similarly, no significant differences were observed between the groups for sex, presence of a family history of glaucoma, IOP, MAP, OPP, central corneal thickness, and for the presence of diabetes or heart disease (all p-values > 0.05).

The results of the retrobulbar blood flow are presented in Table 2. Significant differences between the AD and ED groups were observed for one of three parameters of the four arteries that were assessed (CRA, NPCA, and TPCA), while no significant differences were observed in the OA. In the CRA, participants of AD (0.7 ± 0.08) had a significantly higher RI value compared to those of ED (0.66 ± 0.07) (p=0.04). In the NPCA, participants of AD (2.27 ± 063) had significantly lower EDV values compared to participants of ED (2.91 ± 1.18) (p=0.01). Finally, in the TPCA, participants of AD had significantly higher RI (0.69 ± 0.07) compared to participant of ED (0.65 ± 0.07) (p=0.01). After applying Bonferroni correction for multiple comparisons, the differences in the NPCA and TPCA remained significant, while the difference in the CRA no longer reached statistical significance.

Table 3 shows the results obtained for retinal capillary blood flow expressed in arbitrary units (AU) in each group. No significant differences were obtained in mean retinal flow between participants of AD and ED in the superior and inferior hemifield (p>0.05).

Similarly, no significant differences were found in percent area with no blood flow in either the superior and inferior hemifield (all $p>0.05$).

No significant differences in visual function were observed between the groups, with similar results obtained for MD between the AD (-0.09 ± 1.06) and ED (-0.02 ± 1.01), PSD between the AD (1.57 ± 0.28) and ED (1.61 ± 0.32), and the number of abnormal point triggered on the TD and PD plots at both 5% and 1% (all $p > 0.05$). In the CRA, significant correlations were observed between PSD and PSV ($p=0.02$) and between PSD and EDV ($p=0.04$) in the AD group only (Figure 1). The difference in correlations between AD and ED for PSD and PSV was significant ($p=0.01$). All other correlations between visual function (MD and PSD) and OBF (PSV, EDV and RI) parameters were not significant.

DISCUSSION

The mechanisms underlying the higher susceptibility of people of AD to develop POAG are not fully understood. Several differences have been reported between people of AD and ED with healthy eyes, including larger disc size, larger cup-to-disc ratio, thinner corneas and slightly worse visual function. In patients with POAG, differences in both systemic and ocular blood flow have been previously reported between patients of AD and ED. To the best of our knowledge, this study is the first to assess differences in ocular blood flow in healthy eyes between people of AD and ED.

In this study, we found significant differences between people of AD and ED in retrobulbar parameters in two of the four arteries that were assessed after correcting for multiple comparisons. In the TPCA, the RI was significantly higher in people of AD. People of AD also had significantly lower EDV in the NPCA. Taken together, these results suggest that in healthy eyes, people of AD have lower markers of ocular circulation compared to their counterparts of ED. These differences were observed in the absence of differences in IOP, diabetes, systemic blood pressure and heart disease between the groups. Our results are consistent with previous studies in which reduced ocular blood flow velocities in the retrobulbar blood vessels have been reported in patients with POAG compared to controls; this finding has been reported in cohorts of ED[40-42] and of AD.[43] In addition, Siesky et al[31] reported lower blood flow values in all retrobulbar blood vessels in POAG patients of AD compared to those of ED. Importantly, vascular resistance in the retrobulbar blood vessels has been previously linked to visual field loss[25] and visual field progression.[44] The contribution of ocular blood flow in the retrobulbar vessels to ocular disease may therefore be different in people of AD compared to people of ED. Specifically, the results of our study suggest that ocular vascular health differences between people of AD and ED can also be observed in healthy eyes and may provide a susceptibility mechanism for higher risk of certain eye diseases including POAG for persons of AD.

In addition to ocular blood flow in the retrobulbar vessels, we assessed blood flow in the retinal capillary beds. In this group of participants, no significant differences were observed between the AD and ED groups for mean retinal flow velocity and for areas of avascular space in both the superior and inferior hemifields. Reduced blood flow in the retinal capillaries has previously been associated with the presence of visual field

defects,[45,46] and with changes in structural parameters[47] in patients with POAG. There is also evidence of a significant positive correlation between changes in retinal capillary blood flow and optic nerve head parameters in patients of AD, but not ED.[32] In our sample of healthy eyes, we did not observe differences within the retina between people of AD and ED. This may suggest that the racial differences in retinal capillary blood flow observed in POAG patients may occur secondarily to reductions in retrobulbar flow. It is also possible, however, that alterations in retinal blood flow occur only after changes of retinal vascular auto-regulation during the glaucomatous disease process. It is important to note that the capillary blood flow measurements were obtained in arbitrary units. While this is not a concern in longitudinal studies where each participant can serve as their own control and change over time can be assessed, the use of these arbitrary units complicates direct comparisons in cross-sectional studies such as the present study. In this study, we also did not observe differences in OPP between the AD and ED groups. A previous study has shown significantly higher OPP in POAG patient of AD compared to those of ED.[31] Our finding suggests that differences in OPP may not be responsible, at least initially, for the racial differences in localized ocular blood flow previously described in POAG.

Racette et al reported small but significant differences in visual function between people of AD and ED with healthy eyes in the large African Descent and Glaucoma Evaluation Study.[11] This finding was observed even in participants with normal visual field tests. While we did not replicate this finding, an interesting finding of this study is the presence of a significant correlation between PSD and PSV in the CRA for the AD group, but not for the ED group. In the AD group, increasingly lower PSV values were associated with increasingly worse PSD values. A similar finding was also observed between PSD and

EDV in the CRA. The CRA supplies the nerve fibers that form the optic nerve and our results suggest that blood flow in this artery may have a greater impact on visual function in people of AD compared to people of ED, even in the absence of ophthalmic disease. This may be a contributing pathway to the higher susceptibility of people of AD to POAG.

While the CDI technique is widely used clinically to image several organs, it has some limitations that need to be considered when imaging the eye. Specifically, CDI measurements of retrobulbar vessels are generally limited to the parameters of blood flow velocity due to a lack of reliable quantification of accurate vessels diameter. They cannot be interpreted as blood flow values. This limitation did not influence our results because we used the same technique in both the AD and ED groups and assessed possible differences. Another limitation of the CDI is that measurements depend on the position of the probe and on the Doppler angle. In this study, angle correction was applied when needed and experienced operators obtained all measurements. Finally, the posterior ciliary arteries are smaller than other arteries and the anatomy of these vessels is highly variable between different individuals. Waveforms from bundles of these vessels are used and CDI measurements in the posterior ciliary arteries have been shown to be less reproducible than those taken in the CRA and OA. While the racial differences we report in this study in the NPCA and TPCA may have been affected by the anatomy of these arteries, there is no evidence to suggest racial differences in the anatomy of these arteries and good quality measurements were obtained in both groups.

HRF is a safe, noninvasive technique that overall yields valid and reproducible measurements of retinal blood flow. HRF measurements of mean retinal flow (not percent of avascular area) are, however, affected by the pigmentation of the RPE. The RPE pigmentation between people of AD and ED is different and this likely affected the amount of absorption and reflectance of laser lights. This limits the comparisons of the mean retinal flow between the AD and ED groups. In the present study, we did not identify significant racial differences in mean retinal flow. It is possible that these differences exist and were not observed because of the impact of different RPE pigmentation between the two groups. It is also possible that these differences were not observed due to the relatively small sample size. This pilot study was, to our knowledge, the first to assess racial differences in ocular blood flow. As a result, we were not able to obtain estimates of effect size or variability from the literature to determine the sample size needed to detect differences between the groups. It should be noted that while our sample size was sufficiently large to detect differences in retrobulbar blood flow between the groups. This is particularly notable given the fact that all participants had normal eyes, with all expected results to be in the normal range with relatively small differences between the groups. The results of this pilot study will allow others to generate effect size and variability estimates to design adequately powered studies in the future.

One limitation of the present study is that race was determined based on self-report, which may be subjective. Previous studies, however, have shown that self-reported race correlates well with racial determination based on more objective genetic admixture techniques.[48] Furthermore, a recent study has concluded that defining race with biogeographic ancestry did not improve the associations between race and phenotypic variations in ocular features compared to using self-report.[49] A second limitation of this

study is that we included participants with systemic hypertension, as long as their blood pressure was controlled to 140/90 or better. While it is possible that ocular blood flow measurements were affected by the presence of systemic hypertension or by the medications used to control it, a similar percentage of AD (17%) and ED (24%) participants had hypertension ($p>0.05$). Systemic hypertension therefore affected both groups similarly. A third limitation is that the participants included in this study were on average slightly younger than what might be expected in a glaucomatous population as a whole. Finally, while not a limitation per se, we recognize that several studies have shown that people of AD have thinner corneas than people of ED. No significant differences in CCT between people of AD and ED were observed in our sample. A closer inspection of the results, however, shows a small trend towards lower CCT in people of AD, with lower median CCT in people of AD (555.2) compared to people of ED (558.0), as would be expected based on previous findings reported in the literature.

Overall, the results of this study suggest the presence of differences in blood flow in retrobulbar vessels even in healthy eyes between people of AD and ED. These differences may contribute to the susceptibility of people of AD to develop POAG compared to people of ED. We also found that in people of AD with healthy eyes, increasingly lower blood velocity in the artery perfusing the anterior retina correlated with increasingly worse visual field outcomes. This suggests that changes in the retinal blood supply may have a larger impact on visual function in people of AD compared to people of ED. Future studies are needed to determine the impact of ocular blood flow in POAG in people of AD and to specifically identify how vascular differences contribute to the development and progression of glaucoma.

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FIGURE LEGEND

Figure 1. The association between pattern standard deviation (PSD) and peak systolic velocity (PSV) is shown in Panel A. A significant correlation was observed in the AD group (r=-0.46; p=0.02) but not in the ED group (r=0.26; p=0.14). The difference between these correlations was significant (p=0.01). The association between pattern standard deviation (PSD) and end diastolic velocity (EDV) is shown in Panel B. A significant correlation was observed in the AD group (r=-0.42; p=0.04) but not in the ED group (r=0.09; p=0.62). The difference between these correlations was not significant (p=0.06).