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Original article

Racial differences in the correlations between structural parameters and ocular blood flow in healthy eyes

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Abstract

Purpose: This study aimed to assess differences in the relationship between structural parameters and ocular blood flow between persons of African (AD) and European descent (ED) with healthy eyes.
Methods: The relationship between structural and ocular blood flow parameters was assessed in 46 participants (20 AD, 26 ED) with healthy eyes. Disc area (DA), rim area (RA), and retinal nerve fiber layer thickness (RNFLT) were measured. Retrobulbar blood flow was assessed in the ophthalmic (OA), central retinal (CRA), nasal (NPCA), and temporal short posterior ciliary arteries (TPCA). Peak systolic velocity (PSV), end diastolic velocity (EDV), and resistive index (RI) were assessed. Retinal capillary blood flow was also evaluated. Differences between the correlations were determined using the Fisher r-to-z transformation.
Results: Significant differences in correlations were observed between the AD and ED groups in the CRA, where PSV and DA were positively correlated in AD ($r = 0.43$) and negatively correlated in ED ($r = -0.36$) ($\Delta r = 0.79$; $P = 0.01$). A similar finding was observed for PSV and RA (AD: $r = 0.39$; ED: $r = -0.23$; $\Delta r = 0.62$; $P = 0.04$). In the inferior hemifield, for the ED group only, the percentage of avascular space and RNFLT were positively correlated ($r = 0.51$, $P = 0.01$), while mean retinal flow and RNFLT were

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negatively correlated (r = −0.50, P = 0.01).
Conclusion: The relationship between structural parameters (DA and RA) and the blood flow index (PSV) in the CRA, which supplies blood to the superficial layer of the optic nerve head, was significantly different in the healthy eyes of AD compared to ED. More research is required to show how these differences may affect glaucomatous risk.

Keywords: glaucoma, ocular blood flow, posterior segment, racial difference

1. Introduction

Primary open-angle glaucoma (POAG) is the leading cause of irreversible blindness in the African American population of the United States.[1] Persons of AD are up to six times more likely to be affected by POAG compared to persons of ED.[2,3] In addition, persons of AD are susceptible to earlier development of POAG, higher disease severity, more rapid progression of the disease, and greater visual field impairment compared to persons of ED.[3] The mechanisms underlying the differences in the development and progression rates of POAG between persons of AD and ED remain unknown.

Large population-based trials have linked reduced ocular perfusion pressure (OPP) to the prevalence, incidence, and progression of glaucoma.[4,5] Retinal,[6] choroidal,[7] and retrobulbar[8] blood flow deficiencies have been reported in patients with POAG. Other vascular conditions such as systemic hypertension,[9] aging of the vasculature,[10] and optic disc hemorrhage[11] have also been associated with POAG. Moreover, ocular vascular conditions have been shown to correlate with visual field loss.[6,9] Persons of AD tend to have higher rates of systemic vasculature abnormalities, and it is possible that vascular factors may play a greater role in their higher vulnerability to development and progression of POAG. For example, POAG patients of AD have been shown to have significantly lower blood flow values in all retrobulbar vessels compared to ED patients.[12] One study also showed that in POAG patients of AD, the correlation between changes in ocular blood flow and optic nerve head (ONH) morphology parameters are stronger than in patients of ED. Taken together, this suggests that patients of AD may have a stronger vascular component in the pathogenesis of glaucoma than patients of ED.[13,14]

In healthy eyes, studies have shown thinner corneas, larger optic discs, deeper maximum cup depth, higher intraocular pressure (IOP), and worse performance on visual field tests in persons of AD.[15] Lower blood flow in retrobulbar vessels has been reported in the healthy eyes of AD compared to ED.[16]

A missing element in understanding vascular contributions to the POAG process could be an established knowledge of blood flow changes over the course of development and with aging. Therefore, developing a normative database and

baseline parameters is important with regard to studying racial differences in the development of POAG. Establishing a normative database for ocular blood flow measurements, however, has been historically challenging due to significant overlap between healthy and glaucomatous populations in ocular blood flow measurements, lack of standardization of measurements, and multiple vascular tissue beds relevant to the glaucomatous disease process.[17] The aim of this study was to assess the differences in the correlation between structural parameters and ocular blood flow in the healthy eyes of individuals of AD and ED.

2. Materials and methods

One randomly selected eye from 46 participants (20 AD, 26 ED) with healthy eyes based on a complete ocular examination were included in the study. All eyes had open angles, symmetric optic discs with normal appearance (asymmetry of vertical cup-to-disc ratio (CDR) ≤ 0.2), no hemorrhages or RNFL defects, and IOP of < 22 mmHg. Participants were excluded if they had previously undergone intraocular surgery (except for uncomplicated cataract surgery) or if they had evidence of other ocular diseases. In addition, participants with controlled systemic blood pressure exceeding 140/90 and uncontrolled systemic blood pressure were excluded from the study. Inclusion and exclusion criteria are described in detail elsewhere.[16] All study procedures conformed to the tenets of the Declaration of Helsinki and were approved by the Institutional Review Board at Indiana University School of Medicine. All subjects signed an informed consent prior to entry into the study.

2.1. General methodology

Participants were seen on three different visits, each performed at least one day apart. In order to ensure that the eyes remained healthy throughout the duration of the study, all visits were performed over a short time frame (mean of 41 ± 35 days; range of 5 to 200 days). At baseline, participants underwent a complete ocular examination. The ocular blood flow and structural parameters reported in this study were assessed on the third visit. IOP (measured by Goldmann applanation tonometry) and central corneal thickness (CCT, measured by Pachette 2 ultrasonic pachymeter; DGH Technologies, Exton, PA, USA) were obtained based on the average of two and three measurements, respectively. OPP was calculated as 2/3 mean arterial pressure (MAP) − IOP.

Retinal capillary blood flow was measured utilizing Heidelberg confocal scanning laser Doppler flowmetry (HRF; Heidelberg Engineering, Heidelberg, Germany), which has been shown to be reproducible.[18] Retrobulbar blood flow velocities were assessed with color Doppler imaging (CDI with the Philips HDI 5000 SonoCT Ultrasound System with the microvascular small parts clinical option; Philips Medical Systems, Bothell, WA, USA) using a 7.5 MHz linear probe. The OA, CRA, NPCA, and

Table 1. Demographics and general health data for the AD and ED groups

	AD (n = 20)	ED (n = 26)	P-value
Age (years)	54.00 ± 8.62	53.36 ± 8.67	0.80
Sex (% female)	55	38	0.41
Family history of glaucoma (%)	25	8	0.21
CCT (µm)	548.34 ± 38.19	563.01 ± 29.52	0.16
IOP (mmHg)	15.20 ± 1.85	15.19 ± 2.04	0.99
MAP (mmHg)	96.22 ± 8.54	94.46 ± 7.92	0.48
OPP (mmHg)	48.94 ± 6.53	47.78 ± 5.35	0.52
Diabetes mellitus (%)	0	0	NA
Heart disease (%)	5	12	0.62

µm: micron; mmHg: millimeters of mercury; NA: not applicable; CCT: central corneal thickness; IOP: intraocular pressure; MAP: mean arterial pressure; OPP: ocular perfusion pressure

TPCA were assessed for PSV and EDV blood flow velocities, and Pourcelot's vascular RI, calculated as RI = (PSV − EDV)/PSV.[19] Structural assessment included DA, RA, CDR, and RNFLT using the Heidelberg Retina Tomograph III (Heidelberg Engineering, Heidelberg, Germany). Only images with mean pixel height standard deviation of less than 50 µm were used in the analyses.[20]

2.2. Statistical analysis

The Fisher's exact test and the 2-tailed, unpaired t-tests were used to compare participant-specific categorical and continuous variables, respectively. Associations between structural parameters and ocular blood flow were derived using the Pearson correlation coefficient. Differences between the correlations in the AD and ED groups were assessed using the Fisher r-to-z transformation. The power of this test is lower than that of tests that consider a single correlation.[21] Given sample sizes of 20 (AD) and 26 (ED), and with the significance level set at alpha = 0.05, the power to detect a difference of 0.2 between the correlations of each sample ranged between 0.10 to 0.47 using the Fisher r-to-z transformation.[21] A difference of 0.2 is a convention used when a correlation measure is unknown but different from 0. All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria)[22] and Microsoft Excel 2013 (Microsoft, Seattle, WA, USA). The level of significance (alpha) was set at 0.05. Multiple testing corrections were not initially applied for the report in the results.

Table 2. A comparison of the results for retrobulbar blood flow velocities and peripheral vascular resistance, measured by CDI, between participants of AD (n = 20) and ED (n = 26) is presented. Measurements were taken from the OA, CRA, and NPCA/TPCA. In each vessel, PSV and EDV were determined and the Pourcelot vascular RI was calculated (multiple testing corrections are not applied).

		AD (n = 20)		ED (n = 26)		
		Mean	**SD**	**Mean**	**SD**	**P-value**
OA						
	PSV	22.66	7.64	25.64	9.52	0.24
	EDV	5.44	1.65	6.94	2.56	**0.02**
	RI	1.08	1.44	0.72	0.07	0.28
CRA						
	PSV	8.30	2.07	8.72	2.62	0.55
	EDV	2.31	0.70	2.96	1.14	**0.02**
	RI	0.72	0.09	0.66	0.07	**0.03**
NPCA						
	PSV	7.48	1.42	8.16	2.26	0.22
	EDV	2.44	0.69	2.98	1.28	0.07
	RI	0.67	0.08	0.64	0.08	0.14
TPCA						
	PSV	7.59	1.49	8.55	2.22	0.08
	EDV	2.26	0.48	3.12	1.22	**0.002**
	RI	0.70	0.07	0.64	0.08	**0.01**

3. Results

No significant differences were observed in demographics and general health data between participants of AD and ED including age, sex, family history of glaucoma, cardiovascular diseases, IOP, MAP, CCT, and OPP (Table 1). Persons of AD were found to have significantly lower EDV in the OA (P = 0.02), CRA (P = 0.02), and TPCA (P = 0.002), and higher RI in the CRA (P = 0.03) and TPCA (P = 0.01) compared to persons of ED (Table 2). No significant differences between groups were observed for all other retrobulbar blood flow, retinal capillary blood flow, or structural parameters.

Within each group, we assessed the correlations between structural and vascular parameters. In the ED group, significant negative correlations were observed

Table 3. Correlations (*r*) and correlation comparisons (*Δr*) between structural and ocular blood flow parameters between participants of AD (n = 20) and ED (n=26)

			AD		ED		Δ r
			r	P-value	r	P-value	P-value
OA	PSV	DA	−0.11	0.66	−0.22	0.29	0.73
		RA	−0.01	0.96	−0.06	0.77	0.88
		CDR	−0.09	0.70	−0.09	0.65	0.99
		RNFLT	0.01	0.97	0.03	0.89	0.95
	EDV	DA	−0.14	0.56	−0.15	0.45	0.96
		RA	0.03	0.90	−0.20	0.33	0.47
		CDR	−0.16	0.49	0.16	0.43	0.30
		RNFLT	0.19	0.42	−0.06	0.76	0.42
	RI	DA	0.14	0.56	−0.13	0.53	0.40
		RA	−0.02	0.93	0.19	0.35	0.50
		CDR	0.18	0.45	−0.40	**0.05**	0.06
		RNFLT	0.02	0.92	0.14	0.51	0.73

			AD		ED		Δ r
			r	P-value	r	P-value	P-value
CRA	PSV	DA	0.43	0.06	−0.36	0.07	**0.01**
		RA	0.39	0.09	−0.23	0.27	**0.04**
		CDR	0.15	0.53	−0.28	0.17	0.18
		RNFLT	0.08	0.75	−0.15	0.46	0.47
	EDV	DA	0.29	0.21	−0.29	0.15	0.06
		RA	0.13	0.57	−0.38	0.06	0.09
		CDR	0.28	0.23	0.00	0.98	0.36
		RNFLT	0.10	0.66	−0.18	0.37	0.37
	RI	DA	0.18	0.45	−0.04	0.85	0.50
		RA	0.29	0.21	0.32	0.11	0.94
		CDR	−0.15	0.53	−0.40	**0.04**	0.39
		RNFLT	−0.08	0.73	0.11	0.60	0.55

			AD		ED		Δ r
			r	P-value	r	P-value	P-value
NPCA	PSV	DA	0.27	0.25	−0.31	0.13	0.06
		RA	0.08	0.73	−0.30	0.14	0.23
		CDR	0.17	0.48	−0.02	0.92	0.56
		RNFLT	−0.36	0.12	−0.24	0.24	0.67
	EDV	DA	0.06	0.80	−0.20	0.34	0.42
		RA	0.03	0.91	−0.38	0.06	0.19
		CDR	0.00	0.99	0.21	0.30	0.51
		RNFLT	−0.09	0.70	−0.24	0.24	0.63
	RI	DA	0.12	0.61	−0.14	0.51	0.42
		RA	0.03	0.89	0.27	0.19	0.45
		CDR	0.10	0.67	−0.46	**0.02**	0.06
		RNFLT	−0.22	0.36	0.16	0.45	0.23

			AD		ED		Δ r
			r	P-value	r	P-value	P-value
TPCA	PSV	DA	−0.02	0.93	−0.19	0.36	0.60
		RA	0.04	0.88	−0.26	0.20	0.35
		CDR	−0.14	0.55	0.00	1.00	0.65
		RNFLT	−0.38	0.09	−0.21	0.31	0.54
	EDV	DA	−0.19	0.41	−0.04	0.83	0.63
		RA	−0.17	0.48	−0.26	0.20	0.76
		CDR	0.02	0.93	0.27	0.19	0.44
		RNFLT	0.00	1.00	−0.07	0.72	0.82
	RI	DA	0.28	0.22	−0.14	0.49	0.17
		RA	0.27	0.24	0.12	0.58	0.60
		CDR	−0.07	0.76	−0.41	**0.04**	0.26
		RNFLT	−0.26	0.27	−0.12	0.56	0.65

OA: ophthalmic artery; CRA: central retinal artery; NPCA/TPCA: nasal/temporal short posterior ciliary arteries; PSV: peak systolic velocity; EDV: end diastolic velocity; RI: resistive index; DA: disc area; RA: rim area; CDR: cup-to-disc ratio; RNFLT: retinal nerve fiber layer thickness

Table 4. Correlations (r) and correlation comparisons (Δr) between structural and HRF parameters in the superior and inferior hemifields between participants of AD and ED

			AD (n = 19)		ED (n = 24)		Δ r
			r	P-value	r	P-value	P-value
Inferior hemifield	Mean retinal flow (AU)	DA	−0.01	0.96	0.16	0.47	0.61
		RA	−0.08	0.75	0.12	0.57	0.54
		CDR	0.01	0.97	−0.21	0.31	0.49
		RNFLT	0.07	0.79	−0.50	**0.01**	0.06
	Zero flow pixel (%)	DA	−0.04	0.86	−0.12	0.57	0.80
		RA	0.00	0.99	0.23	0.28	0.49
		CDR	−0.11	0.66	−0.14	0.52	0.92
		RNFLT	0.13	0.59	0.51	**0.01**	0.19
			AD (n = 19)		ED (n = 22)		Δ r
			r	P-value	r	P-value	P-value
Superior hemifield	Mean retinal flow (AU)	DA	−0.30	0.21	0.06	0.79	0.27
		RA	−0.20	0.42	0.18	0.41	0.25
		CDR	−0.18	0.45	−0.32	0.15	0.67
		RNFLT	0.14	0.58	−0.41	0.06	0.09
	Zero flow pixel (%)	DA	0.12	0.63	−0.12	0.60	0.49
		RA	−0.01	0.97	0.10	0.65	0.74
		CDR	0.08	0.73	−0.17	0.45	0.45
		RNFLT	−0.28	0.24	0.25	0.26	0.11

DA: disc area; RA: rim area; CDR: cup-to-disc ratio; RNFLT: retinal nerve fiber layer thickness; AU: arbitrary unit

between RI and CDR in all arteries (r coefficients range: −0.46 to −0.40). These correlations were not significant in the AD group (r coefficients range: −0.15 to 0.18) (Table 3). Similar results were observed in retinal capillary blood flow, where significant correlations were observed between both mean retinal flow (r = −0.50, P = 0.01) and zero flow pixel (r = 0.51, P = 0.01), and RNFLT (in the inferior hemifield) in the ED group only (Table 4).

Finally, we determined whether the correlations between structural and blood flow parameters were different between the AD and ED groups. Significant differences were observed in the CRA, where PSV and DA were positively correlated in the AD group (r = 0.43) and negatively correlated in the ED group (r = −0.36) (Δr = 0.79; P = 0.01) (see Fig. 1; Table 3). A similar finding was observed for PSV and

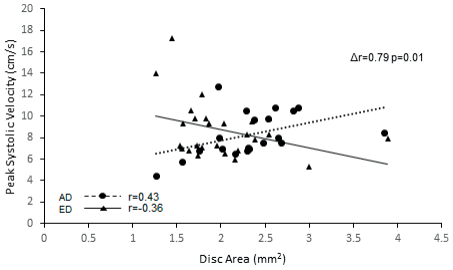

Fig. 1. The association between PSV and DA in the CRA is shown.

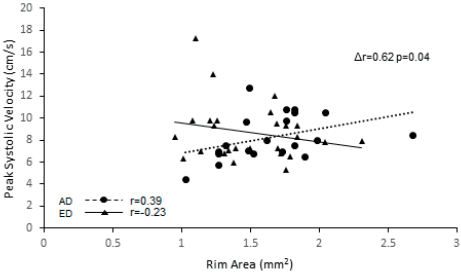

Fig. 2. The association between PSV and RA in the CRA is shown.

RA, with a positive correlation in the AD group (r = 0.39) and a negative correlation in the ED group (r = −0.23) (Δr = 0.62; P = 0.04) (see Fig. 2; Table 3).

4. Discussion

The present study aimed to investigate differences in correlations between ONH morphology and retrobulbar and retinal blood flow in healthy eyes between persons of AD and ED. Some reports have shown correlations between structural measurements (*e.g.*, RNFLT, CDR) and ONH blood flow in POAG patients. Resch *et al.*,[23] for example, have reported that ONH blood flow was negatively correlated with CDR and positively correlated with the RNFL cross-sectional area in POAG patients. In addition, Siesky *et al.*[24] reported significant differences in correlations between reductions in retrobulbar and retinal capillary blood flow and changes in ONH and retinal morphology between patients of AD and ED in a longitudinal cohort of patients with POAG. Our study assessed whether such differences in correlations exist between healthy eyes of AD and ED. If so, these differences could explain, at least in part, disparities in glaucoma development and progression between these populations.

In the present cross-sectional pilot study, we observed different correlations

between structural parameters and ocular blood flow in the AD and ED groups with healthy eyes. In the CRA, which nourishes the superficial layers of the ONH, we found a positive correlation between PSV and both DA and RA in the AD group, while these correlations were negative in the ED group. Although the correlations in each group did not reach statistical significance, the difference in correlations between the two groups was significant.

We found an unanticipated uniform pattern of significant negative correlations between RI and CDR in all retrobulbar arteries in the ED group only. Although RI is known to be highly correlated to downstream vascular resistance in blood vessels, it is not equal to vascular resistance, as it may be influenced by several anatomical and physiological parameters not related to resistance such as vascular compliance and blood pressure profile.[25] Because of the variability in the size of the disc in healthy eyes, CDR can be quite variable in persons with healthy eyes and may not accurately represent all changes at the ONH.[26] The rise in vascular resistance may lead to defective ONH circulation, neuroretinal rim thinning, and expanding CDR. While our sample size was relatively small, we observed a trend of significant correlation between RI and CDR in all retrobulbar vessels in healthy eyes of the ED group only. Although, our study did not look at patients with POAG, it is possible that the difference in trends that we observed between the AD and ED healthy eyes plays a role in explaining the vulnerability of people of AD to develop POAG. This should be explored in future studies, perhaps longitudinally, to determine how this racial difference impacts the development of POAG.

Similar to the results we reported in Kaskan *et al.*,[16] we found significant differences between persons of AD and ED in retrobulbar blood flow. This was expected, given that a subset of participants was included in both studies (22 persons of the ED and 11 persons of the AD group). After correcting for multiple comparisons, EDV was significantly lower and RI was significantly higher in the TPCA in the AD compared to the ED group. These racial differences were observed in healthy eyes, in the absence of differences in IOP, diabetes, systemic blood pressure, and heart disease between the two groups. No significant differences between the groups were observed either in retinal capillary blood flow or in the correlations of ONH morphology and retinal capillary blood flow. However, in the inferior hemifield of the ED healthy eyes, a negative correlation was observed between mean retinal blood flow and RNFLT, and a positive correlation between capillary sparsity and RNFLT. A recent study by Kanakamedala *et al.* longitudinally assessed the correlations between changes of ONH parameters (such as cup area, RA, and linear CDR) and changes in retinal capillary blood flow in POAG patients of AD and ED.[13] In their study, only patients of AD showed significant and positive correlations between changes in retinal capillary blood flow of the temporal retina and changes in ONH morphology. These correlations were weak and not significant in patients of ED. Unlike their finding, we observed significant correlation between structural parameters and retinal capillary blood flow measurements only in the ED group.

The present study has several limitations. First, race was determined based on self-report. However, self-reported race has been shown to correlate well with more sophisticated racial classification, such as genetic admixture techniques.[27] Second, participants with controlled systemic hypertension and family history of glaucoma were included, although both groups had a similar percentage of individuals with systemic hypertension and family history. Third, the power to detect significant differences between the AD and ED groups using Fisher r-to-z transformation was relatively low. However, we found significant differences between the AD and ED groups despite relatively low statistical power. This not only suggests that the differences in correlations exist, but that they are likely greater than 0.2. Additionally, the lack of significant findings between the groups for some of the other correlations may be due to lack of power rather than lack of an underlying difference.

Several factors, such as ocular structural properties and blood flow, as well as ethnicity, may contribute individually, or synergistically, to the development and progression of POAG. While the correlation between many of these factors has been previously studied, isolating each of these factors has been a challenge. Many mathematical approaches have been suggested in conjunction with clinical studies over the last decade in order to quantify the contribution of each possible risk factor for POAG development.[28] The differences in structural and ocular blood flow parameters in healthy eyes which were investigated in our study could be implemented in mathematical models in the future. This could deepen our understanding of the mechanisms underlying racial differences in the development and progression of glaucoma.

In conclusion, the findings of this study suggest the presence of differences in the relationship between structural and ocular vascular parameters in healthy eyes of persons of AD and ED. Our results can be helpful in designing future research to identify the specific mechanisms, including possible vascular factors, which contribute to the POAG disease disparity experienced by persons of AD.

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