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Determinants of Retinal Microvascular Architecture in Normal Subjects

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Abstract

Background—Recent studies have shown that changes in the retinal microvasculature predict cardiovascular disease (CVD); however, little is known regarding influences on the retinal microvasculature in healthy people without overt cardiovascular or metabolic disease.

Methods—We used a semiautomated computerized technique to analyze digitized retinal photographs from a total of 167 healthy people (age range, 45–75 years; 83 female), without clinical CVD, diabetes, or hypertension, randomly sampled from the population-based Beaver Dam Eye Study. We assessed arteriolar and venular narrowing, arteriolar optimality deviation, and other quantitative aspects of the retinal microvasculature.

Results—Arterioles were significantly narrower and longer, had wider branching angles, and were more tortuous than venules. Increased arteriolar length to diameter ratio (an index of arteriolar narrowing) was positively and independently associated with older age and elevated systolic blood pressure. Arteriolar optimality deviation (an index of microvascular endothelial dysfunction) increased with greater body mass index. Current smoking and increased white blood cell (WBC) count was associated with wider venules. After controlling for smoking, WBC was no longer a significant predictor of venular diameter.

Conclusions—CVD risk factors are associated with retinal microvascular changes in healthy individuals without evidence of CVD, diabetes, or hypertension. CVD risk factors have different influences on the arteriolar and venular bed.

Keywords

retina; microvascular; arterioles; venules

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The retinal circulation is closely related to the cerebral circulation and offers a rare opportunity to visualize the arteriolar and venular circulations in man in vivo using noninvasive techniques. Examination of the retinal fundus is commonly used to assess retinal microvascular damage in diabetes and as an indicator of target organ damage in hypertension [9]. Recent studies have shown that the existence of retinopathy and, especially, more quantitative measures of retinal microvascular abnormalities, even in those without diabetes and hypertension, predict incident cardiovascular disease (CVD), including stroke [28,25,18] and ischemic heart disease, [23], heart failure [31], hypertension [32], as well as type 2 diabetes, [33], often independently of other traditionally used risk factors. Nevertheless, it remains unclear to what extent these changes in the retinal microvasculature are simply a late consequence of clinical CVD, and relatively little is known regarding the normal distribution of retinal microvascular geometry and the cardiovascular risk factors influencing these parameters in healthy individuals without overt CVD. Such data are important to determine the extent of early effects of vascular and metabolic risk factors on the microcirculation.

The objective of this study was to use a semiautomated computer-based analysis of retinal photographs to determine the factors influencing the retinal microvasculature in subjects without any evidence of CVD, hypertension, or diabetes mellitus drawn from the population-based Beaver Dam Eye Study.

METHODS

Study Population

The study population was a randomly selected subgroup of the Beaver Dam Eye Study cohort. The Beaver Dam Eye study is a prospective, population-based study, details of which have been published elsewhere. [27]. In brief, a private census of the population of Beaver Dam, Wisconsin, USA, was performed from fall 1987 to spring 1988. Of 5924 individuals eligible, 4926 (83%) participated in the baseline examination. A standardized interview and examination was performed at baseline, including questions relating to a history of CVD, medication use, and cigarette smoking. Self-reported smoking was classified as current, ex-, or never smoker and quantified in terms of pack years. Blood pressure (BP) was measured with a random-zero sphygmomanometer, according to the Hypertension Detection and Follow-up Program protocol [10], and the average of two measurements was used. Nonfasting bloods were obtained from all participants and plasma glycosylated hemoglobin, serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and white blood cell (WBC) count determined, as previously described [27]. Diabetes mellitus was defined as a past history of diabetes or the presence of elevated glycosylated hemoglobin and a random blood sugar >11 mmol/l. Body mass index (BMI) was calculated as weight/height². From this population, we selected a random sample of 167 subjects (83 women) aged <75 years, who had undergone retinal photography and had not experienced a cardiovascular death during a 10-year follow-up period, who had no history of CVD, hypertension, or diabetes mellitus at baseline, and were not receiving medication for any cardiovascular condition (e.g., angina, coronary disease, hypertension, or diabetes).

Image Analysis

Retinal photography techniques and retinal image analysis have been previously described in detail [23,29]. In brief, 30-degree color stereoscopic photographic positives of the ocular fundus centered on the optic disc (field 1) of both eyes were digitized by using a commercial photographic scanner (Nikon LS1000, Nikon UK, Kingston, Surrey, UK) at a resolution of 2700 dpi (yielding images of $\sim 2900 \times 2500$ pixels). Digitized images were converted to monochrome by the extraction of the green layer the digital red, green, and blue (RGB) images. Retinal microvascular and branching parameters were measured from the digitized images, using a custom written program running within the Matlab programming environment on a personal computer [2]. Measurements were made from at least seven vessel segments and at least five bifurcations in both arterial and venous arcades from each subject. A vessel segment was defined as linking two clearly visible bifurcations, or else traversing a linear distance of at least 1.5 disc diameters (the width of an average optic disc in photographic images) from the optic disc boundary without bifurcating (Figure 1).

The analysis was performed on a sequence of complete trees, generally from a single eye, continuing onto the second eye, if necessary, to achieve the required number of vessel segments and bifurcation. Vessel path length was measured along the vessel center line between bifurcations. Arteriolar and venular diameters were measured at a series of intensity cross-sections normal to the vessel at two-pixel intervals along the entire length of the vessel segment. At each cross-section, the vessel diameter was measured to subpixel accuracy, using a sliding linear regression filter (SLRF) technique, as previously described [2], and an average was calculated for each vessel. To derive a measure of vessel narrowing that is applicable to both arterioles and venules (unlike the arterio-venous ratio; AVR) and is unaffected by the refractive properties of the eye, we calculated the length-diameter ratio (LDR) of each segment as a measure of arteriolar and venular narrowing [14]. This ratio may have some advantages over AVR, a widely used measure of arteriolar narrowing, in that it is not influenced by concurrent arteriolar and venular changes. Bifurcation angles (ω) were measured as the angle subtended between branches arising from a bifurcation. The relationship of parent to offspring arteriolar diameters was quantified by the optimality deviation—a measure of the extent to which the optimality ratio (γ_{ratio}) deviates from the theoretically predicted optimum for minimum power losses and uniform shear distribution across bifurcations. Increased deviation is an indicator of microvascular endothelial dysfunction [5]. The γ_{ratio} was calculated from the parent arteriolar diameter (D_0) and the offspring diameters (D_1 and D_2) as:

$$\Gamma_{\text{ratio}} = \sqrt[3]{\frac{D_1^3 + D_2^3}{2D_0^3}}$$

The optimality deviation was calculated as:

$$\Gamma_{\text{ratio}} = -\frac{1}{\sqrt[3]{2}}$$

Vessel tortuosity was measured as the difference between the actual path length of the vessel segment (measured by tracking) and the straight line length of the segment, divided by the straight line length. This simple measure of tortuosity does not distinguish between increased length due to bowing and that due to multiple points of inflection, so we also analyzed vessels by using another measure of tortuosity, based on vessel curvature calculated from the integral of the square of curvature along the path of the vessel, normalized by the total path length [6], but since our findings with this alternative measure of tortuosity did not differ substantially from the more simple measure, we have only presented data using the former analysis. AVR was calculated on the basis of the estimated diameters of the central retinal artery (CRAE) and vein (CRVE), as previously described [8,20,21,28].

Statistical Methods

Two group comparisons were performed using a Student's *t*-test for paired and unpaired data as appropriate, or in the case of skewed data, the nonparametric equivalents. Regression was performed by using ordinary linear regression or quantile regression for data with non-normally distributed residuals, and findings are presented as regression coefficients (beta) with their respective standard errors (SEs) and *P*-values. Other data are presented as means (SD) or medians (ranges) for continuous variables or n (%) for categorical variables. The distribution of pack years was normalized by taking log (pack years +1) for purposes of regression. All statistical analysis was performed by using Intercooled Stata 9.2 (StataCorp, College Station, Texas, USA). A *P*-value<0.05 was considered statistically significant.

RESULTS

The characteristics of the population are shown in Table 1, and retinal measurements are shown in Table 2. There was no gender difference in arteriolar measurements. Women had significantly more acute venular branching angles than men, but no other gender difference was observed (data not shown); consequently, gender-specific analyses are not presented.

Retinal arterioles were significantly narrower and longer than venules (Table 2), had narrower branching angles, and were more tortuous than venules (Table 2). Arteriolar LDR showed a positive relationship with increasing age and SBP. This observation was consistent with our finding of an inverse relationship between arteriolar diameter (CRAE) and age and SBP (Table 3A). Arteriolar optimality deviation increased with increasing BMI (Table 3A). There were no other significant associations between CVD risk factors and arteriolar parameters.

Unlike arterioles, venular narrowing (venular LDR) was unrelated to age or blood pressure. Venular diameters (CRVE) also showed no correlation with age or blood pressure. However, venular LDR was inversely related to WBC and to pack years of smoking (Table 3B), and similarly, venular diameter was positively associated with WBC and to pack years of smoking (Table 3B). Venules tended to be wider (nonsmokers CRVE = 225.1 (2.1) vs. current smokers CRVE = 230.8 (2.5); *P* = 0.09, adjusted for age and sex), and venular narrowing was significantly less in current smokers than in nonsmokers (nonsmokers

venular LDR =10.5 (0.4) vs. current smokers venular LDR =8.8 (0.5); $P=0.009$, adjusted for age and sex).

In a multivariate model adjusted for sex, both age and systolic blood pressure (SBP) were significant independent, negative correlates of arteriolar narrowing (beta = -0.0010 [0.0003] $P=0.01$ and beta = -0.00041 [0.0001] $P<0.001$, respectively).

After the inclusion of log (pack years +1) in a multivariate model, the relationship between WBC and wider venules was attenuated and no longer statistically significant (pack years beta = 0.007 [0.002]; $P=0.004$ and WBC beta = 0.002 [0.002]; $P=0.1$; adjusted for age and sex in a multivariate analysis). The association between arteriolar optimality deviation and increasing BMI remained largely unaffected by statistical adjustment for age, sex, BP, glycosylated hemoglobin (HbA1c), serum total cholesterol, HDL cholesterol, WBC, and pack years (multivariate adjusted beta = 0.0038 [0.0016]; $P=0.02$, including all the above variables).

DISCUSSION

This study compared arterioles and venules in the retinal microvasculature and examined associations with standard cardiovascular risk factors in a community-based sample without any evidence of hypertension, diabetes mellitus, or CVD and not receiving medication for these diseases.

In this generally healthy population, we observed that retinal arterioles were narrower than venules, had wider branching angles, and were more tortuous, than venules. Most previous studies have examined retinal microvascular changes in the context of disease states, such as hypertension [30], metabolic syndrome [19], or diabetes [4]. Numerous studies have consistently shown that hypertension is associated with retinal arteriolar narrowing, and that the relationship between BP and arteriolar narrowing extends across the range of BP in a population [26]. Our data are in keeping with these previous observations showing that elevated BP was independently associated with evidence of arteriolar narrowing, despite participants having blood pressures in the normotensive range. This finding is also consistent with studies in 6–8-year-old healthy children where arteriolar narrowing was related with higher BP levels, suggesting early pathophysiological effects of blood pressure on microvascular caliber, even in the absence of clinically defined hypertension [17]. Our data indicate that LDR may be a useful means of normalizing vessel diameter, so that it may be relatively independent of refraction, although recent data suggest that the impact of differences in refraction is relatively minor [34]. We believe that it is probably useful to present both uncorrected and length-normalized data in future studies. Our findings, however, emphasize the potential limitations of AVR as a measure of arteriolar narrowing [16], since it fails to take account of independent changes in arteriolar and venular caliber.

Factors influencing the retinal venular circulation differ from those influencing the arteriolar circulation. Until recently, the venular system has not been given much attention. Venular changes were not observed to be related to BP in a large population study, [26] and venular diameter has, therefore, been widely used to normalize arteriolar diameter. However, more

recently, it has become clear that venular diameter is affected by disease. Indeed, increased venular diameter, rather than decreased arteriolar diameter, has been reported to be associated with increased risk of stroke [11] and coronary heart disease [24]. It has been proposed that wider venules are an indicator of increased systemic inflammation [12, 15], and our observations support this in showing an association between WBC and venular diameter that appeared to be related to smoking habit. After taking into account smoking in a multivariate model, WBC was no longer a significant predictor of venular narrowing, suggesting that smoking is a closer correlate of chronic inflammation status than a measurement of WBC on a single occasion.

In this study, we also examined possible predictors of optimality deviation, a proposed measure of microvascular endothelial function [5,24]. We showed that increased arteriolar optimality deviation was positively correlated with elevated BMI. Previous studies have reported that obesity is associated with endothelial dysfunction in both the macro- and microvasculature [7,13,22]. Our observations are consistent with these findings in other vascular beds and are in keeping with a generalized adverse effect of obesity on vascular function.

This study had a number of limitations. It was cross-sectional, and consequently, we cannot draw conclusions regarding causality. Subjects were drawn from a limited age range (between 45 and 74 years), and our observations cannot be extrapolated to other age groups. In addition, it is likely that some participants of this age will have undetected or subclinical disease, and this may have influenced some observations. The strengths of the study include the use of a community-based population combined with blinded quantitative assessment of retinal microvascular changes, using a semiautomated approach.

CONCLUSIONS

In conclusion, retinal microvascular changes are evident in normotensive adult subjects without evidence of CVD or diabetes but correlate with known cardiovascular risk factors (e.g., elevated BP, obesity, and smoking). Our data, therefore, suggest that retinal microvascular changes may occur early in the pathoetiology of disease. Further longitudinal studies, particularly in young individuals, would be valuable in establishing if this is the case. Risk factors have differential influences on the retinal arteriolar and venular bed, and it is likely that these changes will have differential prognostic significance for both systemic and ocular diseases.

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Figure 1. Retinal microvascular analysis. The figure shows a typical digitized retinal image viewed in the analysis program after tracking and measurement of several arteriolar trees. An enlargement of one region is shown to illustrate the measured parameters. D_0 = parent diameter, D_1 = 1st offspring diameter, D_2 = 2nd offspring diameter, ω = branching angle, L = vessel segment length.

Table 1

Characteristics of the Population Studied

Variable	All subjects (<i>n</i> = 167)
Age, years	64 (45–74)
Males, <i>n</i> (%)	84 (50)
SBP, mmHg	126 (16)
DBP, mmHg	75 (10)
BMI, kg/m ²	27.8 (5.0)
HbA1c (%)	5.7 (3.1–7.5)
Total cholesterol, mmol/L	6.1 (1.0)
HDL cholesterol, mmol/L	1.3 (0.3–3.7)
WBC, 10 ³ cells/mL	6.5 (5.6–7.7)
Pack years	1.2 (0–132)
Smokers (non/current/ex), <i>n</i> (%)	79 (47)/57(34)/31 (19)

Data are means (SD), medians (ranges), or *n* (%).

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein, WBC, white blood cell count.

Table 2

Arteriolar and Venular Parameters in the Population

Variable	All subjects (<i>n</i> = 167)
Arterioles	
CRAE, μm	205.4 (20.4)
Length, μm	1075 (341)
LDR	14.3 (11.4, 17.8)
ω , $^{\circ}$	69.5 (64.5, 78.3)
Simple tortuosity ($\times 10^{-2}$)	0.40 (0.02, 1.1)
Optimality deviation	0.08 (0.03–0.14)
Venules	
CRVE, μm	228.5 (19.1) **
Length, μm	881 (302) **
LDR	9.8 (3.5) **
ω , $^{\circ}$	73.5 (66.6, 79.2) **
Simple tortuosity	0.03 (0.00, 0.68) **
Other	
AVR _{CR}	0.90 (0.84, 0.95)
Retinopathy, <i>n</i> (%)	8 (5)
AV nicking, <i>n</i> (%)	2 (1)

Data are means (SD), medians (ranges), or *n* (%).

**
 $P < 0.01$;

*
 $P < 0.05$ comparing arterioles vs. venules.

CRAE/CRVE, estimated diameters of the central retinal artery/vein; LDR, length-diameter ratio; AVR, arterio-venous ratio.

Results of Univariate Regression Analysis between Measurements and Retinal Arteriolar Parameters

Table 3A

	CRAE Beta (s); <i>P</i>	Length Beta (se); <i>P</i>	LDR Beta (se); <i>P</i>	ω Beta (se); <i>P</i>	Optimality deviation Beta (se); <i>P</i>
Age, years	-0.18 (0.20); 0.4	13.3 (3.2); <0.001	0.19 (0.05); <0.001	-0.16 (0.10); 0.12	-0.0005 (0.0009); 0.6
SBP, mmHg	-0.35 (0.01); <0.001	3.5 (1.6); 0.03	0.06 (0.02); 0.016	-0.06 (0.05); 0.2	-0.0004 (0.0004); 0.4
BMI, kg/m ²	-0.72 (0.31); 0.022	5.4 (5.3); 0.3	0.10 (0.08); 0.2	0.05 (0.17); 0.8	0.0028 (0.0014); 0.04
WBC, 10 ³ cells/mL	1.09 (0.75); 0.15	-4.7 (12.5); 0.7	0.0103 (0.19); > 0.9	0.68 (0.39); 0.08	-0.0007 (0.0033); 0.8
Pack year	0.19 (0.92); 0.8	19.3 (15.2); 0.2	0.33 (0.23); 0.16	-0.68 (0.47); 0.16	-0.0052 (0.0039); 0.19
Total cholesterol, mol/L	-0.28 (1.53); > 0.9	-9.1 (25.6); 0.7	-0.40 (0.39); 0.3	0.17 (0.79); 0.8	0.0044 (0.0067); 0.5
HDL cholesterol, mol/L	1.14 (3.64); 0.8	43.7 (61.1); 0.5	0.17 (0.93); 0.9	-1.77 (1.92); 0.4	-0.0090 (0.0158); 0.6
HbA1c, %	-2.31 (2.26); 0.3	-3.9 (37.9); > 0.9	-0.02 (0.58); > 0.9	0.52 (1.20); 0.7	-0.0166 (0.010); 0.09

Table 3B

Results of Univariate Regression Analysis between Measurements and Retinal Venular Parameters

	CRAE Beta (se); <i>P</i>	Length Beta (se); <i>P</i>	LDR Beta (se); <i>P</i>	ω Beta (se); <i>P</i>
Age, years	−0.14 (0.19); 0.464	7.5 (2.9); 0.012	0.06 (0.03); 0.08	−0.14 (0.10); 0.15
SBP, mmHg	−0.04 (0.09); 0.705	0.8 (1.5); 0.6	−0.00 (0.02); > 0.9	0.00 (0.05); 0.927
BMI, kg/m ²	0.20 (0.30); 0.497	−4.3 (4.7); 0.4	−0.099 (0.05); 0.07	0.36 (0.16); 0.023
WBC, 10 ³ cells/mL	2.88 (0.66); <0.001	−8.7 (11.1); 0.4	−0.18 (0.09); 0.049	−0.36 (0.37); 0.3
Pack year	1.7 (0.8); 0.047	−26.5 (13.4); 0.05	−0.35 (0.15); 0.026	−0.29 (0.45); 0.5
Total cholesterol, mmol/L	1.07 (1.43); 0.5	4.8 (22.7); 0.8	0.033 (0.26); > 0.9	−0.37 (0.74); 0.6
HDL cholesterol, mmol/L	−5.74 (3.39); 0.09	72.0 (53.6); 0.2	0.95 (0.62); 0.1	−3.24 (1.73); 0.06
HbA1c, %	−2.39 (2.11); 0.3	−22.1 (33.6); 0.5	−0.03 (0.39); > 0.9	−0.77 (1.13); 0.5

Analysis was performed by linear regression or ζ quantile regression for data with non-normally distributed residuals. [¶] Distribution of pack years was normalized by taking log (pack years + 1) for the purposes of regression. There were no significant associations for arteriolar or venular simple tortuosity. CRAE/CRVE, estimated diameters of the central retinal artery; SBP, systolic blood pressure; BMI, body mass index; WBC, white blood cell; HDL, high-density lipoprotein; HbA1c, glycosylated hemoglobin.