Retinal vascular changes and right ventricular structure and function: the MESA-Right Ventricle and MESA-Eye studies

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Abstract

Retinal vessel diameters have been associated with left ventricular morphology and function but their relationship with the right ventricle (RV) has not been studied. We hypothesized that wider retinal venules and narrower retinal arterioles are associated with RV morphology and function. RV end-diastolic mass (RVEDM), end-diastolic volume (RVEDV), end-systolic volume (RVESV), stroke volume (RVSV), and ejection fraction (RVEF) were assessed using cardiac magnetic resonance imaging (MRI) scans of 4204 participants without clinical cardiovascular disease at the baseline examination; retinal photography was obtained at the second examination. Mean diameters of retinal arterioles and venules were measured and summarized as central retinal vein and artery equivalents ("veins" and "arteries," respectively). After adjusting for covariates, wider veins were associated with greater RVEDM and RVEDV in women ($P = 0.04$ and $P = 0.02$, respectively), whereas there was an inverse association with RVEDV in men ($P = 0.02$). In both sexes, narrower arteries were associated with lower RVEDM ($P < 0.001$ in women and $P = 0.002$ in men) and smaller RVEDV ($P < 0.001$ in women and $P = 0.04$ in men) in adjusted models. Narrower arteries were also associated with lower RVEF in men but this was of borderline significance after adjusting for the LVEF ($P = 0.08$). Wider retinal venular diameter was associated with sex-specific changes in RVEDM and RVEDV in adults without clinical cardiovascular disease. Narrower retinal arteriolar diameter was associated with significantly lower RVEDM and smaller RVEDV in both sexes.

Introduction

Retinal vessels are approximately the same size as the coronary microvasculature and may serve as a marker of cardiovascular health. Retinal vessel diameter is precisely measured from retinal photographs; recent studies have shown that older age and hypertension are associated with smaller retinal arteriolar caliber while diabetes, obesity, dyslipidemia, systemic inflammatory markers, and smoking are associated with larger venular caliber.[1–3] Associations of narrower arteriolar diameter and wider venular caliber with incident cardiovascular diseases and outcomes have also

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been reported.[4] For example, retinal arteriolar narrowing is associated with an increased risk of coronary heart disease (CHD) in women only.[5,6] Another study demonstrated that wider retinal venules and narrower arterioles in women aged 49–75 years are associated with an increment risk of CHD death.[7] A meta-analysis confirmed these findings with more robust associations in women compared to men[8] and a more recent study showed that retinal vascular changes were associated with mortality.[6]

Few studies have examined the relationship between retinal microvascular changes and subclinical cardiovascular disease. In the Multi-Ethnic Study of Atherosclerosis (MESA), the presence of retinopathy was associated with higher coronary artery calcium scores, and retinal arteriolar narrowing was associated with left ventricular (LV) concentric remodeling in both sexes while wider retinal venule diameter was associated with LV remodeling in women only.[9,10] However, the relationship between the retinal vasculature and right ventricular (RV) morphology and function has not been investigated. The RV is embryologically and morphologically distinct from the left ventricle and is independently affected by age, sex, race, and a variety of other indicators of endothelial dysfunction.[11–14] The purpose of the current study was to examine the relationship between RV mass and volumes with retinal venular dilation and arteriole narrowing in the MESA. We hypothesized that retinal vascular findings of endothelial dysfunction and microvascular disease would be associated with changes in RV size and function.

Methods

The Multi-Ethnic Study of Atherosclerosis (MESA)

The MESA is a multicenter prospective cohort study designed to investigate the prevalence, correlations, and progression of subclinical cardiovascular disease in Caucasians, African-Americans, Hispanics, and Chinese Americans without clinical cardiovascular disease at baseline.[15] In 2000–2002, MESA recruited 6814 men and women aged 45–84 years from six U.S. communities: Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles, CA. Informed consent was obtained for participation in the study. Exclusion criteria included: clinical cardiovascular disease (physician diagnosis of heart attack, stroke, transient ischemic attack, heart failure, angina, current atrial fibrillation, any cardiovascular procedure); weight >300 lbs; pregnancy; active cancer; or impediment to long-term participation. Hypertension and diabetes were not considered clinical cardiovascular diseases by the parent study, so that participants with these conditions were included. Exam 1 was conducted between 2000 and 2002 while Exam 2 was conducted between 2002 and 2004. The protocols of the MESA and all studies described

herein were approved by the Institutional Review Boards of all collaborating institutions and the National Heart Lung and Blood Institute (NHLBI). NHLBI staff participated in the design of the MESA study.

Cardiac magnetic resonance imaging measures

The cardiac magnetic resonance imaging (MRI) protocol has been previously described.[16] All imaging was performed at Exam 1 (2000–2002) on 1.5-T magnets with a four-element phased-array surface coil positioned anteriorly and posteriorly and electrocardiographic gating. Imaging consisted of fast gradient echo cine images with temporal resolution ≤50 ms.

Methods for interpretation of LV and RV parameters have been previously reported.[17,18] Briefly, RV image analysis was performed by two independent analysts on Windows workstations using QMASS software (Medis, the Netherlands). The endocardial and epicardial borders of the RV were traced manually on the short-axis cine images at the end-systolic and end-diastolic phase. Papillary muscles and trabeculae were included in the RV volumes and excluded from RV mass. RV end-diastolic volume (RVEDV) and RV end-systolic volume (RVESV) were calculated using Simpson's rule by summation of areas on each slice multiplied by the sum of slice thickness and image gap.[19] RV end-diastolic mass (RVEDM) was determined at the end-diastole phase as the difference between end-diastolic epicardial and endocardial volumes multiplied by the specific gravity of the heart (1.05 g/mL). RV stroke volume (RVSV) was calculated by subtracting RVESV from RVEDV. RV ejection fraction (RVEF) was calculated by dividing RVSV by RVEDV. The inter-reader intraclass correlation coefficients from random, blinded re-reads of 240 scans for RV mass, RVEDV, and RVEF were 0.89, 0.96, and 0.80, respectively.

Retinal photography and measurement of baseline retinal vascular caliber

Retinal photography was performed at Exam 2 (2002–2004) using a standardized protocol (Fig. 1).[20] In brief, participants had both eyes photographed with a 45° 6.3-megapixel digital non-mydriatic camera in a darkened room. Two photographic fields were obtained for each eye with one centered on the optic disc and the other centered on the fovea. All images were evaluated by trained graders masked to participants' characteristics at the University of Wisconsin, Madison Ocular Epidemiology Reading Center. Retinal vascular caliber was measured using a computer-based program (IVAN, University of Wisconsin, Madison, WI, USA) guided by a detailed protocol.[21] Optic disc centered right-eye photographs were selected for measurement; the left-eye photograph was used if retinal vascular caliber could not be measured in the right eye. For each photograph, all arterioles and venules coursing through an area

0.5–1 disc diameter from the optic disc margin were measured and the largest six venular and arterial calibers were summarized as the central retinal venular equivalent ("veins") and the central retinal artery equivalent ("arteries"), based on the Knudtson formula (Fig. 1).[22] Intra- and inter-grader correlation coefficients were in the range of 0.78–0.99.[22] Interpretation of RV parameters and retinal photographs was done by independent readers who were blinded to other clinical data.

Covariates

Race/ethnicity was self-reported during the baseline MESA exam according to 2000 US Census criteria as race (Caucasian, African-American, etc.) and ethnicity (Hispanic or non-Hispanic). Participants self-identifying as Hispanic were categorized as Hispanic. Standard questionnaires were used to ascertain smoking status (classified as never, former, or current). Pack-years were calculated using self-reported age of starting to smoke subtracted from the current age (for current smokers) or the age at time of quitting (for former smokers), multiplied by the average number of packs per day. Resting blood pressure was measured three times using the Dinamap Monitor PRO 100 (Critikon, Tampa, FL, USA) automated oscillometric device, and the average of the last two measurements was used. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported hypertension and current use of anti-hypertensive medication. Presence of diabetes mellitus was based on self-reported physician diagnosis, use of medication for hyperglycemia, or a fasting glucose value ≥ 126 mg/dL. Fasting blood samples were drawn and sent to a central laboratory for measurement of serum glucose and lipids. Serum total cholesterol was assessed using standard methods.

Statistical analysis

Basic demographics and descriptive characteristics were summarized for the study individuals. The associations between retinal vascular measures (independent variables) and continuous measures of RV structure and function (dependent variables) were examined with multivariate linear regression. Covariates were chosen based on known associations with ventricular size and heart disease, including demographics and anthropometric variables, as well as variables reflecting co-morbidities, such as smoking, hypertension, cholesterol levels, and diabetes mellitus. Adjustment for potential confounders was performed with sequential models including: (1) demographic and anthropometric variables; (2) variables in (1) plus clinical and laboratory covariates; and (3) variables in (2) plus respective LV measures. Adjustment for weight and height in all models accounted for differences in body size so that indexing of RV parameters to body surface area or other measures was not necessary. Adjustment for LV parameters was performed: (1) to account for the contribution of LV abnormalities to RV changes (for example, increased LV mass causing elevated LV end-diastolic pressure leading to pulmonary venous hypertension and increased RV mass); (2) to better account for differences in body size by "indexing" to this other chamber; and (3) to examine RV-specific associations (rather than more general associations with bi-ventricular morphology). RVSV was not adjusted for LV stroke volume considering the significant inter-dependence of these measures. We performed a subset analysis after adjustment for spirometry (forced expiratory volume in 1 s [FEV1] and forced vital capacity [FVC]), serum cotinine, percentage of emphysema from computed tomography (CT) scan, and type of CT scanner in those with available data from another MESA ancillary study (MESA-Lung).[23,24]

Primary analyses were performed using the vein and artery variables in continuous form. The presence of effect
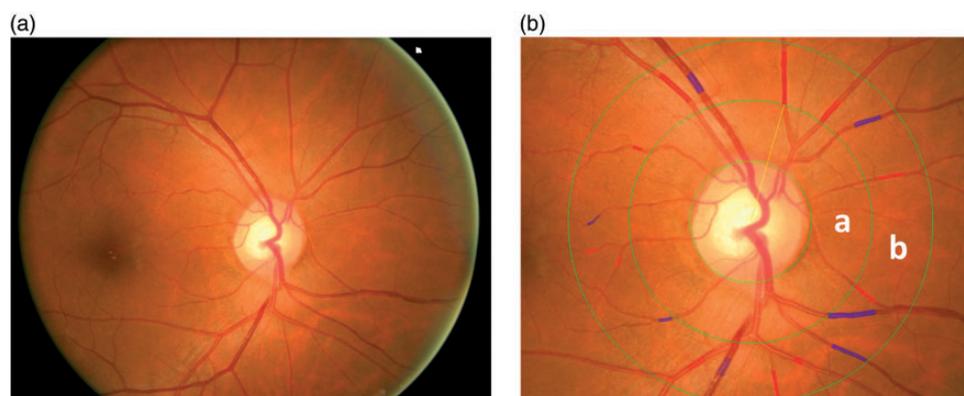

Fig. 1. (a) Stereoscopic 45° color retinal photograph, centered on the optic disc. (b) Retinal vessel caliber measurement using a computer-based program (IVAN, University of Wisconsin, Madison, WI, USA) guided by a detailed protocol. Zone a is a half-disc diameter from the optic disc margin and Zone b is a half-disc to one-disc diameter from the optic disc margin. Individual retinal arterioles (red) and venules (blue) were measured in Zone b. The largest six arteriolar and venular calibers were summarized as the central retinal artery equivalent (CRAE) and the central retinal venular equivalent (CRVE), based on the formula modified by Knudtson, as detailed in "Methods."

modification of retinal measures by age, sex, race/ethnicity, and other variables (such as LV measures) were evaluated with inclusion of interaction terms in the models. P values < 0.05 were considered to indicate statistical significance.

Results

Of the initial 6814 MESA study participants, 5098 had cardiac MRI performed of which 5004 had scans interpretable for the LV (Fig. 2). The MESA-Right Ventricle study is an ancillary study that selected 4634 participants with interpretable cardiac MRIs at the baseline examination, attempted 4484 reads, and completed interpretation of RV morphology in 4204 individuals. For the MESA-Eye study, 6237 participants returned at Exam 2 and 6147 had retinal photography performed. There were 5979 exams that were interpretable for retinal vascular caliber measurements. Overall, 3630 participants had complete data for RV measures, retinal vascular measurements, and covariates and comprised the study sample. Table 1 shows the characteristics of the study sample and those excluded. The study group was slightly younger and was less likely to have diabetes mellitus, but otherwise appeared similar to those excluded.

There were significant interactions between sex and veins for RVEDM, RVEDV, and RVSV (p for interaction <0.002), and sex and arteries for RVEF and RVESV (p for interaction < 0.05) so that all results are shown stratified by sex (Fig. 3). Wider veins were associated with greater RVEDM in women after adjustment for covariates and LV mass (Table 2). In men, wider veins were associated with lower RVEDM after adjustment for covariates, which was no longer present after adjustment for LVEDM. In women, wider veins were significantly associated with larger RVEDV after adjustment for covariates and LVEDV. In men, wider veins were associated with smaller RVEDV in all three models. Wider veins were associated with smaller RVSV in all models in men but not in women. There was a significant inverse relationship between veins and RVEF in the basic model and full model in men, but this was no longer significant after accounting for LVEF.

Table 3 shows the results for arteries and RV parameters. Narrower arteries were associated with lower RVEDM in both sexes after adjusting for covariates and LVEDM. Narrower arteries were also associated with smaller RVEDV in both sexes after adjustment for covariates and LVEDV. Narrower arteries were significantly associated with smaller RVESV in men, but was associated with lower RVSV in women after adjusting for covariates. Lastly, smaller arteries were associated with higher RVEF in men after adjustment for covariates, but this was of borderline significance after further adjustment for LVEF.

For both veins and arteries, similar results were seen in the subset of participants with available lung function and imaging data (n = 2477) and after adjustment for these data albeit with more limited power given the smaller sample size (Supplementary Tables). Moreover, similar results were seen in females after adjustment for hormone replacement therapy. There were no other interactions of veins or arteries with age, race/ethnicity, or LV measures.
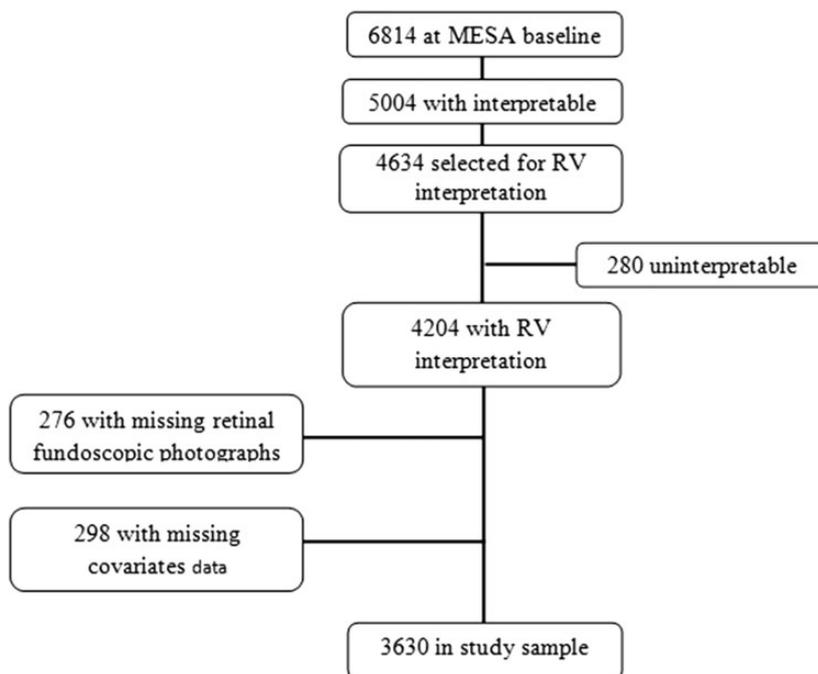

Fig. 2. Study sample.

Table 1. Study participant characteristics.

Variable	Study sample (n = 3630)	Excluded (n = 3184)
Age (years)	62.5 ± 9.7	65.0 ± 10.4
Male sex (n (%))	1742 (48.0)	1471 (46.2)
Race/ethnicity (n (%))		
White	1456 (40.1)	1166 (36.6)
African American	919 (25.3)	974 (30.6)
Hispanic	794 (21.9)	702 (22.0)
Chinese American	461 (12.7)	342 (10.7)
Weight (kg)	77.6 ± 16.0	79.9 ± 19.7
Height (cm)	166.2 ± 9.9	166.0 ± 17.9
Body mass index (kg/m^2)	28.0 ± 5.0	28.9 ± 6.1
Waist circumference (cm)	96.5 ± 13.6	99.8 ± 15.5
Hypertension (n (%))	1579 (43.5)	1599 (50.2)
Diabetes mellitus (n (%))	491 (13.5)	535 (16.8)
Total cholesterol (mg/dL)	192.5 ± 35.8	190.5 ± 36.2
Lipid lowering medication use (n (%))	767 (21.1)	699 (22.0)
Smoking status (n (%))		
Never	1781 (49.1)	1391 (43.8)
Former	1463 (40.31)	1371 (43.1)
Current	386 (10.6)	417 (13.1)
Pack-years	10.4 ± 22.6	12.4 ± 21.7
Education level (n (%))		
Less than high school	556 (15.3)	669 (21.2)
High school/equivalent	658 (18.1)	578 (18.3)
Some college	1023 (28.2)	914 (28.9)
Bachelor's degree	688 (19.0)	483 (15.3)
Master's degree or higher	705 (19.4)	517 (16.4)

Data are presented as mean ± SD or n (%).

Table 2. Linear regression models of central retinal venular equivalent and right ventricular function.

	Male			Female		
	Beta*	SE	P value*	Beta*	SE	P value*
Right ventricle end-diastolic mass (g)						
Basic model†	−0.19	0.08	0.01	0.07	0.07	0.33
Full model‡	−0.16	0.08	0.03	0.10	0.07	0.17
Full model + LV mass	−0.08	0.07	0.27	0.14	0.07	0.04
Right ventricle end-diastolic volume (mL)						
Basic model†	−1.89	0.49	<0.001	0.25	0.47	0.60
Full model‡	−1.59	0.50	<0.001	0.58	0.47	0.22
Full model + LV end-diastolic volume	−0.88	0.36	0.02	0.79	0.34	0.02
Right ventricle end-systolic volume (mL)						
Basic model†	0.06	0.25	0.80	0.12	0.24	0.60
Full model‡	0.09	0.25	0.71	0.17	0.24	0.46
Full model + LV end-systolic volume	−0.12	0.22	0.58	0.24	0.21	0.26
Right ventricle stroke volume (mL)						
Basic model†	−1.95	0.36	<0.001	−0.12	0.35	0.72
Full model‡	−1.68	0.36	<0.001	0.40	0.35	0.25
Right ventricle ejection fraction (%)						
Basic model†	−0.46	0.14	<0.001	−0.15	0.13	0.24
Full model‡	−0.41	0.14	0.003	−0.12	0.13	0.38
Full model + LV ejection fraction	−0.18	0.13	0.17	−0.11	0.12	0.37

*Beta (per 20-μm increase) and P value derived from multivariate linear regression.
†Basic model includes age, sex, race/ethnicity, education, height, weight, and waist circumference.
‡Full model includes basic model + alcohol consumption, smoking (status and pack-years), total cholesterol, HDL, hypertension, lipid-lowering medication, diabetes, hemoglobin A1c, and serum creatinine.
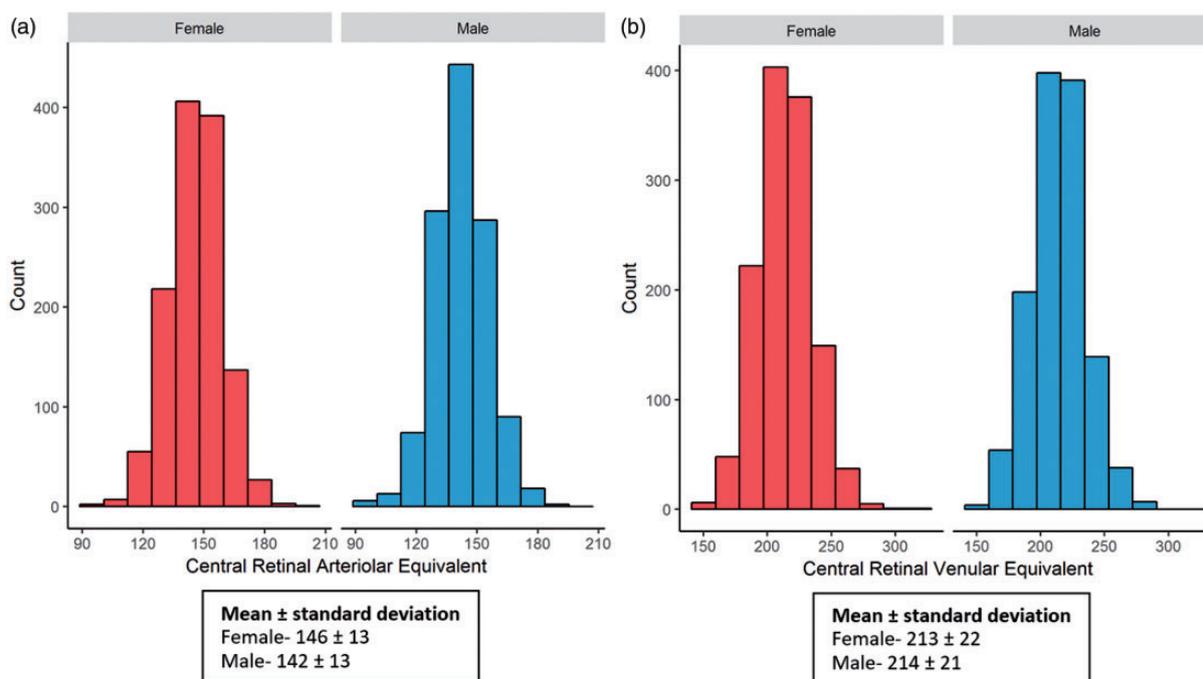

Fig. 3. Distributions of (a) central retinal artery equivalents and (b) central retinal venular equivalents, stratified by sex.

Table 3. Linear regression models of central retinal arteriolar equivalent and right ventricular function.

	Male			Female		
	Beta*	SE	P value*	Beta*	SE	P value*
Right ventricle end-diastolic mass (g)						
Basic model[†]	−0.07	0.12	0.52	−0.22	0.11	0.05
Full model[‡]	−0.14	0.12	0.22	−0.27	0.11	0.02
Full model + LV mass	−0.34	0.11	0.002	−0.42	0.11	<0.001
Right ventricle end-diastolic volume (mL)						
Basic model[†]	−1.15	0.75	0.13	−1.32	0.74	0.07
Full model[‡]	−1.70	0.75	0.02	−1.76	0.74	0.02
Full model + LV end-diastolic volume	−1.12	0.55	0.04	−2.01	0.54	<0.001
Right ventricle end-systolic volume (mL)						
Basic model[†]	−1.32	0.38	<0.001	−0.43	0.37	0.24
Full model[‡]	−1.30	0.38	<0.001	−0.46	0.37	0.22
Full model + LV end-systolic volume	−0.93	0.34	0.006	−0.56	0.33	0.09
Right ventricle stroke volume (mL)						
Basic model[†]	0.17	0.55	0.75	−0.89	0.54	0.10
Full model[‡]	−0.40	0.55	0.47	−1.31	0.54	0.02
Right ventricle ejection fraction (%)						
Basic model[†]	0.66	0.21	0.002	0.13	0.21	0.52
Full model[‡]	0.50	0.21	0.02	0.05	0.21	0.81
Full model + LV ejection fraction	0.34	0.19	0.08	0.05	0.19	0.81

*Beta (per 20-μm decrease) and P value derived from multivariate linear regression.

[†]Basic model includes age, sex, race/ethnicity, education, height, weight, and waist circumference.

[‡]Full model includes basic model + alcohol consumption, smoking (status and pack years), total cholesterol, HDL, hypertension, lipid-lowering medication, diabetes, hemoglobin A1c, and serum creatinine.

Discussion

Our study showed that retinal vein and artery diameters (central retinal venular and artery equivalents) track with differences in the RV in an adult population without clinical cardiovascular disease. Larger retinal venular diameter was associated with larger RVEDM and RVEDV in women, independent of a variety of confounders and LV mass and volume, suggesting a RV-specific relationship. In men, larger retinal venular diameter was associated with smaller RVEDV and RVSV. Interestingly, narrower retinal arteriolar diameter was associated with opposite effects, including lower RVEDM and smaller RVEDV without sex differences, along with smaller RVESV in men and smaller RVSV in women. These results were independent of age, body size, smoking status, cholesterol, diabetes mellitus, serum creatinine, and alcohol consumption. These findings suggest that retinal microvascular structure may reflect similar vascular changes either in the RV or lung, leading to an impact on RV morphology which is sex-specific.

The retinal examination presents an opportunity to directly visualize the manifestations of early subclinical vascular processes on the microcirculation.[25] Studies have found that various metabolic disturbances including hypercholesterolemia, diabetes, and metabolic syndrome (all leading to endothelial dysfunction) are associated with wider retinal venular diameter.[14] A prior study in MESA showed that increased levels of inflammatory markers such as CRP and IL-6 were associated with wider retinal venular diameter, which was confirmed in another cohort.[2,26] Other determinants of wide retinal venular diameter include current smoking, diabetes, high blood pressure, dyslipidemia, and obesity.[27] The cause of dilation is unknown; however, local recruitment of inflammatory cells has been suggested as a possible cause.[28] High blood pressure is associated with narrower retinal arterioles.[2,27,29] While initially postulated to represent a sequel of hypertension, narrower retinal arterioles may in fact be a harbinger of systemic vascular disease, as they precede the onset of hypertension by years in initially normotensive individuals.[30–33]

Prior histopathologic studies have demonstrated that pathological changes seen in the eyes reflect the microvascular changes in other organs including hypertensive arteriolar changes in the brain and myocardium.[34,35] Wider retinal venular diameter predicts the incidence of proteinuria and nephropathy as well.[36] The retinal vasculature is of similar size to the coronary microcirculation, in the range of 100–300 um, and has been associated with various changes in cardiac morphology. Retinal arteriolar narrowing is strongly associated with coronary artery occlusion and a study in MESA has shown a link with decreased myocardial perfusion.[37–39] Several studies have linked wider retinal venular diameters and narrower arteriolar diameters to the incidence of CHD.[7,40,41] Studies have demonstrated that microvascular disease can play a role in cardiac remodeling in a sex-specific fashion. Women are predisposed to microvascular heart disease, which commonly presents as atypical chest pain with EKG changes during stress testing and normal coronaries on angiography, termed Syndrome X or microvascular angina.[42,43] It is thought that various hormonal changes specific to women lead to endothelial dysfunction with changes in the microvasculature.[44] In MESA, wider retinal venular caliber was associated with greater LV mass in women only and specifically concentric LV remodeling, which was not seen in men, supporting sex-specific relationships.[9]

We showed an association between wider veins and greater RVEDM and RVEDV independent of the LV in women only. Wider venular diameter may reflect systemic endothelial dysfunction which may include the pulmonary vasculature, imposing increased afterload on the RV with subsequent increase in RVEDM and RVEDV. The absence of this finding in men (or even inverse associations for RVEDV) may reflect either a general female susceptibility to microvascular disease or a more specific lung vascular susceptibility in women. Another interpretation is that the changes in the RV structure and retinal venular diameters in women represent separate distinct consequences of disease

of both the eye and endomyocardial microvasculature. Least likely is that the venular changes are attributable to clinically important RV dysfunction. Interestingly, a recent study from MESA showed that retinal venular widening was associated with obstructive sleep apnea, but in men only.[45] Wider retinal venular diameter can represent early changes of venous stasis retinopathy which is associated with pulmonary arterial hypertension.[46]

Narrower retinal arteriolar caliber was associated with lower RVEDM and RVEDV, which differs from findings in the LV in MESA.[9] For the LV, narrower arterioles were associated with increased mass in both sexes, but with smaller LV end-diastolic volumes only in men. A study in MESA showed that arteriolar caliber was associated with lower myocardial perfusion in participants without coronary calcification.[39] It is therefore possible that the findings in the RV reflect decreased myocardial vascular volume which might have a greater proportional effect in the thin-walled, low-mass RV than in the LV. In addition, older age is associated with both arteriolar diameter and lower RV mass and smaller RV volumes, so that age-related processes could account for this association despite adjustment for age in our analysis.

The strengths of our study included a large multi-ethnic sample population without cardiovascular disease and the validated measurements of MRI-defined RV morphology and function, along with methodical documentation of retinal vasculature based on retinal photographs. Limitations include the cross-sectional nature of the analysis, the potential for residual or unmeasured confounding, and possible changes in the participants between the first and second exams. We did not perform a comprehensive dilated eye examination, so we do not have intraocular pressure measurements. Age-related macular degeneration was infrequent in MESA and varied by ethnicity.[47] Similarly, we also found retinopathy to be relatively infrequent.[48] An impact of refractive error on retinal vessels has largely been seen in people with high myopia, which affected <5% of the MESA cohort.[49]

In summary, we have shown that wider retinal venular diameter is associated with an increase in RV mass and volume in women independent of the LV in a multi-ethnic population without clinical cardiovascular disease at baseline. In men, lower RV mass and smaller RVEDV were seen. Narrower retinal arterioles were associated with lower RV mass and volumes, again independent of the LV. Retinal vascular changes may serve as a window into RV morphology. Future studies of retinal vascular changes in patients with pulmonary vascular disease and RV dysfunction are warranted, based on these results. The shared mechanisms and potential response to therapies between vascular beds warrant further investigation in diseases characterized by RV morphologic changes.

Acknowledgments

Conflict of interest

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