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Retinal Arteriolar Narrowing and Left Ventricular Remodeling

The Multi-Ethnic Study of Atherosclerosis

Ning Cheung, MBBS,*† David A. Bluemke, MD, PHD,‡ Ronald Klein, MD, MPH,§ A. Richey Sharrett, MD, DRPH,‖ F. M. Amirul Islam, PHD,* Mary Frances Cotch, PHD,¶ Barbara E. K. Klein, MD, MPH,§ Michael H. Criqui, MD, MPH,# Tien Yin Wong, MD, PHD* **

Melbourne, Victoria, Australia; Baltimore and Bethesda, Maryland; Madison, Wisconsin; San Diego, California; and Singapore

Objectives This study sought to examine the relationships of retinal vascular signs with left ventricular (LV) mass, volume, and concentric remodeling.

Background Microvascular disease, reflected as retinopathy lesions, has been shown to predict clinical congestive heart failure. Whether these retinal vascular changes are related to early structural alterations and remodeling of the heart in asymptomatic individuals is unknown.

Methods A cross-sectional, population-based study of 4,593 participants ages 45 to 85 years, free of clinical cardiovascular disease. Retinal vascular calibers and retinopathy were graded from retinal photographs according to standardized protocols. The LV mass and volume were measured from cardiac magnetic resonance imaging. Extent of LV concentric remodeling was determined by the ratio of LV mass to end-diastolic volume (M/V ratio).

Results After controlling for age, gender, race, center, past and current systolic blood pressure, body mass index, smoking, antihypertensive medications, diabetes, diabetes duration, glycosylated hemoglobin, lipid profile, and C-reactive protein, narrower retinal arteriolar caliber was associated with concentric (highest quintile of M/V ratio) remodeling (odds ratio [OR] 2.06, 95% confidence interval 1.57 to 2.70). This association was seen in men and women, and was present even in those without diabetes, without hypertension, and without significant coronary calcification. In multivariate analysis, the presence of retinopathy (OR 1.31, 95% confidence interval 1.08 to 1.61) was also associated with concentric remodeling.

Conclusions Narrower retinal arteriolar caliber is associated with LV concentric remodeling independent of traditional risk factors and coronary atherosclerotic burden, supporting the hypothesis that microvascular disease may contribute to cardiac remodeling. (J Am Coll Cardiol 2007;50:48–55) © 2007 by the American College of Cardiology Foundation

Heart failure is a leading cause of morbidity, mortality, and hospitalization in the U.S. (1,2). It is known that left ventricular (LV) remodeling is an early pathogenic process in the natural history of heart failure (3–6). Consistent with this hypothesis, treatment strategies that slow or even reverse the remodeling process, such as the use of angiotensin-converting enzyme inhibitors and some beta-blockers, improve survival in heart failure patients (7–10). Hemodynamic load and neurohumoral activation are known mechanisms that influence LV remodeling (11,12).

Microvascular disease has also been hypothesized to influence LV remodeling. Studies show that coronary microvascular dysfunction is associated with adverse LV remodeling (13) and subsequent risk of heart failure, partic-

From the *Centre for Eye Research Australia, University of Melbourne, Victoria, Australia; †Royal Melbourne Hospital, Melbourne, Victoria, Australia; ‡Departments of Radiology and Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; §Department of Ophthalmology and Visual Science, University of Wisconsin, Madison, Wisconsin; ‖Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; ¶Division of Epidemiology and Clinical Research, National Eye Institute, National Institutes of Health, Bethesda, Maryland; #Department of Medicine, University of California San Diego, San Diego, California; and **Singapore Eye Research Institute, Yong Loo Lin School of Medicine, National University of Singapore, Singapore. Supported by contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95169 from the National Heart, Lung, and Blood Institute. Additional support was provided by National Institutes of Health grant HL69979-03 (to Drs. Klein and Wong) and a grant from the National Heart Foundation, Victoria, Australia (to Dr. Wong). George Diamond, MD, acted as the Guest Editor for this article.

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ularly in people with hypertrophic cardiomyopathy (14,15) and in people after a myocardial infarction (16,17), even after successful coronary angioplasty (18).

Changes in the retinal vasculature, reflected as retinopathy signs, also have been shown to predict heart failure risk in the general population (19) and in patients after coronary artery bypass surgery (20,21), further supporting a link between the microvascular process and the development of clinical heart failure. Whether retinal microvascular signs are related to early subclinical morphologic alterations and remodeling in the heart in people without symptomatic heart failure is unclear. In this study, we examined the cross-sectional associations of retinal microvascular signs with LV mass, volume, and remodeling, as determined from cardiac magnetic resonance imaging (MRI), in a multiethnic population-based cohort of men and women.

Methods

Study population. The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study of men and women ages 45 to 84 years without a history of clinical cardiovascular disease, sampled from 6 U.S. communities (22). In brief, there were 6,814 participants at the first examination (July 2000 to July 2002) when cardiac MRI was performed. Fundus photography was performed at the second examination (August 2002 to January 2004), which occurred immediately after the baseline examination (23,24). At the second examination, 6,237 participants (92%) returned, 6,147 had retinal photography, and 5,979 had photographs that were suitable for measurement of retinal vascular caliber. Of these, we excluded those without cardiac MRI data (n = 1,386) (because of MRI contraindications, technically inadequate data, or participant refusals), leaving 4,593 participants for the current analysis.

The tenets of the Declaration of Helsinki were observed, and institutional review board approval was granted at each study site. Written informed consent was obtained from each participant.

Retinal photography and retinal grading. Fundus photography was performed at each site, according to a standardized protocol described elsewhere (23,24). Both eyes of each participant were photographed with a 45° digital nonmydriatic camera. All images were evaluated by trained graders who were masked to participants' characteristics.

Retinal vascular caliber was measured with a computer-based program based on a previously validated protocol (25–27). For this study, photographs in the right eye were selected for measurement. The left eye photographs were 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 to 1 disc diameter from the optic disc margin were measured and summarized as the central retinal arteriolar and venular equivalents, using formulae described elsewhere (25,28). These equivalents represented the average of projected calibers for the central retinal vessels, measured away from the optic disc. Reproducibility of retinal vascular measurements has been reported, with intragrader and intergrader intraclass correlation coefficients ranging from 0.78 to 0.99 (25,26).

Abbreviations and Acronyms

BMI = body mass index
BSA = body surface area
LV = left ventricle/ventricular
M/V ratio = mass to volume ratio
MRI = magnetic resonance imaging
OR = odds ratio
ROC = receiver-operator characteristic

Retinopathy was graded using a standardized protocol (24) and considered to be present if any characteristic lesion, as defined by the Early Treatment Diabetic Retinopathy Study severity scale (29), was present: microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading, and new vessels.

MRI protocol and definitions of parameters. Detailed protocols regarding the cardiac MRI procedure have been documented previously (22,30). In brief, MRI images were obtained by 1.5-T MR scanners (Signa LX and CVi, GE Medical Systems, Waukesha, Wisconsin; and Somatom Vision and Sonata, Siemens Medical Solutions, Erlangen, Germany) at baseline examination. Dedicated phase-array coils were used for signal reception. Short-axis cine MRI scans were obtained from the base of the heart to the heart apex. The endocardial and epicardial heart borders were identified to determine LV mass and volumes (30). These LV geometric measurements were determined from each MRI study with a commercially available software package (MASS, version 4.2, Medis, the Netherlands). All MRI studies were evaluated at the core MESA MRI Reading Center at Johns Hopkins Hospital.

The LV mass and volume were normalized to body surface area (BSA) to produce LV mass and volume indexes. The LV concentric remodeling was defined as the highest quintile of mass to volume (M/V) ratio.

Assessment of cardiovascular risk factors. All participants underwent an interview and assessment of cardiovascular risk factors at both baseline and at second examination (22,31). Variables for this analysis were based on data collected at the second examination. Resting blood pressure was measured using standardized protocol, and hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medications. Body mass index (BMI) was calculated as kilograms per square meter, and BSA was derived from the formula below: BSA (m^2) = 0.20247 × height (m) 0.725 × weight (kg) 0.425 (30).

Fasting (>8 h) blood samples were drawn from all participants to measure the serum glucose, lipids, and lipoproteins, and systemic inflammatory markers such as C-reactive protein (31). Diabetes mellitus was defined as fasting glucose ≥7.0 mmol/l (126 mg/dl) or use of insulin or oral hypoglycemic medication. Coronary calcification was assessed by computed tomography as previously described

(32). The Agatston calcium score was used to assess of degree of coronary calcification, and a score of <100 was defined as minimal coronary calcification (33).

Statistical analysis. Analysis of variance or independent sample *t* test was used to compare the means of M/V ratio, LV mass index, and LV volume index for gender, race, and other cardiovascular risk factors; analysis of variance or independent sample *t* tests were appropriate because the MRI parameters were continuous variables that were seen to be normally distributed in the population. The effect of any retinopathy (absence or presence) or the quartiles of retinal arteriolar and venular caliber separately on MRI parameters were estimated by using analysis of covariates, and the results were presented as means and standard errors for both male and female patients. Initial models constructed using analysis of covariates were adjusted for age, race, and study centers.

Logistic regression was used to determine the odds of LV concentric remodeling (highest quintile of M/V ratio), and highest quintiles of LV mass and volume indexes in association with narrower retinal arteriolar caliber (1st vs. 4th quartile), wider retinal venular caliber (4th vs. 1st quartile), retinopathy, and other retinal arteriolar abnormalities (focal arteriolar narrowing and arteriovenous nicking). We constructed two models: model 1 included adjustments for age, gender, race, and study center, and model 2 included additional adjustments for traditional cardiovascular risk factors: systolic blood pressure from the baseline examination (when cardiac MRI was performed) and the second examination (when retinal photography was performed), BMI, glycosylated hemoglobin, diabetes, diabetes duration, total and high-density lipoprotein cholesterol, triglycerides, current cigarette smoking, and C-reactive protein. In all models for retinal arteriolar caliber we adjusted for venular caliber, and in models for venular caliber we adjusted for arteriolar caliber as previously described (34).

In supplementary analysis, we examined the associations in the whole cohort and also stratified by race/ethnicity, diabetes, hypertension, coronary calcification, and retinopathy. In addition, we also derived receiver-operator characteristic (ROC) curves of the M/V ratio to determine the incremental increase in area under the ROC curve with the addition of retinal vascular measurements, using covariates in the multivariate model 2; area under the ROC curve was done first without retinal arteriolar measurement and then with the addition of retinal arteriolar measurement. All analyses were performed in SPSS version 12.0.1 (SPSS Inc., Chicago, Illinois).

Results

Characteristics of our study population, by LV mass, volume, and M/V ratio, are listed in Table 1. Mean M/V ratio was greater in African Americans, current smokers, and those with hypertension and diabetes. Similar pattern of differences was also noted with LV mass index. Mean LV volume index was lower in Chinese patients and in those with diabetes.

Table 2 shows that the presence of a greater LV mass index was found in participants with narrower retinal arteriolar caliber (reducing order of quartiles), wider retinal venular caliber (increasing order of quartiles) (in women only), and retinopathy. There were also significant trends to suggest that smaller retinal arteriolar caliber and wider retinal venular caliber were associated with lower LV volume index in men, but not in women. In both men and women, the presence of a greater M/V ratio was associated with a narrower retinal arteriolar caliber, wider retinal venular caliber, and retinopathy.

Table 3 shows the results of logistic regression models of the relationship of narrower retinal arteriolar caliber (narrowest vs. widest quartile), wider retinal venular caliber (widest vs. narrowest quartile), and retinopathy with the highest quintiles of LV mass index, LV volume index, and M/V ratio (concentric remodeling). After controlling for age, race, study center, past and current systolic blood pressure, BMI, smoking, diabetes, diabetes duration, glycosylated hemoglobin, use of antihypertensive medications, and levels of serum total and high-density lipoprotein cholesterols, triglycerides, and C-reactive protein, a narrower retinal arteriolar caliber was associated with increased odds of LV concentric remodeling in both men (odds ratio [OR] 1.88) and women (OR 2.38). Wider retinal venular caliber was associated with concentric remodeling in women (OR 1.51), but in men, this association was weaker and not significant. The presence of retinopathy was associated with concentric remodeling in men (OR 1.34), but not significantly in women. Additionally, a wider retinal venular caliber was associated with the lowest quintile of LV volume index in both men (OR 1.90) and women (OR 1.53), and retinopathy was associated with the highest quintile of LV mass index in men (OR 1.53). Overall, in the whole cohort, narrower retinal arteriolar caliber (OR 2.06) and retinopathy (OR 1.31) were all associated with increased odds of concentric remodeling (Table 4). Other less common retinal arteriolar abnormalities, including focal arteriolar narrowing and arteriovenous nicking, showed no significant associations with M/V ratio and LV mass and volume indexes (data not shown).

Table 4 also contains results of further analysis stratified by race, diabetes, hypertension, coronary calcification, and retinopathy status, showing that the association between narrower retinal arteriolar caliber and concentric remodeling was consistently present in all ethnic groups and was stronger in diabetic (4.48) than in nondiabetic (OR 1.74) individuals and in persons with retinopathy (OR 2.92) than in those without retinopathy (OR 1.91). This association remained significant even in those with only minimal coronary calcification (Agatston score <100) and in those without hypertension. In contrast, the association of retinopathy with concentric remodeling was only significant in those with diabetes or hypertension, and in those with more

Table 1 Participant Characteristics and LV Mass, Volume, and Remodeling

	Men							Women						
		LV MI, g/m^2		LV VI, ml/m^2		M/V Ratio, g/ml			LV MI, g/m^2		LV VI, ml/m^2		M/V Ratio, g/ml	
	n	Mean	SD	Mean	SD	Mean	SD	n	Mean	SD	Mean	SD	Mean	SD
All	2,193	85.6	16.0	71.4	14.7	1.23	0.25	2,400	70.6	12.5	65.3	11.3	1.10	0.21
Race														
White	878	83.7	14.9	71.4	15.0	1.20	0.25	968	68.4	11.5	65.2	11.4	1.07	0.20
Black	526	89.7	17.6	70.6	15.6	1.30	0.27	625	73.8	13.9	64.4	12.2	1.17	0.23
Hispanic	497	87.7	15.9	73.8	14.2	1.22	0.25	500	72.7	12.4	67.0	10.8	1.10	0.20
Chinese	292	80.5	13.9	68.7	12.3	1.19	0.20	307	67.5	10.1	64.4	9.1	1.06	0.17
p value*		<0.001		<0.001		<0.001			<0.001		<0.001		<0.001	
Hypertension														
Absent	1,185	82.6	13.6	71.7	13.9	1.18	0.22	1,263	67.3	10.5	65.6	10.7	1.04	0.18
Present	1,008	89.2	17.8	71.1	15.7	1.29	0.27	1,137	74.3	13.4	64.9	11.8	1.16	0.22
p value*		<0.001		0.38		<0.001			<0.001		0.16		<0.001	
Diabetes														
Absent	2,181	85.4	15.8	71.9	14.8	1.10	0.21	2,090	70.0	12.2	65.6	11.2	1.08	0.20
Present	219	87.2	17.2	68.5	13.8	1.14	0.21	310	74.7	13.5	63.2	11.6	1.21	0.24
p value*		0.06		<0.001		<0.001			<0.001		0.001		<0.001	
Education														
≤8 yrs	194	86.3	15.9	71.9	14.7	1.23	0.25	231	72.1	11.8	65.6	10.2	1.12	0.21
>8 yrs	1,999	85.6	16.0	71.3	14.7	1.23	0.25	2,169	70.4	12.5	65.2	11.4	1.10	0.21
p value*		0.57		0.62		0.98			0.05		0.65		0.19	
Smoking														
Never/former	1,892	85.1	15.9	71.2	14.6	1.22	0.25	2,181	70.2	12.3	65.2	11.2	1.10	0.21
Current	301	89.3	16.4	72.5	15.4	1.26	0.25	219	74.2	13.0	66.1	11.5	1.14	0.21
p value*		<0.001		0.16		0.001			<0.001		0.25		0.02	

*p values based on analysis of variance or independent sample *t* test comparing racial/ethnic, gender, age, and other risk factors for LV parameters.
LV = left ventricular; MI = mass index; M/V ratio = left ventricular mass-to-volume ratio; VI = volume index.

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Table 2 Relationship of Retinal Vascular Calibers and Retinopathy With LV Mass, Volume, and Remodeling

	Men				Women			
	n	LV MI (g/m^2) Mean (SE)*	LV VI (ml/m^2) Mean (SE)*	M/V Ratio (g/ml) Mean (SE)*	n	LV MI (g/m^2) Mean (SE)*	LV VI (ml/m^2) Mean (SE)*	M/V Ratio (g/ml) Mean (SE)*
Arteriolar diameter, μm								
1st quartile, <136	629	88.0 (0.68)	69.9 (0.63)	1.29 (0.011)	499	72.8 (0.59)	65.1 (0.53)	1.14 (0.009)
2nd quartile, 136–144	536	85.3 (0.69)	69.9 (0.63)	1.25 (0.011)	566	71.7 (0.52)	65.5 (0.47)	1.11 (0.008)
3rd quartile, 144–152	554	84.1 (0.69)	71.3 (0.63)	1.21 (0.011)	590	70.4 (0.52)	64.8 (0.47)	1.10 (0.008)
4th quartile, >152	430	83.1 (0.81)	71.8 (0.74)	1.18 (0.013)	680	68.7 (0.50)	65.0 (0.46)	1.07 (0.008)
p value		<0.001	0.03	<0.001		<0.001	0.70	<0.001
Venular diameter, μm								
1st quartile,<199	548	85.0 (0.77)	71.7 (0.71)	1.21 (0.012)	606	69.5 (0.55)	65.1 (0.50)	1.08 (0.009)
2nd quartile, 199–214	523	84.8 (0.70)	71.4 (0.65)	1.22 (0.011)	609	70.7 (0.51)	65.3 (0.46)	1.10 (0.008)
3rd quartile, 214–228	546	85.5 (0.67)	69.9 (0.62)	1.25 (0.011)	577	70.9 (0.52)	65.1 (0.47)	1.11 (0.008)
4th quartile, >228	525	86.0 (0.73)	69.6 (0.67)	1.27 (0.011)	548	72.1 (0.56)	64.7 (0.51)	1.13 (0.009)
p for trend		0.30	0.02	<0.001		0.002	0.52	<0.001
Any retinopathy								
Absent	1,796	84.8 (0.41)	70.5 (0.38)	1.23 (0.007)	2,014	70.4 (0.30)	65.1 (0.27)	1.10 (0.005)
Present	384	87.9 (0.81)	70.5 (0.74)	1.28 (0.013)	361	73.1 (0.65)	64.5 (0.58)	1.15 (0.010)
p for trend		<0.001	0.94	0.003		<0.001	0.38	<0.001

*Mean (SE) for LV parameter estimated using analysis of covariates with adjustments for age, race/ethnicity, study center, retinal arteriolar caliber (except for arteriolar caliber and retinopathy), and retinal venular caliber (except for venular caliber and retinopathy).

Abbreviations as in Table 1.

than minimal coronary calcification. Potential interactions with these stratified variables and gender were tested and showed no statistically significant interactions ($p < 0.05$).

Finally, we also derived the ROC curves of M/V ratios using covariates in model 2. The area under the ROC curve was 0.707 without including retinal arteriolar caliber, and 0.714 with the addition of retinal arteriolar caliber, an incremental increase of <1%.

Discussion

Our study aimed to correlate retinal vascular changes, objectively quantified from retinal photographs, with early cardiac morphologic alterations, as determined from MRI, in a population-based sample of individuals without clinical cardiovascular disease. Our principal finding was that the presence of narrower retinal arterioles was associated with LV concentric remodeling. This association was consistently present across different ethnic groups; was independent of blood pressure, smoking, and other risk factors; and was seen in men and women, and even in those without diabetes, without hypertension, and with minimal coronary calcification. We also found an association of retinopathy signs with LV concentric remodeling, but the associations were less consistent and were stronger in persons with diabetes, with hypertension, and with significant coronary calcification. The association of wider retinal venules and concentric remodeling was significant only in women in our cohort.

Table 3 Logistic Regression of LV Mass, Volume, and Remodeling by Retinal Vascular Caliber and Retinopathy

	Men			Women		
	LV MI Highest Quintile >97.1 g/m^2	LV VI Lowest Quintile <59.8 ml/m^2	M/V Ratio Highest Quintile >1.40 g/ml	LV MI Highest Quintile >79.8 g/m^2	LV VI Lowest Quintile <56.5 ml/m^2	M/V Ratio Highest Quintile >1.24 g/ml
Retinal arteriolar caliber, narrowest vs. widest quartile						
Model 1*	1.38 (0.95–2.02)	0.78 (0.53–1.14)	1.98 (1.35–2.91)	1.72 (1.20–2.45)	0.66 (0.48–0.94)	2.45 (1.69–3.55)
Model 2†	1.24 (0.84–1.83)	0.73 (0.49–1.09)	1.88 (1.26–2.80)	1.43 (0.98–2.08)	0.72 (0.50–1.05)	2.38 (1.61–3.52)
Retinal venular caliber, widest vs. narrowest quartile						
Model 1*	1.32 (0.90–1.94)	2.15 (1.45–3.19)	1.63 (1.10–2.41)	1.65 (1.15–2.39)	1.61 (1.12–2.31)	2.12 (1.45–3.10)
Model 2†	1.06 (0.70–1.62)	1.90 (1.25–2.88)	1.27 (0.84–1.91)	1.36 (0.92–2.02)	1.53 (1.04–2.25)	1.51 (1.03–2.30)
Retinopathy, present vs. absent						
Model 1*	1.57 (1.21–2.03)	1.02 (0.77–1.35)	1.50 (1.15–1.96)	1.41 (1.08–1.83)	1.18 (0.90–1.56)	1.80 (1.39–2.34)
Model 2†	1.53 (1.16–2.03)	0.92(0.68–1.25)	1.34 (1.01–1.79)	1.06 (0.79–1.41)	1.20(0.90–1.61)	1.26 (0.95–1.68)

Data shown are odds ratios (95% confidence intervals). *Model 1: odds ratio adjusted for age, race, and study center. Model for arteriolar caliber was adjusted for venular caliber, and model for venular caliber was adjusted for arteriolar caliber. †Model 2: model 1 plus further adjustments for pulse pressure, use of antihypertensive medications, body mass index, diabetes, glycosylated hemoglobin, duration of diabetes, total and high-density lipoprotein cholesterol, triglycerides, cigarette smoking status, and C-reactive protein.

Abbreviations as in Table 1.

Table 4 Relationship of Retinal Vascular Caliber, Retinopathy, and LV Concentric Remodeling (Highest Quintile of M/V Ratio*), Stratified by Race, Diabetes, Hypertension, Coronary Calcification, and Retinopathy Status

	Retinal Arteriolar Caliber, Narrowest vs. Widest Quintile	Retinal Venular Caliber, Widest vs. Narrowest Quintile	Retinopathy, Present vs. Absent
All	2.06 (1.57–2.70)	1.56 (0.82–2.96)	1.31 (1.08–1.61)
Race/ethnicity			
White	1.67 (1.02–2.72)	1.33 (0.80–2.21)	1.36 (0.96–1.94)
Black	1.90 (1.17–3.08)	1.22 (0.72–2.07)	1.13 (0.79–1.60)
Hispanic	2.41 (1.30–4.47)	1.32 (0.71–2.45)	1.47 (0.95–2.26)
Chinese	2.79 (1.06–7.33)	0.84 (0.32–2.21)	1.51 (0.84–2.73)
Diabetes			
Absent	1.74 (1.28–2.37)	1.29 (0.94–1.77)	1.17 (0.92–1.48)
Present	4.48 (2.30–8.71)	1.92 (0.99–3.74)	1.72 (1.20–2.47)
Hypertension			
Absent	1.86 (1.30–2.65)	1.37 (0.86–2.20)	1.21 (0.85–1.73)
Present	2.27 (1.45–3.56)	1.40 (0.97–2.02)	1.34 (1.05–1.71)
Coronary calcification score			
<100	1.91 (1.33–2.74)	1.46 (0.94–2.27)	1.25 (0.90–1.73)
>100	2.26 (1.46–3.50)	1.38 (0.95–2.00)	1.34 (1.04–1.73)
Retinopathy			
Absent	1.91 (1.40–2.60)	1.37 (0.99–1.90)	—
Present	2.92 (1.51–5.62)	1.56 (0.82–2.96)	—

Data shown are odds ratios (95% confidence intervals) adjusted for age, gender, race (except race-stratified analysis), study center, pulse pressure, use of antihypertensive medications (except for hypertension-stratified analyses), diabetes, diabetes duration and glycosylated hemoglobin (except for diabetes-stratified analyses), body mass index, total and high-density lipoprotein cholesterol, triglycerides, cigarette smoking status, and C-reactive protein. *M/V ratio >1.32 g/ml.

Abbreviations as in Table 1.

Previous studies have indicated that coronary microvascular disease may be an important risk factor for cardiac remodeling and subsequent congestive heart failure (13,15–18). However, these studies largely have been confined to small and selected samples of participants using highly specialized methods because of difficulties in the assessment of microcirculation. The link between microvascular disease and cardiac remodeling in the general population therefore remains unclear. There has been recent interest in using objective and quantitative methods to examine retinal vascular changes and their cardiovascular associations, with increasing data from population-based studies showing that retinal vascular changes are related to risk of both clinical and subclinical cardiovascular diseases (19,35–40). In the ARIC (Atherosclerosis Risk In Communities) study, for example, participants with retinopathy signs were 2 to 3 times more likely to develop congestive heart failure events than those without retinopathy, even after controlling for pre-existing coronary heart disease, diabetes, hypertension, and other risk factors (19).

We now show that narrower retinal arterioles and retinopathy signs are independently associated with LV concentric remodeling. This is consistent with findings from the ARIC study (19) and other studies showing association of retinopathy signs with the development of heart failure after coronary artery bypass surgery in persons with diabetes (20,21). Thus, our data provide further support to the theory that in diabetic patients, myocardial ischemia induced by coronary microvascular disease is an important risk factor for LV dysfunction, even in the absence of epicardial coronary atherosclerosis (41).

Interestingly, our data also show ethnic variations in the association between narrower retinal arterioles and LV concentric remodeling. Although there was no significant interaction with ethnicity, the association seems to be stronger in Chinese and Hispanic patients than in black and white patients (Table 4). It is unclear why there may be such differences, but both retinal vascular caliber and LV geometry have been shown to vary significantly in different ethnic groups (27,30). For example, the MESA study previously has reported that LV mass and volume are smallest in Chinese and largest in African-American patients (30), an observation that is somewhat contradictory to our finding of a stronger association between narrower retinal arterioles and increased M/V ratio in Chinese patients. On the other hand, retinal arteriolar caliber has been shown to be narrowest in the Chinese population among all of the ethnic groups in the MESA study (27). Further research is required to elucidate the possible mechanisms underlying the ethnic differences seen in our study.

Multiple factors may contribute to LV remodeling at different stages before manifestation of symptomatic heart failure (1,2). Although our results suggest that microvascular disease may be one of these factors, the exact underlying pathophysiological mechanisms are unclear. Small vessel damage seen in the retina may represent widespread microcirculatory disease, which places an impedance burden, in part through reflected waves, on the LV. This, in turn, can

increase LV load and impinge on LV emptying, predisposing the LV to undergo physiological (adaptive) or pathological (maladaptive) concentric remodeling. This theory is supported by our finding of a positive association between small artery elasticity (quantified from pulse waveform analysis) and retinal arteriolar caliber (age, gender, race, center-adjusted correlation coefficient 0.05, $p < 0.001$), as well as an inverse correlation between small artery elasticity and M/V ratio (age, gender, race, and center-adjusted correlation coefficient −0.10, $p < 0.001$) in the MESA study (T. Y. Wong, unpublished data, 2007). However, our hypothesis clearly requires further validation from future studies.

Strengths of our study include its large multiethnic and population-based design with all participants free of clinical cardiovascular disease at baseline, use of a previously validated computer-based technique to quantify retinal vascular caliber and standardized evaluation of retinopathy with a high proportion of gradable digital fundus photographs, as well as the use of cardiac MRI, a robust imaging technology for accurate assessment of LV geometric parameters (42). However, several important limitations of the study may merit consideration. First, the cross-sectional design of our study prevented inferring temporality. Thus, the temporal sequence of reported associations cannot be certified. However, there is no plausible hypothesis from the current literature to suggest that cardiac remodeling can induce retinal microvascular changes. Second, although we used the highest quintile of M/V ratio to define advanced concentric remodeling, it may not necessarily represent pathological remodeling. Many aspects of the transition process from physiological (adaptive) to pathological (maladaptive) remodeling still remain unclear (11,12), and therefore an evidence-based definition of abnormal concentric remodeling is yet to be established. Lastly, at the time of this study, the MESA study did not have available data on ocular factors that may affect measurement of retinal vascular caliber, such as refractive error (26) and axial length (43). These factors, nevertheless, have been shown to have only a small impact on the measurement of absolute retinal vascular caliber and may not affect the association between retinal vascular caliber and cardiovascular disease in an epidemiological study setting (44).

In conclusion, our study shows that in generally healthy middle-age adults without a history of clinical cardiovascular disease, narrower retinal arteriolar caliber, and to a lesser extent wider retinal venular caliber and retinopathy, are associated with increased LV concentric remodeling. These data may lend further support to the potential microvascular role in the pathogenesis of early cardiac remodeling and subsequent development of heart failure.

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Reprint requests and correspondence: Dr. Tien Yin Wong, Centre for Eye Research Australia, University of Melbourne, 32 Gisborne Street, East Melbourne 3002, Australia. E-mail: twong@unimelb.edu.au.

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