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Retinal Arteriolar Narrowing and Risk of Coronary Heart Disease in Men and Women

The Atherosclerosis Risk in Communities Study

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THE RELATIVE CONTRIBUTION OF microvascular and macrovascular processes to the risk of coronary heart disease (CHD) is unknown, but its elucidation is important from etiological, preventive, and therapeutic perspectives.^{1,2} Coronary microvascular disease may explain the occurrence of myocardial ischemia without overt coronary artery blockage,³⁻⁷ as well as risk of heart failure^{8,9} and mortality⁹ after myocardial infarction (MI). Because women with chest pain are more likely to have normal coronary arteries,^{1-4,7} have higher mortality rates after an MI,^{10,11} and have poorer outcomes after coronary artery bypass graft surgery,¹² it has been hypothesized that microvascular disease may play a more prominent role in the development of myocardial ischemia and definite CHD in women.^{13,14} However, most studies of microvascular dysfunction have been conducted in small numbers of highly selected symptomatic patients,^{3-7,9} few have been prospective,⁹ and none have been population based. This is partly because

Context Microvascular processes have been hypothesized to play a greater role in the development of coronary heart disease (CHD) in women than in men; however, prospective clinical data are limited.

Objective To examine the association between retinal arteriolar narrowing, a marker of microvascular damage from hypertension and inflammation, and incident CHD in healthy middle-aged women and men.

Design, Setting, and Participants The Atherosclerosis Risk in Communities Study, an ongoing prospective, population-based cohort study in 4 US communities initiated in 1987-1989. Retinal photographs were taken in 9648 women and men aged 51 to 72 years without CHD at the third examination (1993-1995). To quantify retinal arteriolar narrowing, the photographs were digitized, individual arteriolar and venular diameters were measured, and a summary arteriole-to-venule ratio (AVR) was calculated.

Main Outcome Measure Risk of CHD associated with retinal arteriolar narrowing.

Results During an average 3.5 years of follow-up, 84 women and 187 men experienced incident CHD events. In women, after controlling for mean arterial blood pressure averaged over the previous 6 years, diabetes, cigarette smoking, plasma lipid levels, and other risk factors, each SD decrease in the AVR was associated with an increased risk of any incident CHD (relative risk [RR], 1.37; 95% confidence interval [CI], 1.08-1.72) and of acute myocardial infarction (RR, 1.50; 95% CI, 1.10-2.04). In contrast, AVR was unrelated to any incident CHD in men (RR, 1.00; 95% CI, 0.84-1.18) or to acute myocardial infarction (RR, 1.08; 95% CI, 0.85-1.38).

Conclusion Retinal arteriolar narrowing is related to risk of CHD in women but not in men, supporting a more prominent microvascular role in the development of CHD in women than in men. Future work is needed to confirm these findings.

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methods to assess the coronary microcirculation are invasive and applicable only in experimental settings.¹⁻⁷

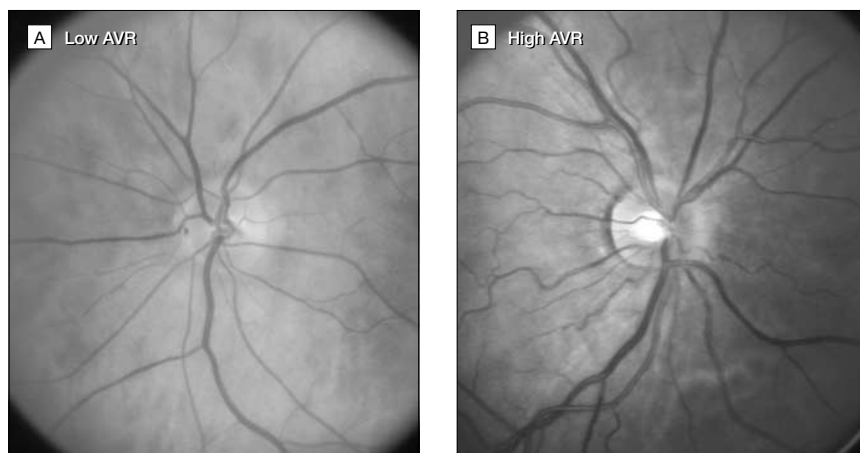
The retinal arterioles offer an opportunity to noninvasively explore the relation of systemic microvascular disease to CHD.¹⁵ These arterioles narrow, and their media thicken and show sclerotic changes, in response to hypertension and other processes.¹⁶ In the population-based Atherosclerosis Risk in Communities (ARIC) study, we developed a computer-assisted, digital

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Figure. Digitized Retinal Photographs Showing Examples of Low vs High Arteriole-to-Venule Ratio (AVR)



A, AVR = 0.789; B, AVR = 0.973. Arterioles are lighter in intensity compared with venules.

method to quantify retinal arteriolar narrowing based on measurements of individual arteriolar and venular calibers.¹⁷ We have previously shown that retinal arteriolar narrowing is strongly related to concurrently measured blood pressure¹⁷ and also to past blood pressure,¹⁸ inflammation, and endothelial dysfunction,¹⁹ suggesting that arteriolar narrowing in the retina is an independent marker of microvascular damage from hypertension, inflammation, and other processes.

The purpose of this study was to examine the association between retinal arteriolar narrowing and incident CHD in healthy middle-aged women and men participating in the ARIC study.

METHODS

Study Population

The ARIC study included 15 792 women and men 45 through 64 years of age at recruitment in 1987 through 1989.²⁰ Population samples were selected from 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi (black participants only); suburbs of Minneapolis, Minnesota; and Washington County, Maryland.²⁰ Participants underwent a second examination 3 years later (1990 through 1992), and a third examination 3 years after that (1993 through

1995). There was an 86% return rate for the third examination.

Retinal photographs were taken at the third examination.¹⁷ Of the 12 887 participants who returned for this examination, 2329 were excluded: 211 who had not participated in the second examination, 38 whose race was neither black nor white, 42 nonwhite residents in Minneapolis and Maryland, 13 with missing blood pressure data, 230 with no retinal photographs, 1774 with ungradable photographs, and 21 with retinal vascular occlusions. Also excluded were 618 participants with CHD at baseline and 292 who developed CHD prior to the third examination, leaving 9 648 for this analysis. Baseline characteristics of participants with and without gradable retinal photographs have been reported.¹⁷ Persons with gradable photographs were generally younger and more likely white but did not differ significantly by sex or smoking status.¹⁷

Measurement of Retinal Arteriolar Diameter

The retinal photography procedure followed standardized methods.¹⁷⁻¹⁹ Briefly, after 5 minutes of dark adaptation, a 45° retinal photograph was taken of 1 randomly selected eye using an autofocus camera. The photo-

graph was centered on the region of the optic disc and the macula. The photographs were digitized by a high-resolution scanner and the diameters of individual arterioles and venules coursing through a zone located one half to 1 disc diameter from the optic disc margin were measured on the computer by trained graders who were masked to subject identity.¹⁷ These measurements were summarized as an arteriole-to-venule ratio (AVR).¹⁷ The AVR accounts for magnification differences between photographs and is distributed normally in the general population.¹⁷ A smaller AVR indicates narrower arterioles since venular diameters vary little with blood pressure.^{17,18} Intragrader and intergrader reliability coefficients for repeated AVR measurements were 0.84 and 0.79, respectively.¹⁷ Examples of low and high AVR are shown in the FIGURE.

Graders also evaluated photographs for lesions typical of hypertensive retinopathy (eg, microaneurysms, retinal hemorrhages, soft exudates) according to a standardized “light box” protocol.¹⁷ Retinopathy was defined as present if these lesions were graded definite or probable.¹⁷ Intragrader and intergrader κ statistics for retinopathy lesions ranged from 0.61 to 1.00.¹⁷

Identification of CHD

Ascertainment of CHD events in the ARIC study has been previously described.²¹ Any incident CHD was defined as acute (definite or probable) MI, fatal coronary heart disease, silent MI, and myocardial revascularization (eg, coronary angioplasty or coronary artery bypass graft surgery). For hospitalized patients, trained abstractors recorded presenting signs and symptoms, cardiac enzymes, and related clinical information. Up to three 12-lead electrocardiogram tracings were visually coded with the Minnesota code.²² Out-of-hospital deaths were investigated by means of death certificates, physician questionnaires, and next-of-kin interviews. Coroner reports and autopsy reports, when available, were used for validation. Two physicians assigned the

CHD diagnostic classification while a third adjudicated discrepancies. A more detailed description of the quality control procedures for CHD ascertainment appear elsewhere.²¹

Definition of CHD Risk Factors

Participants underwent standardized assessment of cardiovascular risk factors.²³ Three blood pressure measurements were taken with a random-zero sphygmomanometer and the mean of the last 2 was used. Mean arterial blood pressure was computed as two thirds of the diastolic value plus one third of the systolic value, and the average of this mean pressure over all 3 examinations was used to assess blood pressure-independent associations of retinal arteriolar narrowing.¹⁹ Diabetes, cigarette smoking, alcohol consumption, use of medication and hormone replacement therapy, and physical activity were ascertained from examiner-administered questionnaires. Hypertension was defined as systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or use of antihypertensive medication during the previous 2 weeks. Diabetes mellitus was defined as a fasting glucose level of 126 mg/dL or greater (7.0 mmol/L), a nonfasting glucose level of 200 mg/dL or greater (11.1 mmol/L), or a self-reported history of physician-diagnosed diabetes or treatment for diabetes. A person was considered to have hypertension or diabetes if these criteria were met at any examination. Physical activity was characterized by a sports index, ranging from 0 (low) to 5 (high).²⁴ Measurement of carotid intima-media thickness (IMT) by ultrasound and collection of fasting blood samples and processing for total cholesterol, high-density lipoprotein (HDL) cholesterol, white blood cell counts, plasma fibrinogen, factor VIII, and von Willebrand factor are described in detail elsewhere.²³ The waist-hip ratio was computed as the circumference of the waist (umbilical level) divided by the hips (maximum buttocks). Variables were based on data from the third examination, except for hypertension

and diabetes, which were based on all 3 examinations.

Statistical Methods

All analyses were sex specific unless otherwise indicated. We analyzed the AVR as both a continuous variable (per SD change) and as a categorical variable (stratified into quintiles using cut-points from the total sample, with the first quintile indicating the most severe arteriolar narrowing and the fifth the least narrowing). Analysis of covariance was used to compare baseline characteristics between quintile extremes in AVR, adjusting for age (years), race (white and black), and field center. We estimated the 3-year cumulative incidence of CHD (defined as $100 \times [1 - \text{Kaplan-Meier estimators}]$) according to AVR quintiles. Follow-up time was defined as the time from the third examination to the date of the particular CHD event (for any incident CHD, defined as the time to the first event). For noncases, follow-up continued until the date of death, last contact, or December 31, 1997. We used Cox proportional hazards regression to estimate the relative risk (RR) of CHD events comparing a specific AVR quintile vs the fifth, a 1-SD decrease in AVR, or presence vs absence of retinopathy. The proportional hazards assumption was visually verified by plotting the log of the cumulative hazard function of CHD comparing quintiles of AVR over the 3.5 years of follow-up, and confirmed by showing that a time-dependent interaction variable with AVR was not statistically significant ($P = .78$ in the multivariable model). We initially adjusted for age, race, and field center. We used 2 multivariable models. In model 1, we further adjusted for traditional CHD risk factors, including 6-year mean arterial blood pressure, diabetes (yes, no), waist-hip ratio, sports index (0 to 5), total cholesterol, HDL cholesterol, cigarette smoking (ever, never) and alcohol consumption (yes, no). In this model, we also adjusted for use of antihypertensive medication (yes, no), since this is an indicator of severity of

hypertension. In model 2, we adjusted for the covariates in model 1 plus white blood cell count (1000 cells/mm^3), plasma fibrinogen, factor VIII, von Willebrand factor, and carotid IMT, since inflammation, hemostatic factors, and macrovascular disease are possible confounders of the association between AVR and risk of CHD.¹⁹ In a supplementary analysis, we also adjusted for hormone replacement therapy use (yes, no) in postmenopausal women.

Finally, in models of the entire sample, we tested interactions with sex, and in sex-specific models, interaction with age group (51-60 years, 61-72 years), race, hypertension (yes, no) and diabetes (yes, no), by adding cross-product terms with AVR as a continuous variable. Analyses were performed with SPSS version 9.0 (SPSS Inc, Chicago, Ill). A P value of .05 was considered statistically significant.

RESULTS

The mean (SD) AVR in the population was 0.843 (0.08). TABLE 1 shows the baseline characteristics of women and men, comparing the first with the fifth AVR quintile. In general, the first AVR quintile (greater arteriolar narrowing) was associated with black race and—after adjusting for age, race, and field center—with a poorer cardiovascular risk profile in both women and men, with the exception of diabetes and HDL cholesterol in women, and total cholesterol, HDL cholesterol, and alcohol consumption in men.

Over an average follow-up of 3.5 years, 271 persons (84 women and 187 men) experienced incident CHD events. TABLE 2 shows the cumulative incidence and RR of any incident CHD, in relation to quintiles of AVR. In women, decreasing quintiles of AVR were associated with increasing risk of any incident CHD, with a crude RR of 2.3 comparing the lowest (first) to the highest (fifth) quintile. These estimates were not substantially altered after adjustment for age, race, and field center or for cardiovascular risk factors in model 1. In men, AVR was not associated with risk of any incident CHD.

Further analyses were performed with AVR treated as a continuous variable and for specific CHD events (TABLE 3). In women, each 1-SD decrease in AVR was associated with a crude RR of 1.39 for any incident CHD. This association persisted after adjustment for age, race, and field center and in multivariate models (models 1 and 2), and was similar for acute MI only and acute MI/fatal CHD, but was weaker and statistically insignificant ($P=.13$) for cardiac revascularization. In men,

AVR was not associated with any CHD end points. Analysis repeated using the logarithmic transformation of AVR did not improve the fit of the models presented. This association was seen in women with and without hypertension and diabetes (TABLE 4). There was no association between AVR and CHD in men with and without these conditions.

Among postmenopausal women, controlling for hormone replacement therapy had little effect on the RR of any

incident CHD (for each 1-SD decrease in AVR, adjusting for use of hormone replacement and covariates in model 1: RR, 1.28; 95% confidence interval, 1.00-1.63).

In models based on the total population, the interaction between AVR and sex was statistically significant ($P=.03$ for the cross-product term between AVR and sex for any incident CHD, adjusting for covariates in model 1). In sex-specific models, there were no significant interactions between AVR and

Table 1. Baseline Characteristics, by Quintile Extremes of AVR*

Characteristic	Women			Men		
	First AVR Quintile (Range: 0.57-0.78) (n = 944)	Fifth AVR Quintile (Range: 0.92-1.22) (n = 1289)	P Value†	First AVR Quintile (Range: 0.57-0.78) (n = 985)	Fifth AVR Quintile (Range: 0.92-1.22) (n = 640)	P Value†
Age, mean (SE), y	59.5 (0.18)	59.1 (0.15)	.24	60.0 (0.18)	59.3 (0.22)	.09
Black, %	32.2	16.7	<.001	21.3	14.5	<.001
Hypertension, %	56.2	33.0	<.001	58.5	28.4	<.001
Arterial blood pressure, mean (SE), mm Hg	91.8 (0.31)	83.3 (0.26)	<.001	94.2 (0.29)	86.0 (0.36)	<.001
Diabetes, %	16.7	14.9	.63	20.7	15.6	.001
Total plasma cholesterol, mean (SE), mg/dL‡	218.1 (1.23)	211.1 (1.05)	<.001	202.8 (1.15)	198.1 (1.43)	.16
HDL cholesterol, mean (SE), mg/dL‡	58.4 (0.60)	59.7 (0.52)	.25	44.7 (0.45)	45.0 (0.56)	.90
Waist-hip ratio, mean (SE)	0.92 (0.002)	0.90 (0.002)	<.001	0.98 (0.002)	0.96 (0.002)	<.001
Sports index (0-5), mean (SE)	2.37 (0.03)	2.48 (0.02)	.001	2.61 (0.03)	2.79 (0.03)	<.001
Cigarette smoking, ever, %	50.8	45.5	.02	74.8	66.7	.009
Alcohol consumption, ever, %	70.9	64.2	.01	88.4	85.1	.22

*Values are adjusted for age, race, and field center (except for age and black, which are unadjusted for age and race, respectively). AVR indicates arteriole-to-venule ratio; HDL, high-density lipoprotein. See "Methods" section for definitions of characteristics.

†Represents overall difference among AVR quintiles. Ranges of AVR values for quintiles: first, 0.57-0.78; second, 0.79-0.82; third, 0.83-0.86; fourth, 0.86-0.91; fifth, 0.92-1.22.

‡To convert values for total plasma cholesterol and HDL cholesterol to mmol/L, multiply values by 0.029.

Table 2. Cumulative Incidence and Relative Risk of CHD, by AVR Quintiles*

	AVR Quintile									
	Women					Men				
	1 (Range: 0.57-0.78)	2 (Range: 0.79-0.82)	3 (Range: 0.83-0.86)	4 (Range: 0.87-0.91)	5 (Range: 0.92-1.22)	1 (Range: 0.57-0.78)	2 (Range: 0.79-0.82)	3 (Range: 0.83-0.86)	4 (Range: 0.87-0.91)	5 (Range: 0.92-1.22)
No. at risk	944	1026	1103	1206	1289	985	904	827	724	640
CHD events, No.	19	22	16	15	12	47	39	39	37	25
CHD cumulative incidence, %†	2.54	3.38	2.35	1.86	1.56	7.66	6.76	6.42	7.41	6.43
CHD RR (95% CI)										
Crude‡	2.3 (1.1-4.8)	2.5 (1.2-5.0)	1.7 (0.8-3.5)	1.4 (0.7-2.9)	Reference	1.3 (0.8-2.2)	1.2 (0.7-2.0)	1.3 (0.8-2.2)	1.3 (0.8-2.2)	Reference
Age-, race-, center-adjusted	2.4 (1.2-5.0)	2.6 (1.3-5.2)	1.7 (0.8-3.6)	1.4 (0.7-3.0)	Reference	1.3 (0.8-2.2)	1.2 (0.7-2.0)	1.3 (0.8-2.1)	1.3 (0.8-2.1)	Reference
Multivariate-adjusted, model 1§	2.2 (1.0-4.6)	2.3 (1.1-4.8)	1.6 (0.8-3.4)	1.3 (0.6-2.8)	Reference	1.1 (0.7-1.8)	1.0 (0.6-1.7)	1.2 (0.7-1.9)	1.2 (0.7-2.1)	Reference

*CHD indicates coronary heart disease; AVR, arteriole-to-venule ratio; RR, relative risk; and CI, confidence interval.

†Three-year cumulative incidence defined as $100 \times (1 - \text{Kaplan-Meier estimators})$.

‡Specific AVR quintile vs the fifth quintile.

§Model 1: Relative risk adjusted for age, race, field center, 6-year mean arterial blood pressure, diabetes, waist-hip ratio, sports index, total cholesterol, high-density lipoprotein cholesterol, cigarette smoking, alcohol consumption, and antihypertensive medication use. See "Methods" section for definitions of covariates.

age group, race, hypertension, or diabetes ($P > .10$ for all interaction terms).

Finally, we evaluated the association between retinopathy and risk of CHD. Retinopathy was associated with increased risk of any incident CHD in women (RR, 1.83; 95% CI, 1.00-3.38, adjusting for covariates in model 1), but not in men (RR, 0.84; 95% CI, 0.46-1.52).

COMMENT

In this large, prospective, population-based study, we show that retinal arteriolar narrowing, assessed quantitatively from digitized retinal photographs, is related to the risk of CHD in women but not men. In women, decreasing retinal arteriolar diameters were associated with increasing risk of CHD despite adjustment for long-term blood pressure, diabetes, smoking, increased levels of plasma lipids, and other risk factors. On average, every 1-SD decrease in the retinal AVR was associated with a 37% increase in

CHD risk. This association was similar for the more severe CHD events (acute MI only and acute MI/fatal CHD), was not altered after controlling for markers of inflammation, presence of macrovascular disease, or hormone replacement therapy use, and persisted in subgroups stratified by hypertension and diabetes status.

Retinal arteriolar narrowing is thought to be an early indicator of microvascular damage from aging, hypertension, and other processes, and reflects intimal thickening and medial hyperplasia, hyalinization, and sclerosis.¹⁶ Because similar pathological features are also seen in the coronary^{25,26} and renal arterioles²⁷ of persons with hypertension, changes in the retinal arterioles may offer useful information regarding the state of the systemic microcirculation in health and in disease. We previously reported that the AVR, as a quantitative index of retinal arteriolar narrowing, is related to long-term average blood pressure¹⁸ and to

markers of inflammation and endothelial dysfunction,¹⁹ but is unrelated to measures of atherosclerosis (eg, carotid IMT).¹⁹

Thus, the independent association we report between AVR and incident CHD in women likely reflects microvascular rather than macrovascular processes. This hypothesis is supported by a number of observations in the current study. First, we showed that adjustment for macrovascular disease (carotid IMT) had little effect on the association between AVR and incident CHD. Second, AVR was unrelated to cardiac revascularization procedures in men or women (see Table 3), as these procedures are usually performed to treat occlusions in larger coronary vessels (ie, macrovascular disease). Finally, women with signs of retinopathy, a marker of more severe microvascular damage from hypertension, were also more likely to have incident CHD compared with women without these signs.

Table 3. Relative Risk of CHD and MI per SD Decrease in AVR*

CHD Event	Adjustment	Women			Men		
		No. of Events	RR (95% CI) per SD Decrease in AVR	P Value	No. of Events	RR (95% CI) per SD Decrease in AVR	P Value
Any incident CHD	Crude	84	1.39 (1.12-1.75)	.003	187	1.08 (0.93-1.25)	.33
	Age-, race-, center-adjusted		1.42 (1.14-1.78)	.002		1.07 (0.92-1.25)	.36
	Multivariate-adjusted, model 1†		1.37 (1.08-1.72)	.008		1.00 (0.84-1.18)	.98
	Multivariate-adjusted, model 2‡		1.40 (1.03-1.92)	.03		0.94 (0.76-1.16)	.59
Acute MI only	Multivariate-adjusted, model 1	49	1.50 (1.10-2.04)	.009	78	1.08 (0.85-1.38)	.53
Acute MI/fatal CHD	Multivariate-adjusted, model 1	54	1.35 (1.01-1.81)	.04	91	1.06 (0.85-1.33)	.60
Cardiac revascularization	Multivariate-adjusted, model 1	53	1.23 (0.93-1.66)	.13	135	0.93 (0.77-1.11)	.41

*CHD indicates coronary heart disease; MI, myocardial infarction; AVR, arteriole-to-venule ratio; RR, relative risk; and CI, confidence interval.

†See Table 2 footnote for model 1 covariates.

‡Adjusted for covariates in model 1 plus white blood cell count, plasma fibrinogen, factor VIII, von Willebrand factor, and carotid intima-media thickness. See "Methods" section for definitions of covariates.

Table 4. Relative Risk of CHD per SD Decrease in AVR, by Hypertension and Diabetes Status*

Status	Women		Men	
	RR (95% CI) of Any Incident CHD per SD Decrease in AVR	P Value	RR (95% CI) of Any Incident CHD per SD Decrease in AVR	P Value
Hypertension or diabetes present†	1.30 (0.99-1.72)	.08	1.11 (0.89-1.38)	.34
No hypertension†	1.52 (1.03-2.24)	.03	0.90 (0.96-1.15)	.40
No diabetes‡	1.45 (1.08-1.94)	.01	0.97 (0.81-1.17)	.77
No hypertension or diabetes‡	1.81 (1.18-2.79)	.007	0.85 (0.64-1.21)	.24

*CHD indicates coronary heart disease; AVR, arteriole-to-venule ratio; RR, relative risk; and CI, confidence interval.

†Adjusted for covariates in model 1. See Table 2 footnote for covariates.

‡Adjusted for all covariates in model 1, except diabetes.

Our findings are supported by cross-sectional data from the National Health Examination Survey.²⁸ In that study, the association between retinal arteriolar narrowing (as detected from clinical ophthalmoscopy) and prevalent CHD in women was also found to be stronger than in men (odds ratio of 6.4 for women compared to 3.7 for men aged 35 to 54 years, and 2.4 for women compared to 1.2 for men aged 55 to 79 years).²⁸

These data offer insights into differences in the epidemiology and pathogenesis of CHD between women and men. It has been suggested that microvascular processes may play a more significant role in the pathogenesis of myocardial ischemia in women,^{13,14} largely based on observations that women more often experience the syndrome of angina pectoris with normal coronary arteries.^{3,4,6} However, it is unclear why women have higher mortality rates after developing an MI,^{10,11,29} or have poorer outcomes after coronary artery bypass graft surgery than do men.^{12,29} Additionally, it is uncertain why hypertension, diabetes, and inflammation appear to be stronger risk factors for CHD in women compared with men.³⁰⁻³³ One hypothesis to explain these sex differences is that hormonal or other influences protect women from the development of atherosclerosis, leaving microvascular processes to play a relatively greater role in the development of CHD in women.³⁴ Our study now provides data to support this hypothesis by showing that arteriolar damage, resulting from hypertension, diabetes, and inflammation, is more strongly related to risk of CHD in women than in men. We are unable to offer an adequate explanation of the strong sex difference or, in particular, of why a lower AVR, as an indicator of more severe coronary microvascular disease, is unrelated to risk of CHD in men. We can only note that this sex difference is consistent with the often-made clinical observation that angina without angiographic stenosis is much less frequent in men than in women.

Four limitations of this study warrant consideration. First, our data do not provide direct evidence of an association between coronary microvascular disease and risk of CHD, as there was no assessment of the coronary microcirculation. However, coronary microvascular dysfunction appears to be part of a systemic microvascular process,^{35,36} and similar histopathological changes in retinal¹⁶ and coronary arterioles^{25,26} are associated with hypertension. Second, selection bias may have obscured some associations and enhanced others, as a sizeable number of photographs were ungradable because pharmacological pupil dilation was not performed prior to photography. However, this would not explain the contrasting sex pattern seen, since the proportion of photographs that was ungradable was similar in women (15.0%) and men (14.6%). Third, it is not clear whether other unmeasured factors (eg, use of vasodilator medications) could have affected these associations. Finally, we have only shown a short-term association between AVR and incident CHD in women; further study involving analysis of more outcome events is required to determine whether similar long-term associations also exist.

In conclusion, our study suggests a sex difference in the contribution of arteriolar narrowing to the development of CHD in a large community-based population. This finding suggests that microvascular disease may play a greater role in the risk of CHD in women than in men, which may have important clinical implications in the prevention and treatment (eg, decisions regarding revascularization surgery vs medical therapy³⁷) of CHD in women.

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Analysis and interpretation of data: Wong, R. Klein, Sharrett, Duncan, Couper, Tielsch, B. Klein.

Drafting of the manuscript: Wong.

Critical revision of the manuscript for important intellectual content: Wong, R. Klein, Sharrett, Duncan, Couper, Tielsch, B. Klein, Hubbard.

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The responsibility of a writer is to excavate the experience of the people who produced him.
—James Baldwin (1924-1987)