Retinopathy and Risk of Congestive Heart Failure

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Context  Congestive heart failure (CHF) affects a substantial proportion of adults including those without preexisting coronary heart disease. The pathogenesis of CHF is uncertain, but microvascular disease has been hypothesized as a possible factor.

Objective  To determine the relationship of retinopathy, a marker of systemic microvascular disease, to risk of CHF.

Design, Setting, and Participants  Population-based, prospective 7-year cohort study in 4 US communities using the Atherosclerosis Risk in Communities Study database. Participants (n=11612, aged 49 to 73 years) had retinal photographs taken between 1993 and 1995. The photographs were graded according to a standardized protocol for the presence of retinopathy (eg, microaneurysms, retinal hemorrhages, soft exudates, arteriovenous nicking, focal arteriolar narrowing, and generalized arteriolar narrowing).

Main Outcome Measures  Association between retinopathy and incident CHF, identified from hospitalization and death records.

Results  The 7-year cumulative incidence of CHF was 5.4% (492 events). Participants with retinopathy had a higher incidence of CHF compared with those without retinopathy (15.1% vs 4.8%, P<.001). After controlling for age, sex, race, preexisting coronary heart disease, mean arterial blood pressure, diabetes, glucose level, cholesterol level, smoking, body mass index, and study site, the presence of retinopathy was associated with a 2-fold higher risk of CHF (relative risk, 1.96; 95% confidence interval, 1.50-2.54). Among participants without preexisting coronary heart disease, diabetes, or hypertension, retinopathy was associated with a 3-fold higher risk of CHF (relative risk, 2.98; 95% confidence interval, 1.50-5.92).

Conclusions  Retinopathy is an independent predictor of CHF, even in persons without preexisting coronary heart disease, diabetes, or hypertension. This suggests that microvascular disease may play an important role in the development of heart failure in the general population. Some asymptomatic persons with retinopathy on an opthalmologic examination may benefit from further assessment of CHF risk.

JAMA. 2005;293:63-69

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diabetes, and other processes, and narrowed retinal arterioles have been found to predict incident coronary heart disease in women. In this study, we examined the relationship of retinopathy signs to risk of CHF in a population-based cohort of healthy, middle-aged men and women.

METHODS

Study Population

The Atherosclerosis Risk in Communities (ARIC) study is a population-based cohort study of cardiovascular disease and its risk factors. The original cohort included 15792 participants aged 45 to 64 years selected by probability sampling from 4 US communities: Forsyth County, North Carolina; Jackson, Miss; suburbs of Minneapolis, Minn; and Washington County, Maryland. The Jackson sample included African Americans only; in the other field centers, samples were representative of the populations in these communities (mostly white in Minneapolis and Washington County, and about 15% African American in Forsyth County). Race was determined by self-report with fixed categories (white, African American, American Indian, Asian/Pacific Islander). While Hispanic ethnic status was ascertained, it was not used in this analysis due to insufficient numbers.

Initial participation rates were 46% in Jackson and approximately 65% in the other communities. Differences between participants and nonparticipants at the baseline examination have been presented elsewhere. White participants generally reported a higher socioeconomic status, better general health, and a lower prevalence of cardiovascular disease and associated risk factors than did nonparticipants. Differences in these characteristics between African American participants and nonparticipants were of smaller magnitude or absent, particularly among African American women.

Of the 15792 participants at baseline, 14346 (93% of survivors) returned for a second examination 3 years later in 1990-1992, and 12887 (86% of survivors) returned for a third examination 3 years after the second in 1993-1995. At each study visit, participants underwent an interview assessing demographic characteristics and medical history, a brief clinical examination including measurement of blood pressure and weight, and a set of laboratory tests including levels of blood lipids and serum glucose.

We first obtained retinal photographs at the third ARIC study examination. Characteristics of participants with and without gradable retinal photographs have been previously reported. Individuals with gradable photographs were younger and more likely to be white, but did not differ in sex or smoking status from participants with ungradable photographs. Of the 12887 participants who returned for the third examination, we excluded 245 who had no retinal photographs, 738 with ungradable photographs, 26 with retinal vascular occlusions, 186 hospitalized for prevalent CHF (as defined below), 38 whose race was neither African American nor white (due to small numbers in other racial groups), and 42 African American residents in Minneapolis and Washington County (so that race and field center could be adjusted in 5 categories: Jackson, Forsyth whites, Forsyth African Americans, Minneapolis, and Washington County), leaving 11612 (aged 49 to 73 years) who provided data for this study.

Institutional review boards at each study site approved the study. Written informed consent was obtained from all participants at each examination.

Assessment of Retinal Microvascular Signs

The procedures for retinal photography and the assessment of photographs are described in detail elsewhere. Briefly, we took photographs of the retina from 1 randomly selected eye after 5 minutes of dark adaptation. Trained graders masked to all participant characteristics used a standardized protocol to evaluate the photographic slides for microvascular signs. We recorded 4 categories of retinal microvascular signs: retinopathy, arteriovenous nicking, focal arteriolar narrowing, and generalized arteriolar narrowing. Retinopathy was defined as present if any of the following lesions were graded definite or probable: blot hemorrhages, flame-shaped hemorrhages, microaneurysms, soft exudates (cotton-wool spots), hard exudates, macular edema, intraretinal microvascular abnormalities, and other less-common lesions. Arteriovenous nicking and focal arteriolar narrowing were defined as present if graded definite or probable. To estimate the generalized retinal arteriolar narrowing, photographs were digitized and diameters of individual retinal vessels coursing through a specified area were measured using a computer and summarized as the arteriole-to-venule ratio. A smaller ratio represents narrower arterioles (since venule diameters vary little), and generalized arteriolar narrowing was defined as the lowest quintile of the sample distribution of the arteriole-to-venule ratio. Intragradable and intergrader k statistics for various signs of retinopathy ranged from 0.61 to 1.00. For arteriole-to-venule ratio, intragradable and intergrader reliability coefficients were 0.84 and 0.79, respectively.

Incident CHF

We assessed CHF events by contacting participants annually by telephone to identify self-report of all hospitalizations during the previous year, by ongoing surveillance of community hospital discharges, and by surveying death certificates from state vital statistics. Medical records from all hospitalizations were obtained and discharge codes investigated by trained medical record abstractors. A hospitalization was considered a CHF event if it contained a hospital discharge diagnosis code of CHF (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 428 or 518.4). Death certificates with an underlying cause of death coded as heart failure (ICD-9-CM code 428 or ICD-10...
code 150) and not identified through the above process were also included as events. Because retinal photography was performed at the third examination, incident CHF was defined as new hospitalizations for CHF or death from CHF subsequent to this examination. Prevalent CHF cases that occurred up to and including the third examination (n = 186) were excluded from this study.

Definitions of Risk Factors
We evaluated all participants for cardiovascular risk factors at each examination. Ascertainment and definition of coronary heart disease in the ARIC study followed a standardized protocol. In this study, patients were defined as having preexisting coronary heart disease if they had had acute myocardial infarction, silent infarction, or coronary revascularization procedures (eg, coronary angioplasty) in the period up to and including the third examination. A history of angina or use of antianginal medications in the absence of the above events was not considered a criterion for coronary heart disease.

Blood pressure was measured with a random-zero sphygmomanometer according to a standardized protocol. The mean arterial blood pressure was computed as two thirds of the diastolic value plus one third of the systolic value. We used the average of this over the first 3 examinations (6-year mean arterial blood pressure) to assess blood pressure–independent association of retinal signs and incident CHF. 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 (7.0 mmol/L) or greater, a nonfasting glucose level of 200 mg/dL (11.1 mmol/L) or greater, or a self-reported history of or treatment for diabetes. Height and weight were measured with participants wearing scrub suits, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Blood collection and processing for levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, and glucose are described elsewhere. Education, cigarette smoking, and alcohol consumption status were ascertained from interview. All covariates were based on data collected at the third examination, except for education (first examination) and 6-year mean arterial blood pressure (all 3 examinations).

Statistical Analysis
We estimated the 7-year cumulative incidence of CHF (defined as 100 × [1 – Kaplan-Meier cumulative CHF-free survival at 7 years]) according to presence or absence of retinal microvascular signs. Follow-up time was defined as the number of days from the third examination visit to the date of the first CHF hospitalization, death, last contact, or December 31, 2000. The relative risk (RR) for CHF associated with presence of retinal signs was derived from Cox proportional hazards regression. We initially adjusted for age, sex, race, and examination center. In multivariable analyses, we further adjusted for education (up to and including grade school, high school without diploma, high school graduate, vocational school, college graduate, graduate school, or professional school), preexisting coronary heart disease, 6-year mean arterial blood pressure, use of antihypertensive medications, diabetes, cigarette smoking status (never, current, past), glucose level, low-density lipoprotein cholesterol level, and BMI. Analyses were repeated stratifying the population by sex, race, preexisting coronary heart disease, diabetes, and hypertension. We also formally tested for interaction by adding cross-product terms of these variables into the models of the total population.

Because of the strong associations of CHF with preexisting coronary heart disease, and of retinopathy with diabetes and hypertension, we also performed 3 post hoc analyses. We repeated the analyses excluding participants with preexisting coronary heart disease at the third examination (n = 396), stratified according to diabetes and hypertension status; performed an analysis excluding participants who first developed incident coronary heart disease and subsequently developed CHF; and used a standard formula to estimate the population-attributable fraction for CHF associated with retinopathy. Power calculations were performed to determine the lowest RR detectable for these associations. For the whole cohort, we had approximately 80% power to detect an RR of 1.4 and 90% power to detect an RR of 1.46.

All analyses were performed with SPSS version 10.0 (SPSS Inc, Chicago, Ill) and P < .05 was set as the threshold for statistical significance.

RESULTS
There were 719 persons with retinopathy at baseline and 492 incident CHF events over a mean follow-up of 6.2 years (cumulative incidence, 5.4%). Of the 492 cases, 20 (4.1%) were based on death certificate data. In general, persons with retinopathy were older and more likely to be African American; to have a history of coronary heart disease, hypertension, or diabetes; to have higher systolic and diastolic blood pressure, glucose level, triglycerides level, and BMI; and to report less alcohol use (TABLE 1). Persons who had an incident CHF event were older and more likely to be men; to be current cigarette smokers; to have a history of coronary heart disease, hypertension, or diabetes; to have higher systolic blood pressure, glucose level, triglycerides level, and BMI; and to report less alcohol use.

The 7-year incidence of CHF was higher in persons with retinal microvascular lesions compared with those without the retinal lesions (15.1% vs 4.8%, P < .001) (TABLE 2). After controlling for age, sex, race, and field center, the RR of CHF ranged from 1.20 (95% confidence interval [CI], 0.95–1.52) for focal arteriolar narrowing to 4.02 (95% CI, 2.75–5.86) for soft exudates. After further adjustment for prevalent coronary heart disease, mean arterial blood pressure, diabetes, glucose
level, and other risk factors, retinopathy remained independently related to incident CHF (any retinopathy: RR, 1.96 [95% CI, 1.51-2.54]; microaneurysms: RR, 2.20 [95% CI, 1.61-3.01]; retinal hemorrhages: RR, 1.89 [95% CI, 1.37-2.60]; and soft exudates: RR, 1.87 [95% CI, 1.22-2.84]). The associations for arteriovenous nicking and for focal and generalized arteriolar narrowing were not statistically significant after multivariable adjustment.

The pattern of association of retinopathy and CHF was similar in men and women (RR, 1.85 [95% CI, 1.31-2.61] vs 2.10 [1.40-3.15]), in whites and African Americans (1.76 [1.26-2.44] vs 2.28 [1.47-3.53]), and in persons with and without preexisting coronary heart disease (1.57 [0.81-3.06] vs 2.01 [1.51-2.68]). Interaction terms for these variables were not statistically significant (P> .20 in all models).

There were significant associations between retinopathy and incident CHF in persons without preexisting coronary heart disease, stratified according to diabetes and hypertension status (Table 3). The strongest association was seen among diabetic persons without hypertension (RR, 4.32; 95% CI, 2.13-8.76), although there was also a substantial association in persons without either diabetes or hypertension (RR, 2.98; 95% CI, 1.50-5.92). However, unlike diabetes, hypertension alone did not contribute to the increased risk of CHF in patients with retinopathy. The population-attributable fraction was highest (30.5%) in the subgroup with diabetes but no hypertension.

Finally, we conducted an additional multivariable analysis excluding participants with preexisting coronary heart disease and participants who developed incident coronary heart disease and subsequently developed CHF. The results of this analysis were essentially similar (RR for retinopathy, 2.21; 95% CI, 1.57-3.10).

**COMMENT**

In this prospective study of middle-aged persons, we found an association between retinal microvascular signs, as quantified from photography, and 7-year risk of CHF. Participants with signs of retinopathy (eg, microaneurysms, retinal hemorrhages, and soft exudates) were twice as likely to develop CHF as those without these signs, even in models that controlled for preexisting coronary heart disease, long-term blood pressure levels, diabetes, cigarette smoking, and other risk factors. This association was present in men and women and in whites and African Americans. In lower-risk participants without preexisting coronary heart disease, diabetes, or hypertension, the presence of retinopathy was associated with a 3-fold higher risk of CHF. Weaker associations with incident CHF were seen for other retinal arteriolar signs, and these associations were not significant in multivariable-adjusted models.

Retinal microvascular signs examined here represent small-vessel damage associated with increased age, hypertension, and diabetes. We have previously shown that these retinal signs are also associated with systemic markers of inflammation and endothelial dysfunction.
lial dysfunction in persons without diabetes, independent of blood pressure.30 Thus, the association between retinopathy and incident CHF supports a role of systemic microvascular disease in the development of heart failure, possibly related to a combination of elevated blood pressure, hyperglycemia, inflammation, and endothelial dysfunction. Our findings in this generally healthy, middle-aged community population extend previous smaller studies that have implicated microvascular mechanisms in CHF pathogenesis in subgroups with diabetic heart disease,9,31,32 hypertensive heart disease,10-12,33,34 and nonischemic dilated cardiomyopathy.13-18

It is important to note that there is not a perfect correlation of microvascular disease in the retina with systemic or coronary microvascular disease. Although some of the histopathological features of retinopathy signs (arteriolar narrowing, intimal thickening, medial hyalinization, and capillary occlusion and leakage)23 are also seen in histological studies of patients with coronary microvascular disease and hypertension,35,36 experimental studies indicate significant differences in the response to acute ischemia of retinal and myocardial microcirculation, possibly related to differing contractile properties of the capillary walls.37 In addition, not all retinal microvascular signs were strongly associated with CHF. In contrast to retinopathy, the associations for retinal arteriolar narrowing and arteriovenous nicking were weaker and nonsignificant after multivariable adjustment. The heterogeneity of these associations may reflect different pathophysiological processes associated with specific retinal microvascular signs.22

Nevertheless, comparison of the retinopathy associations in persons with diabetes and hypertension provides further insights into the relative importance of microvascular disease mechanisms to the risk of CHF.33,34 We found a higher RR of CHF and a greater population-attributable fraction associated with retinopathy in persons with diabetes than in those with hypertension. Among persons with diabetes but without preexisting coronary heart disease and hypertension, the population-attributable fraction for CHF associated with retinopathy was 30.5%, which suggests that nearly a third of heart fail-

| Table 2. Incidence and Relative Risk of Congestive Heart Failure, According to Retinal Microvascular Signs |
|---------------------------------|-------------|-----------------|-----------------|-----------------|
| Sign                          | No. at Risk | 7-Year Cumulative Incidence, % | Adjusted RR (95% CI)† | Multivariable-Adjusted RR (95% CI)‡ |
| Retinopathy                   |             |                               |                         |                              |
| Present                       | 719         | 15.1                          | 3.18 (2.50-4.04)       | 1.96 (1.51-2.54)              |
| Absent                        | 10,893      | 4.8                           | Reference              | Reference                   |
| Microaneurysms                |             |                               |                         |                              |
| Present                       | 427         | 17.3                          | 3.99 (3.03-5.26)       | 2.20 (1.61-3.01)              |
| Absent                        | 10,332      | 4.8                           | Reference              | Reference                   |
| Retinal hemorrhages           |             |                               |                         |                              |
| Present                       | 380         | 18.7                          | 3.69 (2.77-4.91)       | 1.89 (1.37-2.60)              |
| Absent                        | 10,855      | 4.9                           | Reference              | Reference                   |
| Soft exudates                 |             |                               |                         |                              |
| Present                       | 185         | 19.1                          | 4.02 (2.75-5.86)       | 1.87 (1.22-2.84)              |
| Absent                        | 11,245      | 5.1                           | Reference              | Reference                   |
| Arteriovenous nicking         |             |                               |                         |                              |
| Present                       | 1612        | 8.0                           | 1.46 (1.16-1.84)       | 1.18 (0.93-1.48)              |
| Absent                        | 9798        | 4.9                           | Reference              | Reference                   |
| Focal arteriolar narrowing    |             |                               |                         |                              |
| Present                       | 1649        | 7.2                           | 1.20 (0.95-1.52)       | 1.16 (0.90-1.48)              |
| Absent                        | 9,556       | 4.8                           | Reference              | Reference                   |
| Generalized arteriolar narrowing |         |                               |                         |                              |
| Present                       | 2151        | 8.1                           | 1.46 (1.18-1.81)       | 1.18 (0.95-1.48)              |
| Absent                        | 8622        | 4.7                           | Reference              | Reference                   |

Abbreviations: CI, confidence interval; RR, relative risk.
*Numbers at risk may not sum to 11,612 because data on all retinal microvascular signs are not available for some participants.
†Adjusted for age, sex, race, and field center.
‡Adjusted for age, sex, race, field center, educational levels, prevalent coronary heart disease, 6-year mean arterial blood pressure, use of antihypertensive medication, diabetes, glucose level, low-density lipoprotein cholesterol level, cigarette smoking, and body mass index.
ure cases in these patients are related to microangiopathic processes as evident by a retinal examination. These results therefore support the concept of a systemic microvascular effect on the myocardium in diabetes beyond the indirect effects of accelerated atherosclerosis, concomitant coronary heart disease, and hypertension. In contrast, among persons with hypertension but without diabetes, the population-attributable fraction was only 1.4%, suggesting that only a small proportion of CHF events in patients with hypertension may be related to microvascular mechanisms.

The strengths of our study include a large sample size with participants drawn from the general population rather than a specialized sample, the objective evaluation of retinal microvascular signs, and the standardized identification of incident CHF events. Certain limitations of this study need to be considered. First, CHF events were defined from hospitalization or death records. Self-report may result in underreporting of hospitalization, and milder CHF cases that did not require hospitalization were not included. The latter may limit the applicability of our results to a wider spectrum of CHF cases not requiring inpatient treatment. Additionally, data derived from death certificates may have limited accuracy and it is possible that some CHF events may have been misclassified, although less than 5% of CHF events in this analysis were based on death certificate data. Second, retinal photography data were available from only 1 eye for each patient, and some of the photographs were ungradable because of media opacity or poor pupil dilation, so that retinopathy status may have been misclassified. However, we have no reason to expect a biased presence of misclassification from these 2 factors. Third, although we controlled for hypertension and diabetes, it is possible that residual confounding from these conditions and other unmeasured CHF risk factors (such as valvular heart disease) could have affected these associations. Furthermore, in analyses among participants without preexisting coronary heart disease, a history of angina and the use of antianginal medications were not used as criteria for exclusion; thus, milder forms of coronary heart disease could be a confounder. Some signs of retinopathy can be caused by factors other than microvascular disease such as anemia and carotid artery disease, and it is possible that these factors could also play a role in the development of CHF independent of their effect on the microvasculature. Finally, diabetes can lead to both small- and large-vessel disease and could thus promote the development of retinopathy and CHF by separate pathways.

Our study has 2 potential clinical applications. First, our findings support the value of specifically targeting the microcirculation in trying to reduce cardiovascular morbidity and mortality, particularly in persons with diabetes. The UK Prospective Diabetes Study has already demonstrated the efficacy of aggressive glycemic control in reducing microvascular events (retinopathy, nephropathy) as well as risk of CHF in type 2 diabetes. There is increasing evidence that an antihypertensive agent such as an angiotensin-converting enzyme inhibitor may have direct beneficial effects on microvascular structure and function beyond its primary effect on lowering blood pressure. Such agents may therefore have added therapeutic value in preventing and treating CHF. Second, these findings raise the possibility that a retinal examination may improve risk prediction for CHF. In particular, patients with diabetes and signs of retinopathy may benefit from further assessment of CHF risk, such as echocardiography to detect asymptomatic left ventricular dysfunction, if clinically indicated.

In conclusion, we demonstrate a prospective association of retinopathy and risk of CHF hospitalization or deaths in healthy, middle-aged people in the community, even in those without pre-existing coronary heart disease, diabetes, or hypertension. Our study suggests that microvascular disease may play an important role in the pathogenesis of heart failure and that some asymptomatic persons with retinopathy on an ophthalmologic examination may benefit from further assessment of CHF risk.

Author Contributions: Dr Wong had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Study concept and design: Wong, Hubbard. Acquisition of data: Rosamond, Couper, Hubbard, Folsom, Klein. Analysis and interpretation of data: Wong, Rosamond, Chang, Couper, Sharrett, Hubbard. Drafting of the manuscript: Wong. Critical revision of the manuscript for important intellectual content: Wong, Rosamond, Chang, Couper, Sharrett, Hubbard, Folsom, Klein. Statistical analysis: Wong, Rosamond, Couper. Obtained funding: Hubbard. Administrative, technical, or material support: Rosamond, Hubbard, Klein. Study supervision: Hubbard.

Funding/Support: This study was supported by contracts N01-HC-35125, N01-HC-35126, N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55020, N01-HC-55021, and N01-HC-55022 from the National Heart, Lung, and Blood Institute. Additional support was provided by the Sylvia and Charles Viertel Clinical Investigator Award and the Biomedical Research Council Singapore ID’Wong.

Role of the Sponsors: The organizations funding this study had no role in the design and conduct of this study; the analysis and interpretation of data; or the preparation, review, or approval of the manuscript.

Acknowledgment: We thank the staff and participants in the ARIC study for their important contributions.

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