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Retinal Microvascular Abnormalities and their Relationship with Hypertension, Cardiovascular Disease, and Mortality

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Abstract. Retinal microvascular abnormalities, such as generalized and focal arteriolar narrowing, arteriovenous nicking and retinopathy, reflect cumulative vascular damage from hypertension, aging, and other processes. Epidemiological studies indicate that these abnormalities can be observed in 2–15% of the nondiabetic general population and are strongly and consistently associated with elevated blood pressure. Generalized arteriolar narrowing and arteriovenous nicking also appear to be irreversible long-term markers of hypertension, related not only to current but past blood pressure levels as well. There are data supporting an association between retinal microvascular abnormalities and stroke, but there is no convincing evidence of an independent or direct association with atherosclerosis, ischemic heart disease, or cardiovascular mortality. New computer-related imaging methods are currently being developed to detect the presence and severity of retinal arteriolar narrowing and other microvascular characteristics. When reliably quantified, retinal microvascular abnormalities may be useful as risk indicators for cerebrovascular diseases. (**Surv Ophthalmol 46:**59–80, 2001.

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Cardiovascular disease, including ischemic heart disease and stroke, remains the most common cause of death in the USA.[133] Traditional risk factors for cardiovascular disease, such as hypertension, hyperlipidemia, and cigarette smoking (among others) allow physicians to identify, monitor, and treat high-risk patients.[38,48,49,115,183,184,203,217,218,220] However, a substantial proportion of cardiovascular morbidity and mortality is not explained by these risk factors.[16,35,90,109,110,123,124,149,155,213] As a result, there is interest in finding additional variables for cardiovascular risk stratification.[69,105,106,138,140]

The retinal arteriole, which can be visualized easily and noninvasively, shares similar anatomical and physiological characteristics with the cerebral and

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coronary circulations.[7,43,63,200,201,210,211,216] Retinal microvascular abnormalities, such as generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, and retinopathy, reflect arteriolar damage from hypertension and other processes,[7,10–12,59,60,70–72,200,201,216] and have, therefore, been hypothesized as markers for cardiovascular disease.[63,210]

I. Historical Perspective

The potential of retinal microvascular abnormalities to serve as markers of cardiovascular disease was recognized as early as the late nineteenth century by Marcus Gunn, who described associations between retinal microvascular characteristics and hypertension, renal and cerebrovascular diseases.[65,66] Friedenwald and others suggested that these microvascular abnormalities were related to a systemic arteriosclerotic process.[53,136] In 1939, Keith, Wagener, and Barker showed that the severity of retinal microvascular abnormalities were predictive of mortality in patients with hypertension.[88] The 3-year survival of persons with Grade I changes (mild to moderate retinal arteriolar narrowing and sclerosis) was 70%, compared to only 6% in those with Grade IV changes (optic disk swelling). The authors concluded that "because the arterioles are small and are difficult to visualize in the peripheral organs—for example, in the skin, mucous membranes, and voluntary muscle—the retina, as seen through the ophthalmoscope, offers a unique opportunity for observing these small vessels clinically from time to time. Therefore, we think that certain visible changes of the retinal arterioles have been of exceptional value in affording a clearer clinical conception of altered arteriolar function throughout the body." Subsequently, Wagener et al,[206] Scheie,[170] Leishman,[113] Breslin et al,[23,24] and others,[15,32,50,52,113,136,142,164,169,181,202,205–207] went on to propose additional classification schemes for hypertensive retinopathy, and describe its association with cardiovascular disease and mortality.

However, more recently, there has been less clinical interest in retinal microvascular abnormalities for a number of reasons. First, the association between these abnormalities and cardiovascular disease has been demonstrated in some studies,[13,23,24,62,131,139,156] but not in others.[6,41,85] Most did not report specific cardiovascular outcomes (such as cause-specific mortality rates) or potential confounders (such as hypertension), were clinic- or hospital-based series, and had no appropriate control group.[23,24,41,85,139,156] Second, early studies were conducted in populations with untreated hypertension.[23,24,32,50,52,113,120,136,142,164,169,181,202,206,207] The more severe abnormalities described in these studies (e.g., Keith, Wagener and Barker's Grade III and IV retinopathy[88]) have been shown to be relatively uncommon in populations with better blood pressure control.[93,94,100,101,221] Third, despite many attempts to improve the earlier grading systems, there are still no accepted or standardized classification.[42,70,171,208] Finally, the detection of retinal microvascular abnormalities with ophthalmoscopy has been demonstrated to be subjective and unreliable.[6,41,42,85,171,208]

Over the last decade, new technologies have been introduced to quantify objectively retinal microvascular characteristics.[25–28,39,47,61,67,104,116,134,135,147,151,154,158,159,165,172,189,191,192,219] In the Atherosclerosis Risk in Communities (ARIC) study, retinal microvascular characteristics were evaluated from retinal photographs, using a standardized grading protocol.[79] In addition, generalized retinal arteriolar narrowing was quantified by measuring retinal vessel widths from high-resolution digitized photographs.[79,175] These grading methods have been shown to be fairly reliable.[79] In the ARIC study, retinal microvascular abnormalities were strongly related not only with current but also past blood pressure levels,[175] as well as a variety of markers for endothelial dysfunction and inflammation.[102] The ARIC study data also suggest strong associations with small subclinical stroke detected by MRI (Cooper LS, unpublished data, 2000), and incident clinical stroke (Wong TY, unpublished data, 2000), independent of blood pressure and other stroke risk factors.

As a result of new approaches to measure retinal arteriolar narrowing and new data regarding their associations with cardiovascular disease, we conducted this review to provide a summary of the pathology and epidemiology of various retinal microvascular abnormalities, their relationship to hypertension, cardiovascular disease and mortality, and their potential as markers for risk of cardiovascular disease.

II. Terminology and Definitions

In this review, retinal microvascular abnormalities or characteristics are used to include all retinal microvascular pathology. Retinal arteriolar changes refer to those abnormalities related to the retinal arterioles only, such as generalized and focal arteriolar narrowing, and arteriovenous (AV) nicking. Retinopathy is used to include all microvascular characteristics not explicitly arteriolar in nature, such as retinal hemorrhages, microaneurysms, cotton-wool spots, hard exudates, macular edema and optic disk swelling. Arteriosclerosis is a general pathological term used to define hardening and thickening of arterial wall and includes both atherosclerosis (large vessel arteriosclerosis) and arteriolosclerosis (small vessel arteriosclerosis).

III. Pathophysiology of Retinal Microvascular Abnormalities

Detailed pathophysiology of retinal microvascular abnormalities in hypertension are described elsewhere.[10–12,31,32,43,55,56,59,60,70,200,201] Retinal microvascular abnormalities are thought to be part of a spectrum of pathological processes that involve not only the retinal but also the choroidal and optic nerve circulation.[201,202] The changes appear to be associated with both aging (age-related "hardening" of the arteriolar wall, or arteriosclerosis) and elevated blood pressure (increased arteriolar tone, vasospasm, media hyperplasia and intimal thickening).[7,12,59,60,70,108,200,201] Some of the lesions appear to represent transient alterations of retinal arterioles to periods of elevated blood pressure, while others represent permanent structural damage from sustained hypertension.[7,12,59,60,200,201]

Tso and colleagues have divided the retinal microvascular changes into four overlapping phases.[200,201] The pathological changes and corresponding clinical features in each phase will be briefly described.

A. VASOCONSTRICTIVE PHASE

Elevated blood pressure has been observed to cause an increase in arteriolar tone by autoregulatory processes, leading to generalized retinal arteriolar narrowing (Fig. 1).[12,60,200] However, this is usually seen only in vessels without significant arteriosclerosis. In vessels with moderate to severe arteriosclerosis, arteriolar narrowing may be patchy, with areas of focal narrowing (in segments without sclerosis) and dilatation (in sclerotic segments) occurring simultaneously. Thus, generalized retinal arteriolar narrowing appears to be more prominent in younger persons than in older persons with similar severity of hypertension. The primary site of the vasoconstriction process appears to be the precapillary arteriole.[60] Arteriolar narrowing is, therefore, most prominent in second- and third-order arterioles, and less common in arterioles closer to the disk.

B. SCLEROTIC PHASE

Persistently elevated blood pressure may lead to the sclerotic phase, which manifests pathologically as hyperplasia of the tunica media and hyaline degeneration of the arteriolar wall. Clinically, this is associated with generalized arteriolar narrowing, AV nicking (Fig. 2A), focal arteriolar narrowing (Fig. 2B), alteration in the arteriolar light reflex, arteriolar tortuosity, and an increase in the angle of arteriolar branching.[187,200,201] These changes correspond to the Keith, Wagener and Barker's Grade I and II hypertensive retinopathy classification.[88]

C. EXUDATIVE PHASE

The exudative phase occurs with sustained hypertension, although the exact pathophysiological alterations in this phase are not clear.[200,201] Ashton and coworkers described disruption of the blood–retinal barrier, with degeneration of vascular smooth muscle and endothelial cell necrosis leading to blood and fluid exudation.[11,12] However, Tso and colleagues have challenged this hypothesis, as exudation has been observed without concomitant endothelial necrosis.[200,201] Other pathological changes include fibrinoid necrosis of the arteriolar wall, narrowing of the arteriolar lumen, impairment of blood flow, and ischemic complications.[11,12,59,60,200,201] The classical features are the appearance of microaneurysms and retinal hemorrhages (Fig. 3A), which can occur in the superficial nerve fiber layer (clinically corresponding to flame-shaped hemorrhages), the deeper layers of the retina (blot and dot hemorrhages), and in the subhyaloid space (boat-shaped pre-retinal hemorrhage). There is also leakage of plasma lipoproteins, phospholipids, cholesterol and triglycerides (hard exudates), and disruption of axoplasmic transport mechanism with ischemia of the nerve fiber layer (cotton-wool spots, Fig. 3B).[10–12,59,60,70–72,200,201] Disk swelling can occasionally be seen at this time (Fig. 4). These changes correspond to the Keith, Wagener and Barker's Grade III and IV hypertensive retinopathy[88] and are less frequently observed in contemporary hypertensive populations due to better control of blood pressure.[93,94,100–102,221]

D. COMPLICATIONS PHASE

With longstanding hypertensive and arteriosclerotic changes in the vessels, retinal and vitreous complications develop. These include arteriolar thrombosis, central or branch retinal artery and vein occlusions, macroaneurysms, cystoid macular edema, and proliferative vitreoretinopathy.[82,200,201]

Despite the better understanding of the pathology of hypertensive retinopathy, there are a number of unresolved issues. First, the natural history is not clear. Tso has emphasized that the stages described are not meant to be sequential; for example, the exudative phase has been observed to occur before the sclerotic phase.[200] Second, most of the existing data are derived from animal models.[11,12,60,70–72] The exact pathophysiological basis of the clinical signs seen in humans remains to be determined. Finally, current pathological data do not explain all the clinical changes observed. For example, dilatation of narrowed arterioles with aggressive blood pressure lowering has been observed clinically in one study,[157] but not in another.[19] Spontaneous resolution of exudative retinopathy has been described in hyperten-

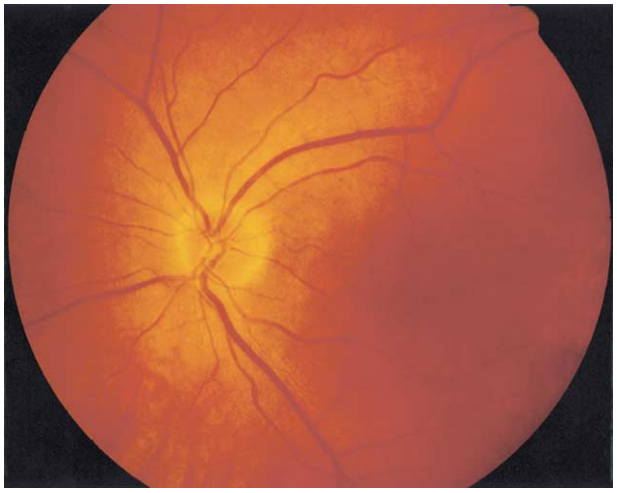

Fig. 1. Fundus photograph showing generalized arteriolar narrowing.

sive persons with uncontrollable blood pressures,[114] but whether similar resolution occurs pathologically is not known. Even the mechanisms of blood pressure lowering may have an effect on the retinal arteriolar calibers. In a clinical trial of hypertension treatment comparing enalapril (an angiotensin converting enzyme inhibitor) and hydrochlorothiazide (a diuretic), altered light reflexes, arteriolar narrowing, and AV nicking were clinically observed to resolve in the group treated on enalapril, but persisted in the group treated with hydrochlorothiazide, despite similar blood pressure control.[36] The authors hypothesized that enalapril exerts a positive influence on the microcirculation, in addition to blood pressure control.

IV. Epidemiology of Retinal Microvascular Abnormalities

The original descriptions of retinal microvascular abnormalities were in persons with hypertension and renal disease.[65,66,113,102,136,169,206,207] Similar abnormalities were later described in persons without hypertension,[31,113,170,211,212] in persons with carotid artery disease,[18,76,87] and in persons with AIDS.[54] Until recently, however, limited data on the prevalence and incidence of these abnormalities existed (Table 1).

A. PREVALENCE AND INCIDENCE

In the Framingham Eye Study, 2.5% of participants who had a dilated screening ophthalmoscopic examination were observed to have retinopathy.[113] After excluding persons with diabetes, the prevalence of retinopathy was only 0.8%. Rates of AV

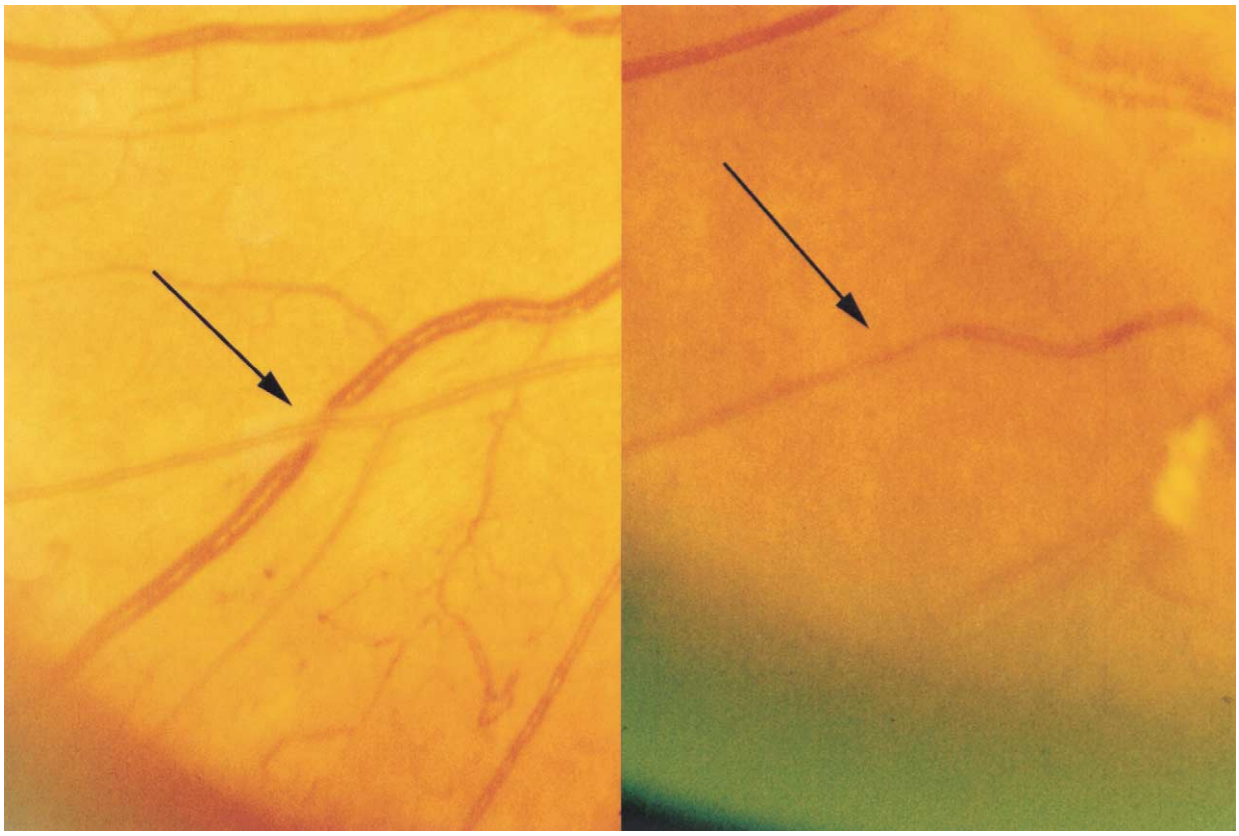

Fig. 2. Fundus photograph showing (*left*) arteriovenous nicking and (*right*) focal arteriolar narrowing.

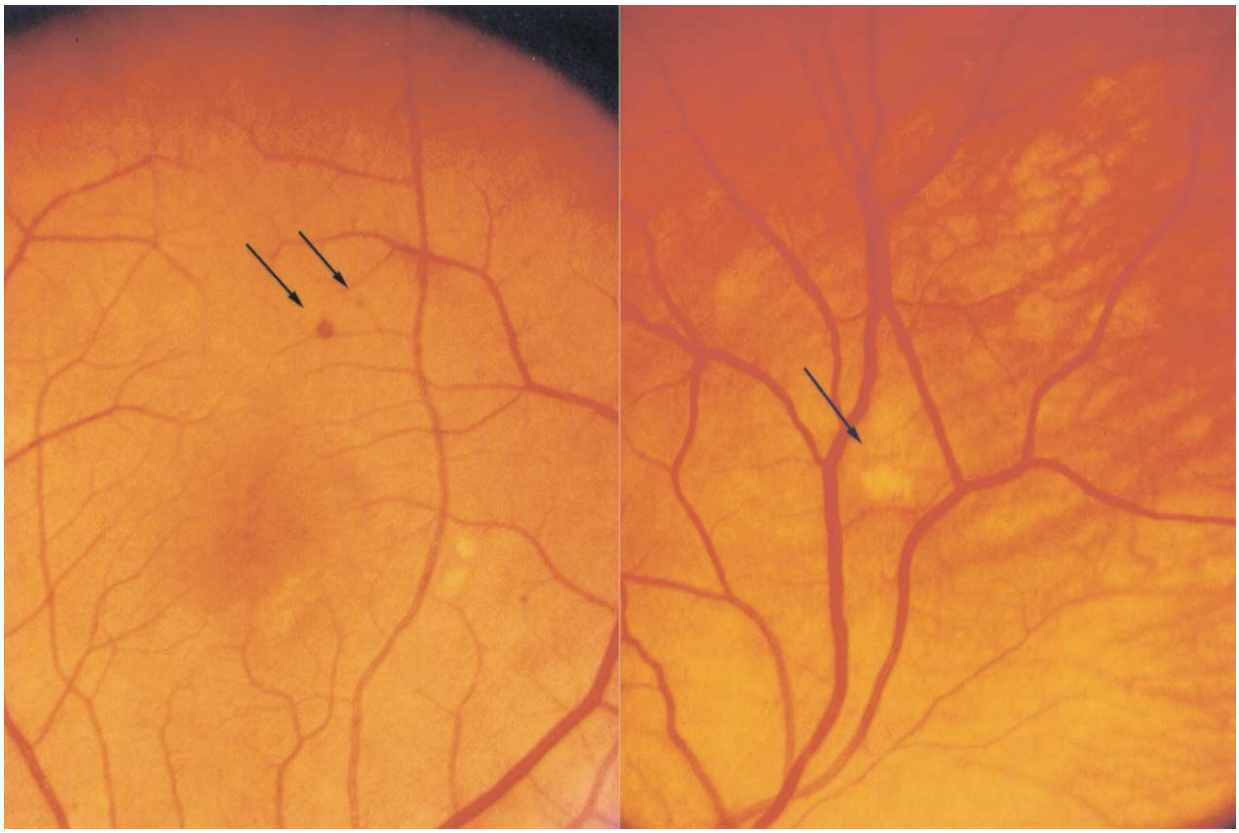

Fig. 3. Fundus photograph showing (*left*) microaneurysm and retinal hemorrhage and (*right*) cotton-wool spot.

nicking and focal arteriolar narrowing were not reported.

In a series of reports from the Beaver Dam Eye study in Wisconsin, Klein and colleagues described in detail the prevalence[93,100,101] and 5-year incidence[94] of retinal microvascular abnormalities, and their relationship with hypertension in a white nondiabetic population aged 43–86 years. In this cohort, retinal microvascular characteristics were objectively graded, using 30-degree stereoscopic color fundus photographs based on a standardized protocol.[92,95–99] The prevalence of focal retinal arteriolar narrowing was 14%, retinopathy 8%, and AV nicking 2%.[100,101] After 5 years, the incidence of these changes was observed to be 10%, 6%, and 7%, respectively.[95] Even when persons with hypertension were excluded, the prevalence of focal arteriolar narrowing was 11%, retinopathy 6%, and AV nicking 2%. Based on these data, Klein and colleagues have suggested that retinal microvascular abnormalities are common in the general nondiabetic population, although they are more prevalent in persons with hypertension.

In the Blue Mountains Eye Study in Australia, using a photographic grading technique similar to that used in Beaver Dam, the prevalence of retinopathy was reported at 10%.[221] Although this was slightly higher than in Beaver Dam study, the age-specific rates of retinopathy in men and women were similar between the two studies.[100,101,221] Rates of other retinal changes were not reported in the Blue Mountains study.

In the ARIC study, retinal microvascular characteristics were graded from a single 45-degree retinal photograph of one randomly selected eye, using a similar standardized protocol.[79] The prevalence of

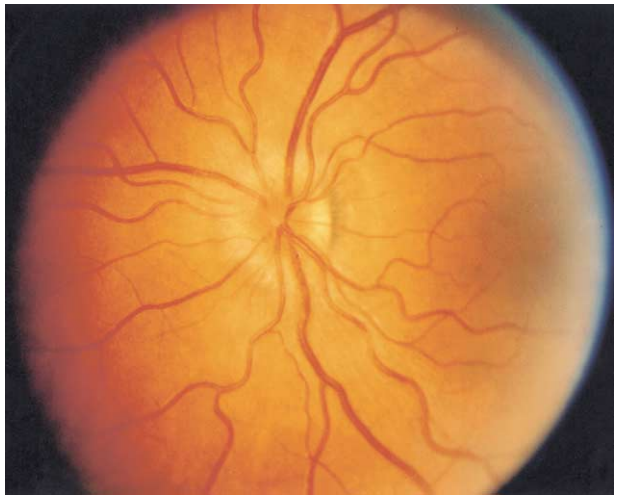

Fig. 4. Fundus photograph showing disk swelling in malignant hypertension.

focal arteriolar narrowing was 6%, retinopathy 3%, and AV nicking 6%. The higher prevalence of retinopathy observed in Beaver Dam, Blue Mountains, and the ARIC study, compared to Framingham, may be due to the higher sensitivity of photographic grading techniques over clinical ophthalmoscopy.

Four other studies provide additional prevalence data, but include persons with diabetes (Table 1); observed rates therefore do not necessarily reflect the true frequencies in the nondiabetic general population.[120,174,188,193] Further, in three of these studies, it is not clear that a standardized protocol was used to detect retinal microvascular abnormalities.[120,174,193] The one exception was the Rotterdam Study in Holland, where standardized photographic grading was performed. In Rotterdam, the prevalence of retinopathy was reported to be 5%.[188] The lower prevalence of retinopathy, compared to Beaver Dam, was attributed to different photographic grading techniques (e.g., stereoscopic pictures were not used in Rotterdam).

B. DEMOGRAPHIC VARIATIONS

Data from both Beaver Dam and the ARIC study suggest that focal arteriolar narrowing and AV nicking appear to be age-dependent changes.[94,100–102] In contrast, the relation between retinopathy and age is not clear. In Beaver Dam and Blue Mountains, the prevalence of retinopathy was age-dependent,[100,101,221] but in the ARIC study, it was not.[102]

There is no consensus regarding the relationship between the different retinal microvascular abnormalities and sex. A higher age-adjusted prevalence of retinopathy was seen in men than women in both Beaver Dam and the ARIC study.[100–102] However, in Blue Mountains and Rotterdam, no sex difference was observed.[188,221] In a study in Evans County, Georgia, the prevalence was in fact higher in women than men.[120] In Beaver Dam, the age-adjusted prevalence of AV nicking was lower, but the prevalence of focal narrowing was similar in men compared with women.[100,101] However, in the ARIC study, no sex difference for either characteristic was observed.[94] There are no adequate explanations for these apparently inconsistent findings between men and women.

Limited data on racial variation are currently available. In Evans County, the prevalence of all retinal microvascular abnormalities was higher in blacks than whites.[120] In the ARIC study, a higher prevalence of retinopathy and AV nicking, but lower prevalence of focal arteriolar narrowing, was seen in blacks than whites.[79] In a study in London, retinopathy was more frequent in persons of Afro-Caribbean origin than those of European origin.[174] The higher prevalence of retinopathy has been hypothesized to be related to a higher prevalence of severe hypertension among black persons.[79,174]

In summary, available epidemiological data suggest that retinal microvascular abnormalities can be found in 2–14% of the general nondiabetic population, and are fairly common even in persons without hypertension. Focal retinal arteriolar narrowing and AV nicking, but probably not retinopathy, appear to be age-dependent changes. The variation with sex is not clear, based on available data, but differences in race may be explained in part by differences in rates of hypertension. Furthermore, dissimilarity in population sampling, definitions of retinal microvascular abnormalities and methodology of retinal assessment complicate comparison between studies.

V. Relationship between Retinal Microvascular Abnormalities and Hypertension, Cardiovascular Disease, and Mortality

A. RELATIONSHIP WITH HYPERTENSION

Numerous studies have reported that retinal microvascular abnormalities are related to both the presence and severity of hypertension[3,13,17,23–28,37,80,88,93,94,100,101,113,122,123,125,139,141,143,144,152,164,169,174–177,197,198,202,206,207,221] and left ventricular hypertrophy.[23,24,36,139,153,163,176–178] Selected studies are presented in Table 2, and a summary of the relation between a specific abnormality and hypertension is presented in Table 3.

Data from population-based studies show that retinal microvascular abnormalities are consistently more frequent in persons with hypertension than in those without.[93,94,100,101,175,193,221] In the Beaver Dam Eye study, both the prevalence[100,101] and 5-year incidence[95] of retinal microvascular abnormalities were higher in hypertensive than in normotensive persons. After controlling for age, persons with hypertension were more likely to have retinopathy (odds ratio of 1.5 and 1.7, in men and women, respectively), focal arteriolar narrowing (1.3 and 1.4), and AV nicking (1.8 and 1.7).[100] Furthermore, hypertensive persons whose blood pressure was elevated despite use of antihypertensive medications had higher risk, compared with those whose blood pressure was controlled with medications and those who were normotensive. Similar associations between retinopathy and blood pressure were demonstrated in the Blue Mountains Eye Study (odds ratio of 1.5 and 1.7 in men and women, respectively).[221]

The strength of association between retinal microvascular abnormalities and hypertension has been observed to vary with age,[79,100,175] and race,[1,79,84,107,120,174] but inconsistently with sex.[94,100,174,175,221] The association appears to be stronger in younger compared to older persons,[79,100,175] and whites compared to blacks.[79,175] The reasons for these variations are not known, but are likely related to demographic

TABLE 1

Prevalence and Incidence of Retinal Microvascular Characteristics (Population-based studies, most recent listed first)

Study and Location	Population	Method of Quantifying Characteristics	Prevalence and Incidence of Retinal Arteriolar Abnormalities				
			Generalized Arteriolar Narrowing	Focal Arteriolar Narrowing	AV Nicking	Retinopathy	Reference
ARIC Study, four U.S. communities	9300 nondiabetic persons	Standardized photographic grading, and computer-assisted measurement of retinal vessels from digitized images	Not applicable[2]	6.4% (At the disc) 7.3% (Elsewhere)	5.9%	3.3%	Klein et al[102]
Blue Mountains Eye Study, Australia	3275 nondiabetic persons	Standardized photographic grading	–	–	–	9.9%	Yu et al[221]
Rotterdam Eye Study, Holland	6191 persons	Standardized photographic grading	–	–	–	4.9%	Stolk et al[188]
Beaver Dam Eye Study, Wisconsin	4420 nondiabetic persons	Standardized photographic grading	–	13.5% 9.9%[1]	2.2% 6.5%[1]	7.8% 6%[1]	Klein et al[94,100,101]
Gothenburg, Sweden	855 men, aged 50 years	Ophthalmoscopic and photographic grading	15.4%	6%	8.9%	0.4%	Svardsudd et al[193]
London, England	651 persons	Photographic grading	–	–	–	14.7%	Sharp et al[174]
Framingham Eye Study, Massachusetts	2375 nondiabetic persons	Ophthalmoscopic grading	–	–	–	0.9%	Leibowitz et al[112]
Evans County, Georgia	2210 persons	Ophthalmoscopic grading	34%[3]	34%[3]	13.2%	2.2%	McDonough et al[120]

[1] Five-year incidence data are available from the Beaver Dam Eye Study.
[2] In ARIC, generalized arteriolar narrowing was quantified as a continuous variable.
[3] The percentage shown includes any arteriolar narrowing (generalized and focal) and altered arteriolar light reflex.

TABLE 2

Relationship Between Retinal Microvascular Abnormalities and Hypertension (Selected Studies, with Most Recent Listed First)

Type of Study	Population	Method of Quantifying Characteristics	Classification	Summary of Main Findings	References
Population-based (ARIC Study)	9300 nondiabetic persons	Computer-assisted grading of generalized arteriolar narrowing form digitized retinal photographs. Photographic grading of focal arteriolar narrowing, AV nicking and retinopathy.	Generalized arteriolar narrowing, measured on a continuous scale. Focal narrowing, AV nicking, retinopathy, and retinopathy classified as present versus absent.	Related of hypertension. Generalized arteriolar narrowing and AV nicking related to current and past BP (measured 3 and 6 years ago). Focal narrowing and retinopathy related to current, but not past BP.	Sharrett et al[175]
Clinic-based	174 untreated hypertensive persons	Ophthalmoscopic grading using modified KWB classification.	Grade I to IV	Related to left ventricular hypertrophy by echocardiography.	Saitoh et al[162]
Population-based	651 persons	Ophthalmoscopic grading using modified KWB classification.	Grade I to IV	Related to hypertension. Stronger relationship in Europeans compared to Afro-Caribbeans.	Sharp et al[174]
Population-based (Beaver Dam Eye Study)	4420 nondiabetic persons	Photographic grading of focal arteriolar narrowing, AV nicking and retinopathy.	Each change classified as present versus absent.	Related to hypertension. Stronger relationship in persons whose BP was uncontrolled despite use of hypertensive medications.	Klein et al[94,97,100,101]
Clinic-based	348 hypertensive persons	Ophthalmoscopic grading using the KWB classification.	Grade I to IV	Related to hypertension. Related to 24 hour BP.	Palatini et al[141]
Clinic-based	25 hypertensive persons	Ophthalmoscopic and photographic grading using KWB classification.	Grade I to IV	Grade I and II changes not related to hypertension.	Dimmit et al[41]
Clinic-based	28 hypertensive persons	Photographic grading using modified KWB classification.	Grade I to IV	Related to hypertension and left ventricular hypertrophy by echocardiography.	Dahlof et al[36]
Population-based	855 men aged 50 years	Ophthalmoscopic and photographic grading of generalized and focal arteriolar narrowing, AV nicking and retinopathy.	Each change classified as not present versus absent	Related to hypertension.	Svardsudd et al[193]
Clinic-based	50 hypertensive persons and 100 normotensive controls	Photographic grading of generalized and focal arteriolar narrowing, AV nicking.	AV nicking classified as present versus absent. No specific classification of generalized and focal narrowing.	AV nicking related to hypertension. Generalized and focal narrowing not related to hypertension.	Stokoe and Turner[187]
Clinic-based	220 subjects with heart diseases	Ophthalmoscope grading of generalized arteriolar narrowing, AV nicking and retinopathy.	Grade I to VI	Related to hypertension and to cardiomegaly by eletrocardiographic definition.	O'Sullivan et al [139]
Clinic-based	540 hypertensive persons	Ophthalmoscopic grading using modified KWB classification.	Grade I to IV	Related to hypertension and cardiomegaly by electrocardiographic definition.	Breslin et al[23,24]
Clinic-based	108 hospitalized persons with hypertension	Ophthalmoscopic grading (Keith, Wagener and Barker classification).	Grade I to IV	Related to hypertension.	Keith, Wagener and Barker[88]

AV nicking = Arteriovenous nicking; BP = Blood pressure; KWB = Keith, Wagener, Barker classification.[88]

variation in the severity of hypertension or retinal arteriolosclerosis. Similar age and race patterns have also been observed between retinal microvascular abnormalities and ischemic heart disease (see Section V.C), which suggest that the retinal abnormalities may be better indicators of cardiovascular risk in those who are younger and of Caucasian ethnicity.

The relation between retinal microvascular characteristics and past blood pressure levels was also evaluated in the ARIC study. Generalized retinal arteriolar narrowing and AV nicking (but not focal arteriolar narrowing and retinopathy) were found to be related to past blood pressure levels measured 3 and 6 years before the retinal assessment, even after adjustment for current blood pressure levels.[175] This suggests that generalized arteriolar narrowing and AV nicking may be microvascular markers of cumulative hypertensive damage.

B. RELATIONSHIP WITH ATHEROSCLEROSIS

The relationship between retinal microvascular abnormalities and atherosclerosis is weak (Table 4). Most studies have drawn conclusions based on indirect and circumstantial associations between these abnormalities and either risk factors for atherosclerosis (e.g., hypertension, hyperlipidemia, and smoking) or cardiovascular diseases secondary to atherosclerosis (e.g., ischemic heart disease) rather than on the direct quantification of atherosclerosis itself.[126,173,193,199]

The association between retinal microvascular abnormalities and hypertension has already been noted in Section V.A. In contrast, the relationships with hyperlipidemia and smoking are inconsistent. One study found an association between serum total cholesterol and smoking with generalized retinal arteriolar narrowing, focal arteriolar narrowing, and AV nicking, after controlling for blood pressure.[193] In Beaver Dam, serum total cholesterol or HDL cholesterol was not related to any retinal microvascular characteristics, and current smoking status was weakly related only to AV nicking, after controlling for age, sex, and hypertension (Klein R, unpublished data, 2000).

In the ARIC study, associations between retinal microvascular abnormalities, clinical atherosclerotic artery disease, and subclinical markers of atherosclerosis were inconsistent.[102] For example, although generalized retinal arteriolar narrowing was related to the presence of carotid artery plaque (as detected via ultrasonography), smoking, serum triglyceride, and HDL cholesterol levels, it was not related to serum total cholesterol levels, carotid artery thickening, or popliteal artery plaque and thickening. In contrast, AV nicking was associated with carotid artery thickening, popliteal artery plaque and thickening, but not with carotid artery plaque and serum total cholesterol levels.

In the ARIC study, new associations were observed for a number of hematological alterations. Generalized arteriolar narrowing was associated with elevated white cell counts, elevated fibrinogen levels, and reduced albumin levels, whereas AV nicking was associated with elevated serum von Willebrand factor and Factor VIII. These hematological factors have been previously reported as markers for inflammation[33,57] and endothelial dysfunction.[89,90,118] Whereas inflammation has been implicated in the pathogenesis of atherosclerosis,[161] the relationship between endothelial dysfunction and atherosclerosis is not clear. Thus, the significance of these associations awaits further research.

C. RELATIONSHIP WITH ISCHEMIC HEART DISEASE

Few studies have directly investigated the relationship between retinal microvascular characteristics and ischemic heart disease (Table 5). In a large cross-sectional study based on the National Health Examination Survey, persons with retinal arteriolar changes, as detected on ophthalmoscopy, were more likely to have prevalent ischemic heart disease, after controlling for hypertension, diabetes, and serum cholesterol levels.[62] The strength of association was stronger in women than in men, and in younger persons than in older persons (odds ratio of 6.4 vs 3.7 between women and men aged 35 to 54, and 2.4 vs 1.2 between women and men aged 55 to 79). Other studies have described varying associations with incident ischemic heart disease,[148] ischemia-related changes on electrocardiogram,[23,24] and presence and severity of coronary artery blockage on angiography.[126] However, most of these studies were limited by imprecise ascertainment of retinal lesions by ophthalmoscopy. At the same time, data from other studies, including the ARIC study, show no association between retinal microvascular characteristics and ischemic heart disease or myocardial infarction.[102,117,193]

D. RELATIONSHIP WITH STROKE

In contrast to the inconsistent relationship with ischemic heart disease, several epidemiological studies have shown that retinal microvascular abnormalities are independently related to stroke, even taking into account blood pressure and other stroke risk factors (Table 5).[4,5,8,103,131,137,166,167,179,195,196] In Japanese populations, various associations with prevalent strokes,[4,5,166] 6-year incident ischemic strokes,[137] 15-year incident ischemic and hemorrhagic strokes in men (but not women),[122] and subclinical strokes diagnosed through MRI[103] have been reported. In addition, data from autopsy studies[44] and animal models[68] provide a biological basis for the clinical associations observed.

TABLE 3

Relationship Between Specific Retinal Microvascular Abnormality and Hypertension, Cardiovascular Diseases and Mortality

Retinal Arteriolar Characteristic	Relationship of Characteristic with:			
	Hypertension	Atherosclerosis	Cardiovascular diseases	Mortality
Generalized arteriolar narrowing	Related to current and past BP levels.[175] Prevalence related to hypertension.[193]	Related to presence of carotid artery plaque and triglyceride and HDL levels.[102]	Related to MRI-detected subclinical stroke.[1]	Not related to 12-year all-cause mortality.[193]
Focal arteriolar narrowing	Related to current BP levels.[175] Prevalence and incidence related to hypertension.[94,100]	Not related to any risk factors or clinical outcomes of atherosclerosis.[102]	Related to MRI-detected subclinical stroke.[1] Related to 12-year incidence of clinical stroke.[193]	Related to 12-year cancer mortality.[193]
AV nicking	Related to current and past BP levels.[175] Prevalence but not incidence related to hypertension.[94,100]	Related to carotid artery thickening, popliteal artery plaque and thickening, and HDL levels.[102]	Related to MRI-detected subclinical stroke.[1] Related to 12-year incidence of clinical stroke.[193]	Related to 12-year cardiovascular and all-cause mortality.[193]
Retinopathy	Related to current BP levels.[175] Prevalence and incidence related to hypertension.[94,100,221]	Related to carotid artery plaque and total cholesterol levels.[102]	Related to MRI-detected subclinical stroke.[1]	Not related to 12-year all-cause mortality.[193]

AV nicking = Ateriovenous nicking; BP = Blood pressure; HDL = High-density lipoprotein.
[1]Cooper LS, unpublished data, 2000.

Few studies have been conducted outside Japan, where risk factors, at least for hemorrhagic stroke, may be different.[179,195] In a study from Gothenburg, Sweden, retinal microvascular changes were related with 12-year incidence of clinical stroke.[193]

In the ARIC study, the association between retinal microvascular abnormalities and stroke was recently evaluated. Strong associations were found for both MRI-detected subclinical stroke and incident clinical stroke, independent of blood pressure levels and other established risk factors for stroke (blood glucose, lipids, use of antihypertensive and diabetic medications, and smoking status). For MRI-stroke, the adjusted odds ratio was 2.3 for generalized retinal arteriolar narrowing, 2.0 for AV nicking, and 1.9 for focal arteriolar narrowing. The association was significantly stronger in persons with hypertension (adjusted odds ratios of 3.2, 2.5, and 2.0 for respective retinal lesions) (Cooper LS, unpublished data, 2000). For 3-year incident clinical stroke, the adjusted relative risks ranged from 1.6 for AV nicking to 3.1 for microaneurysms (Wong TY, unpublished data, 2000).

E. RELATIONSHIP WITH MORTALITY

The evidence for an association between retinal microvascular characteristics and mortality is presented in Table 6. Keith, Wagener, and Barker's study was among the first to show a dose-dependent increase in mortality with severity of retinal changes.[88] Other studies conducted in the 1950s and 1960s showed similar mortality findings in persons with hypertension.[22–24,52,142,176] In general, inferences from these studies are limited for reasons noted already, including subjective evaluation of retinal microvascular characteristics, lack of data on cause-specific mortality rates, and inadequate control for potential confounders. In Gothenburg, Sweden, after controlling for systolic blood pressure and other risk factors, 50-year-old men with focal arteriolar narrowing or AV nicking were observed to have increased 12-year all-cause and cardiovascular mortality rates.[193] An unexpected association with cancer and other non-noncardiovascular-related mortality was also found. The authors hypothesized that retinal lesions might be markers for overall health and not necessarily for cardiovascular health only. However, the relationship with cancer and noncardiovascular mortality has not been confirmed elsewhere. In another study based on a population of 2859 men and women aged 40 to 65 years in the Netherlands, retinal microvascular abnormalities, as detected by ophthalmoscopy, were associated with slightly higher 15-year all-cause mortality in men (relative risk of 1.4) and 25-year all cause mortality in women (relative risk of 1.3), after adjusting for blood pressure, cholesterol, smoking, proteinuria, and relative

TABLE 4

Relationship Between Retinal Microvascular Abnormalities and Atherosclerosis (Selected Studies, Most Recent Listed First)

Type of study	Population	Method of Quantifying Changes	Classification	Associations	References
Population-based (ARIC study)	9300 nondiabetic persons	Computer-assisted grading of generalized arteriolar narrowing from digitized retinal photographs. Photograph grading of focal arteriolar narrowing, AV nicking and retinopathy.	Generalized arteriolar narrowing, measured on continuous scale. Focal narrowing, AV nicking retinopathy and retinopathy classified as definite versus questionable/absent.	Generalized arteriolar narrowing related to carotid plaque, smoking, obesity, TG and HDL levels. AV nicking related to carotid thickening, popliteal plaque and popliteal thickening. Focal narrowing related to carotid plaque. Retinopathy related with carotid plaque and history of stroke.	Klein et al[102]
Population-based (Beaver Dam Eye study)	4926 nondiabetic subjects	Photograph grading of focal narrowing, AV nicking and retinopathy.	Each change classified as definite versus questionable/absent.	AV nicking related to smoking. Focal narrowing and retinopathy not related with smoking or lipid levels.	Klein R (unpublished data, 2000)
Clinic-based	25 hypertensive persons	Ophthalmoscope and photographic grading using KWB classification.	Grade I to IV.	Not related to smoking or cholesterol.	Dimmit et al[41]
Population-based	855 men aged 50 years	Ophthalmoscope grading of generalized arteriolar narrowing, focal narrowing, broadened light reflex, AV nicking and retinopathy.	Each change classified as not present, present or marked.	Generalized arteriolar narrowing, focal narrowing and AV nicking related to smoking and cholesterol.	Svardsudd et al[193]

AV nicking = Arteriovenous nicking; TG = Triglyceride; HDL = High density lipoprotein; KWB = Keith, Wagener, Barker classification.[88]

TABLE 5

Relationship Between Retinal Microvascular Abnormalities and Cardiovascular Disease (Selected Studies, Most Recent Listed First)

Type of Study	Population	Method of Quantifying Changes	Classification	Associations	References
Population-based (ARIC study)	1849 nondiabetic persons	Computer-assited grading of generalized arteriolar narrowing from digitized retinal photographs. Photograph grading of focal arteriolar narrowing, AV nicking and retinopathy.	Generalized arteriolar narrowing, measured on continuous scale. Focal narrowing, AV nicking retinopathy and retinopathy classified as definite versus questionable/absent.	Related to MRI-detected subclinical stroke (OR 2.3 for generalized narrowing, 1.9 for focal narrowing and 2.0 for AV nicking), after controlling for BP and other risk factors. Relationship stronger in persons with hypertension.	Cooper LS, (unpublished data, 2000)
Clinic-based	933 neurologically normal persons	Photograph grading of retinal arteriolar changes using KWB classification.	Present (KWB Grade I or higher) versus absent.	Related to MRI-detected subcortical thrombotic stroke (OR 2.1), after controlling for BP and other risk factors.	Kobayashi et al[103]
Population-based (NHES)	6672 persons	Ophthalmoscope grading of generalized arteriolar narrowing, AV nicking, tortuosity and increased light reflex.	Classified as positive (Any change present) versus negative.	Related to definite IHD in white men and women aged 35 to 54 years (OR 3.7 and 6.4, respectively) and white women aged 55 to 79 years (OR 2.4), after controlling for BP and cholesterol. Related to IHD in black men and women (overall OR 4.0).	Gillum[62]
Clinic-based	70 nondiabetic, nonhypertensive persons undergoing coronary angiography	Ophthalmoscope grading of generalized arteriolar narrowing, AV nicking, vessel tortuosity and light reflex changes.	Generalized arteriolar narrowing classified as normal, mild, moderate and considerable. AV nicking and vessel tortuosity classified as normal, mild, moderate and marked. Light reflex changes classified in as Grade 0 to IV.	Abnormal light reflex sensitive indicator of presence and extent of angiographically-defined IHD. Generalized arteriolar narrowing and vessel tortuosity specific but less sensitive indicator.	Michelson et al. [126]
Population-based	2303 persons	Photograph grading of retinal arteriolar changes using KWB classification.	Classified as definite versus none.	Related to 15-year incident stroke in men (OR 4.5), after controlling for BP and other risk factors.	Nakayama[131]
Population-based	855 men aged 50 years	Ophthalmoscope grading of generalized arteriolar narrowing, focal narrowing, broadened light reflex, AV nicking and retinopathy.	Each change classified as not present, present or marked.	Focal narrowing and AV nicking related to 12-year incident stroke. Not related to myocardial infarct.	Svardsudd et al[193]

(*continued*)

TABLE 5
Continued

Type of Study	Population	Method of Quantifying Changes	Classification	Associations	References
Population-based	4186 persons	Ophthalmoscope grading of retinal arteriolar changes using KWB classification and Scheie classification.	Present (KWB Grade II or higher) versus absent.	Related to 6-year incident thrombotic stroke. Not related to hemorrhagic stroke.	Okada et al[135]
Population-based	115 stroke cases and 230 controls	Ophthalmoscope grading of generalized arteriolar narrowing, focal narrowing, altered light reflex, AV nicking and retinopathy.	Each change classified as present or absent	Generalized narrowing, focal narrowing and retinopathy related to hemorrhagic stroke, after controlling for BP and other risk factors. Altered arteriolar reflex, focal narrowing and AV nicking related to thrombotic stroke.	Aoki[4,5]

AV nicking = Arteriovenous nicking; BP = Blood pressure; OR = Odds ratio; IHD = Ischemic heart disease; NHES = National Health Examination Survey; KWB = Keith, Wagener, Barker classification.[88]

weight.[170] However, cause-specific mortality rates were not reported in this study.

In summary, epidemiological studies indicate a strong association between presence and severity of retinal microvascular abnormalities and hypertension. A fairly consistent association with stroke, perhaps independent of blood pressure, has also been shown. However, there are few recent data on the association between retinal microvascular abnormalities and atherosclerosis, ischemic heart disease, and cardiovascular and noncardiovascular mortality. Therefore, further prospective studies with precise definition of retinal lesions, specific cardiovascular endpoints, cause-specific mortality data and appropriate control of potential confounders are needed to assess the significance and utility of these changes as markers for cardiovascular health.

VI. Evaluation Techniques

A. RETINAL MICROVASCULAR ABNORMALITIES

The evaluation of retinal microvascular characteristics through direct visualization with the ophthalmoscope has been demonstrated to be subjective and unreliable.[6,41,85] Kagan et al described large interobserver (20–42%) as well as intraobserver (10–33%) variations in the assessment of different retinal lesions with direct ophthalmoscopy,[85] while Dimmitt et al showed that direct ophthalmoscopy was particularly unreliable in persons with mild to moderate hypertension.[41]

Developments in the evaluation of diabetic retinopathy for clinical trials using stereoscopic retinal photographs, standardized protocols, and masked graders led to more precise and objective quantification of the retinal microvascular changes.[40,46,128] These techniques have been adopted for use in several population-based studies, such as the Beaver Dam Eye Study, the ARIC study, the Blue Mountains Eye Study, and the Rotterdam Study.[79,94,100,101,188,221]

Generalized retinal arteriolar narrowing is one of the earliest signs of hypertensive retinopathy, but also the most difficult to quantify objectively. The concepts and approaches for measuring retinal arteriolar caliber and quantifying arteriolar narrowing will be described in the following section to highlight the evolution, problems, and potential solutions in the evaluation of retinal microvascular characteristics.

B. RETINAL ARTERIOLAR NARROWING

Wagener and colleagues first proposed that retinal arteriolar narrowing should be quantified either by direct comparison of "narrowed" arteriolar caliber in persons with hypertension with the "normal"

TABLE 6

Relationship Between Retinal Microvascular Abnormalities and Mortality (Selected Studies, Most Recent Listed First)

Type of Study	Population	Method of Quantifying Changes	Classification	Associations	References
Population-based	2859 persons	Ophthalmoscope grading of tortuosity, AV nicking, and retinal hemorrhages.	Present (any change) versus absence.	Related to 15-year all-cause mortality in men (OR 1.7), and 25-year all-cause mortality in women (OR 1.3), after controlling for BP and other risk factors.	Schouten et al[170]
Population-based	855 men aged 50 years	Ophthalmoscope grading of generalized arteriolar narrowing, focal narrowing, broadened light reflex, AV nicking and retinopathy.	Each change classified as not present, present or marked.	Related to 12-year cardiovascular mortality, after controlling for BP, smoking and cholesterol levels.	Svardsudd et al[193]
Clinic-based	540 hypertensive persons	Ophthalmoscope grading using KWB classification.	Grade I to IV.	Related to 10-year and 20-year all-cause mortality.	Breslin et al[23,24]
Clinic-based	299 hospitalized hypertensive persons	Ophthalmoscope grading using KWB classification.	Grade I to IV.	Related to all-cause mortality.	Simpson and Gilchrist[181]
Clinic-based	128 hypertensive persons	Ophthalmoscope grading using KWB classification.	Grade I to IV.	Related to 9-year all-cause mortality.	Frant and Groen[52]
Clinic-based	430 hypertensive persons hospitalized for related complications	Ophthalmoscope grading using KWB classification.	Grade I to IV.	Related to 8-year all-cause mortality.	Palmer et al[142]
Clinic-based	108 hypertensive persons hospitalized for treatment	Ophthalmoscope grading using KWB classification.	Grade I to IV.	Related to 5-year all-cause mortality.	Keith, Wagener and Barker[88]

AV nicking = Arteriovenous nicking; BP = Blood pressure; OR = Odds ratio; KWB = Keith, Wagener, Barker classification.[88]

caliber in persons without hypertension, or by an estimation of the ratio of the caliber of arterioles to venules ("arteriole to venule ratio").[206] However, while both approaches were theoretically sound, in practice clinical evaluation of retinal arteriolar narrowing proved to be extremely problematic, partly because of marked variability in branching pattern between individuals,[187] and observations that the range of "normal" arteriolar calibers overlap extensively with those described to have "pathological" narrowing.[29]

Subsequently, semi-objective methods based on retinal photography or slide projection systems were developed in the 1960s and 1970s,[20,21,29,34,75,86,119,125,127,132,145,146,157,180] with more sophisticated variations described in the 1980s and 1990s.[9,78,80,91,185,186,215] In general, these can be classified as micrometric methods, which rely on observers visually locating the retinal vessel edge from an enlarged or projected retinal image, and measuring the vessel diameter with the aid of some form of measuring device, such as calipers or microscopes with micrometer eyepiece.

Many of these methods rely on obtaining a ratio between arteriolar and venular widths (similar to the "arteriole-to-venule ratio" proposed by Wagener) as an index of arteriolar narrowing.[79,80,185,186] Although techniques differ, the principles are similar. As an example, in one of these studies, retinal photographic slides were projected onto a screen such that the optic disk filled a circle of radius 5 cm, and the widths of all arterioles and venules crossing the border of a concentric circle of radius 20 cm were measured.[185] The arteriolar and venular widths were then summarized, and an "arteriole to venule ratio" was calculated as an index of arteriolar narrowing. The resultant ratio in that study was shown to correlate inversely with blood pressure ($r = 0.48$, $p < 0.001$). Other studies report similar findings.[79,80]

There are inherent advantages in using an "arteriole to venule ratio" to quantify retinal arteriolar caliber and arteriolar narrowing. The ratio introduces some adjustment for the wide range of vessel caliber in the nonhypertensive, nondiabetic population (persons with narrower arterioles tend to have correspondingly narrow venules). It also offers protection against variable magnification from differences in refractive errors,[73] poor photographic focus or ocular media clarity, and interobserver variation in micrometric techniques.[186,187] However, the ratio is limited by observations that significant pathological distension (instead of narrowing) may occur in arterioles with advanced sclerosis,[157] and that retinal venular widths also decrease along with arteriolar widths in persons with very severe hypertension.[2]

Other approaches to the quantification of retinal arteriolar narrowing were described by Parr and colleagues.[144–146] First, arteriolar calibers should be measured at some distance away from the disk margin, where these vessels become unambiguously arteriolar rather than arterial in their structure. Second, the calibers of arterioles should be summarized using the square of their diameters, since the carrying capacity are represented by their cross-sectional area rather than their diameter. Third, the branching pattern of the arterioles should be taken into consideration in the final equation, as the total cross-section of the arteriolar system increases with each bifurcation. Parr and colleagues developed a model to evaluate arteriolar narrowing. In their technique, retinal arterioles were measured in a zone from a half disk-diameter to one disk-diameter away from the optic disk margin (based on data that showed that arteriolar calibers appear to decrease markedly after this distance from the optic disk in persons with hypertension[194]). The measured arteriolar widths were summarized as the "central retinal artery equivalent." Hubbard and colleagues later extended Parr's method to measure venular widths (the "central retinal vein equivalent") to calculate the "arteriole to venule ratio".[80] The modified Parr–Hubbard technique was used in the ARIC study to quantify arteriolar narrowing, and was shown to be reliable and sensitive to moderate blood pressure changes.[79]

Since the mid 1980s, various computer-related and imaging methods have been developed to measure retinal arteriolar widths.[25–28,39,47,58,61,67,104,116,129,130,134,135,147,151,154,158,159,165,168,172,189,191,192,214,219] One widely used method is densitometry (or microdensitometry), based on an analysis of density profile of photographic or computer images, using specific criteria and algorithms.[25–28,39,47,58,61,67,104,116,134,135,147,154,158,159,165,172,189,191,192,219] In this approach, a densitometric trace is usually taken perpendicularly along the vessel, and illumination values of the photographic or computer image (pixels) along the trace are analyzed. The vessel edge is considered to be a point with an illumination value that is halfway between the value of the background retinal pigmentary epithelium and the value of the vessel interior (this widely used method is termed the "half height" algorithm, although other algorithms have also been suggested[158]). Older scanning densitometry approaches have been criticized as being inaccurate,[14,64,74,75] but newer computer-based microdensitometry methods have been shown to be much more precise and reproducible than micrometry techniques.[39,61,135,192] In addition to hypertensive retinopathy, microdensitometry methods have been used to quantify changes in retinal arteriolar caliber in glaucoma,[51,172,191] diabetic retinopathy,[104,134,147,159] systemic vascular diseases,[204] as well as other retinal lesions such as drusen[150] and hard exu-

dates.[209] A microdensitometry method based on the Parr–Hubbard formula to measure retinal arteriolar widths is currently under investigation in a study on cardiovascular consequences of a cohort of persons with diabetes (Klein R, unpublished data, 2000).

In summary, new technology over the past three decades has enabled more precise methods of measuring retinal vessel widths and the grading of generalized arteriolar narrowing. However, several important issues remain unresolved. First, although quantification of retinal vessel calibers, either based on sophisticated micrometry or microdensitometry methods, may be practical in research settings, it is currently of little value in a clinical setting or for population screening. Research on automated vessel-tracking systems,[77,121,129,182,198] or on direct "real time" retinal vessel measurements[191,192] to increase the speed and reproducibility these methods offers promise that a more efficient method may be developed for clinical use in the future. Second, the optimal timing of the measurement is not known, as retinal vessel calibers change with posture,[67] blood pressure,[180] cardiac cycle,[30,45,162] and autonomic nervous system activity.[111] Third, different statistical algorithms may have to be developed and used to overcome misclassification in vessel width measurements due to refractive errors,[73] glaucoma,[83,190] diabetes,[160] and fundus pigmentation.[79] Finally, the relationship between the widths of retinal vessels based on photographic images and the actual caliber of the vessel lumen and blood flow is not clear and needs to be further investigated.[75,81]

VII. Clinical Implications and Conclusions

There are limitations in solely relying on traditional risk factors to identify and predict risk of cardiovascular disease.[16,35,90,109,110,123,124,149,155,213] Hypertension, for example, has long been used for cardiovascular risk stratification. However, recent studies indicate that cardiovascular diseases occur throughout the range of "normal" and "abnormal" blood pressures.[115,155,203] Further, prognosis among persons with hypertension is highly variable, depending largely on factors other than blood pressure, such as age, sex, other risk factors and history of cardiovascular disease.[115] Genetic and environmental variations among patients make it difficult to assess the actual pathological damage on cardiac and cerebral vasculatures due to blood pressure elevation. Finally, current blood pressure measures represent isolated "snapshots" in time, while lifetime history of blood pressure elevation is difficult to quantify, especially in populations where hypertension is aggressively treated.

Retinal microvascular abnormalities reflect cumulative microcirculatory damage from hypertension, aging, and other processes, and allow us to investigate, noninvasively, the relation of microvascular pathology to cardiovascular disease. In fact, the information obtained from a detailed retinal evaluation is qualitatively different from that of measuring a person's blood pressure, as the presence of retinal abnormalities suggests susceptibility to microvascular damage. This clinical relevance has long been recognized, since early studies described associations with cardiovascular mortality and morbidity in persons with hypertension. However, as our review has shown, many of the historical studies were inadequate. Current data suggest that retinal microvascular abnormalities, as detected by retinal photography in a research setting, are related independently to past blood pressure levels and risk of stroke. Retinal photography may therefore be potentially useful for characterizing blood pressure history and stroke risk in appropriate populations (e.g., hypertensive persons).

In contrast, the relationship with other cardiovascular disease is fairly inconsistent, and further inference is limited at this time (See Tables 2–6). It also appears that direct ophthalmoscopic examination by physicians is too unreliable to be of clinical value, particularly in the detection of subtle retinal microvascular changes. However, it is uncertain that other forms of clinical examination (e.g., indirect ophthalmoscopy by ophthalmologists) will provide more precise information.

Clearly, well-designed prospective studies using objective methods to determine retinal characteristics, and both subclinical and clinical cardiovascular endpoints, are needed to address these issues before retinal lesions are ultimately used for cardiovascular risk stratification and screening. Automated, computer-based imaging systems appear to hold much promise in the near future.

In conclusion, retinal microvascular abnormalities are common in the adult nondiabetic population. Retinopathy is associated with severe hypertensive end-organ damage, but is absent in the majority of people with well-controlled blood pressure. On the other hand, generalized retinal arteriolar narrowing and arteriovenous nicking appear to be irreversible long-term markers of mild to moderate hypertension, related not only to current and past blood pressure levels, but to cerebrovascular diseases as well.

Method of Literature Search

A systematic MEDLINE search on National Institute of Health's PubMed (Website: www.ncbi.nlm.nih.gov/PubMed, 21 January 2000) was conducted initially using the following keywords: *Retinal arterioles* (421 citations), *retinal arteriolar changes* (70), *retinal arteriolar narrowing* (42), *retinal arteriovenous ratio*

(9), *retinal arteriovenous nicking* (6), *hypertensive retinopathy* (167), *arteriosclerotic retinopathy* (46), *retinal arteriosclerosis* (494), *retinal arteriolosclerosis* (473), *retinal atherosclerosis* (185), *retinal vascular narrowing* (47), *retinal vessel grading* (29), *retinal vessel measurement* (294), *retinal arterioles and cardiovascular disease* (212), *retinal arterioles and stroke* (18), and *retinal arterioles and ischemic heart diseases* (4). Relevant abstracts and computer links to these abstracts were reviewed, and a preliminary list of possible articles from this search was compiled.

Next, the original articles from this list were retrieved and evaluated. From these articles, relevant bibliography references to manuscripts published prior to MEDLINE inclusion (prior to 1966), non–MEDLINE-based manuscripts, books and book chapters were also reviewed. In addition, unpublished data and ongoing research were included.

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Outline

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