BLOOD PRESSURE, HYPERTENSION AND RETINOPATHY IN A POPULATION

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INTRODUCTION

SYSTEMIC HYPERTENSION IS ASSOCIATED WITH AN INCREASED RISK OF stroke, heart attack, and renal disease.[1] In the past, prior to the widespread use of antihypertensive medications, the presence of ocular signs such as blot hemorrhages, microaneurysms, cotton-wool spots, hard exudates, arteriolar narrowing, and arteriovenous nicking was used to classify the severity of hypertension.[2-8] However, data from other studies suggest that these retinal lesions may be no more common in people with systemic hypertension than in those without.[9-11] The purpose of this report is to describe the relationship of various retinal lesions to hypertension in a population of persons without diabetes mellitus or known retinal vascular diseases such as central or branch retinal venous occlusions. The data are from the large population-based Beaver Dam Eye Study.

METHODS AND MATERIALS

The Beaver Dam Eye Study population has been described in detail in previous reports.[12-14] In brief, a private census of the population of Beaver Dam, WI was performed from September 15, 1987 to May 4, 1988. Eligibility requirements for entry into the study included living in the city or township of Beaver Dam and being 43 to 84 years of age at the time of the census. There were a total of 5,924 individuals, of whom 4,926 participated in the examination phase between March 1, 1988, and September 14, 1990.

Nonparticipants consisted of 226 persons (3.8%) who had died before the examination, 100 (1.7%) who had moved out of the area, 18 (0.3%) who

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could not be located, 276 (4.7%) who permitted an interview only, and 378 (6.4%) who refused to participate. Comparisons between participants and nonparticipants have been presented elsewhere.[14]

PROCEDURES

Informed consent was obtained at the beginning of the examination. A standardized questionnaire was administered by the examiners and included the following questions pertinent to this report: "Has a doctor ever said you had diabetes, sugar in your urine, or high blood sugar?" and "How old were you when you learned this?" There also were questions regarding use of diet and oral hypoglycemic agents or insulin for the management of hyperglycemia and questions regarding history of cigarette smoking, hypertension, and use of antihypertensive medications for the management of high blood pressure.

The blood pressure was measured according to the Hypertension Detection and Follow-up Program protocol.[15] Nonfasting blood specimens also were obtained from participants. Serum glucose was determined by using the hexokinase method,[16] and plasma glycosylated hemoglobin was determined by using affinity chromatography (Isolab Inc, Akron, OH).[17]

Stereoscopic 30° color fundus photographs centered on the disc (Diabetic Retinopathy Study [DRS] Standard Field 1) and macula (DRS Standard Field 2), and a nonstereoscopic color fundus photograph temporal to but including the fovea of each eye were taken.[18] Additional fundus photographs were taken if any lesions were found outside these fields.

The presence of retinal microaneurysms only, blot hemorrhages only, hemorrhages and/or microaneurysms, cotton-wool spots, hard exudates, intraretinal microvascular abnormalities, venous beading, arteriovenous nicking, new vessels on the disc and elsewhere, and preretinal and vitreous hemorrhages were graded in a masked fashion using an abbreviation of the modified Airlie House classification scheme.[19,20] Focal arteriolar narrowing was graded by using a standard photograph from the Wisconsin Age-Related Maculopathy Grading protocol in which focal narrowing of small arterioles in the posterior pole (Field 2) involves a total length of ⅓ disc diameter.[21] Arteriolar narrowing was graded as absent, questionable, less than the standard, and greater than or equal to the standard for all arterioles more than ½ to 1 disc diameter from the disc in all three standard fields. When there were multiple but separate areas of focal arteriolar narrowing, the composite length of involvement was compared with the standard. For purposes of analyses, two categories were used: (1) absent or questionably present and (2) present. Arteriovenous nicking was graded for all arteriovenous crossings that were more than ½ to 1 disc diameter from the disc

in all three fields. Arteriovenous nicking was graded as present if there was a decrease in the diameter of the venule on both sides of the arteriole that was crossing it. The presence of other retinal disease, such as central and branch retinal arterial or venous occlusion, retinal cholesterol emboli, and surface wrinkling retinopathy, was graded using a detailed protocol.

When two eyes of a participant were discrepant in the presence of a lesion, the grade assigned for the participant was that of the more severely involved eye. For example, in assigning the presence of arteriolar narrowing, if the narrowing was present in one eye but not the other, the participant would be considered to have arteriolar narrowing. When lesions could not be graded in one eye, the participant was assigned a score equivalent to that in the other eye.

DEFINITIONS

Current age was defined as the age at the time of the examination. The mean systolic blood pressure was the average of the two systolic blood pressure determinations, and the mean diastolic blood pressure was the average of the two diastolic blood pressures. The pulse pressure was computed by taking the difference between the mean systolic and the mean diastolic blood pressure. Hypertension was defined as a mean systolic blood pressure $\geq$ 160 mm Hg and/or a mean diastolic blood pressure $\geq$ 95 mm Hg and/or history of hypertension with use of antihypertensive medication at the time of examination.

STATISTICS

SAS was used for calculating prevalence proportions, means, chi-square statistics, and *t*-tests.[22] Trends in proportions were tested for significance by the Mantel-Haenszel procedure.[23] Age-adjusted prevalences were calculated by the direct method.[24] Relative risks and 95% confidence intervals were also calculated. The positive predictive value for hypertension was defined as the probability that a person actually has hypertension if a specific retinal lesion is present.

RESULTS

Of the 4,926 persons examined, we excluded 395 persons with a previous history of diabetes mellitus, 50 persons newly diagnosed at examination to have diabetes, and 61 suspected to have diabetes, leaving 4,420 persons. Of these, 76 were excluded because the photographs could not be graded for retinopathy lesions and 33 were excluded because of central or branch retinal venous occlusions, retinal detachments, or macular edema due to a

condition other than diabetes. Of the remaining 4,311 persons, 2,831 (65.7%) were normotensive and 1,479 (34.3%) were hypertensive; the presence of hypertension could not be determined in one person. The frequency of hypertension rose with increasing age in both men and women (Fig 1). Prior to 65 years of age, hypertension was more frequent in men; thereafter, it was more frequent in women.

For men and women, the frequencies of blot hemorrhages, more severe retinopathy (defined as microaneurysms and blot hemorrhage, hard exudates, cotton-wool spots, intraretinal microvascular abnormalities, or venous beading), focal arteriolar narrowing, and arteriovenous nicking rose significantly with increasing age (Table I).

After controlling for age, men were found to have significantly higher prevalences of retinal microaneurysms (6.0% versus 4.4%, relative risk [RR] 1.36; 95% confidence interval [CI] 1.05,1.76) and any retinopathy (9.0% versus 6.8%, RR 1.31; 95% CI 1.07,1.61) than women and women were more likely than men to have arteriolar narrowing (15.1% versus 11.6%, RR 1.30; 95% CI 1.11,1.51).

The relationships between systolic or diastolic blood pressure and the prevalence of retinal lesions are presented in Table II. The frequencies of

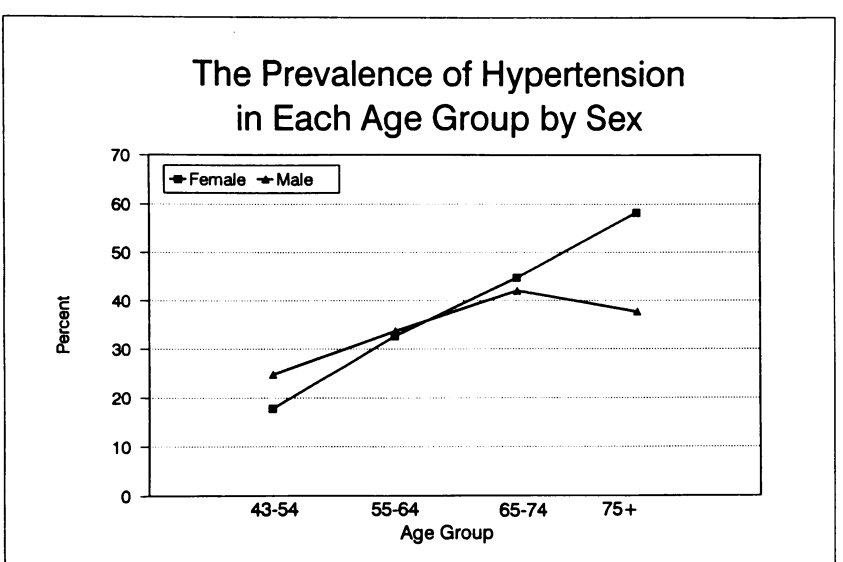

FIGURE 1
Relationship of prevalence of hypertension to age by sex in Beaver Dam Eye Study, 1988-1990.

TABLE I: RETINAL LESIONS BY GENDER IN DIFFERENT AGE GROUPS IN THE NONDIABETIC POPULATION PARTICIPATING IN THE BEAVER DAM EYE STUDY (1988-1990)

LESIONS	FREQUENCY (%)								*P* VALUE (TEST OF TREND)	
	43-54 YR		55-64 YR		65-74 YR		75+ YR			
	MALE (n=680)	FEMALE (n=749)	MALE (n=541)	FEMALE (n=619)	MALE (n=460)	FEMALE (n=631)	MALE (n=231)	FEMALE (n=400)	MALE	FEMALE
Blot hemorrhages alone	0.4	0.3	0.9	1.3	2.6	2.4	3.9	3.0	< .0001	< .0001
Microaneurysms alone	6.0	3.5	6.7	5.0	5.7	4.6	5.2	5.0	.27	.24
More severe nonproliferative retinopathy*	0.3	0.4	1.3	1.0	3.0	1.1	0.9	2.0	.01	.01
Any retinopathy†	6.8	4.1	8.9	7.3	11.3	8.1	10.0	10.0	.02	< .0001
Arteriolar narrowing	2.7	4.1	7.8	12.6	17.0	20.3	29.7	35.1	< .0001	< .0001
Arteriovenous nicking	0.6	1.1	2.0	1.9	2.4	2.9	5.6	4.5	< .0001	< .0001

*Presence of hemorrhages and blot hemorrhages with or without other, more severe lesions (hard exudates, intraretinal microvascular abnormalities, soft exudates, and/or venous beading).

†Presence of blot hemorrhages alone, microaneurysms alone, or more severe nonproliferative retinopathy.

TABLE II: GENDER-SPECIFIC, AGE-ADJUSTED PREVALENCE OF DIFFERENT LESIONS BY BLOOD PRESSURE QUARTILES IN THE BEAVER DAM EYE STUDY (1988-1990)

	MALES					FEMALES				
LESION	NO. AT RISK	AGE-ADJUSTED PREVALENCE (%)	RR	95% CI	*P* VALUE (TEST OF TREND)	NO. AT RISK	AGE-ADJUSTED PREVALENCE (%)	RR	95% CI	*P* VALUE (TEST OF TREND)
Blot hemorrhage										
Systolic*										
1st Quartile	413	0.2	1.00	—		683	1.2	1.00	—	
2nd Quartile	525	2.0	10.00	1.07-93.57	.05	573	1.0	0.83	0.29-2.41	.08
3rd Quartile	527	1.2	6.00	0.61-59.22		534	1.3	1.08	0.40-2.96	
4th Quartile	446	2.4	12.00	1.29-112.07		609	2.4	2.00	0.86-4.67	
Diastolic†										
1st Quartile	385	0.9	1.00	—		711	1.9	1.00	—	
2nd Quartile	416	1.8	2.00	0.56-7.09	.51	631	0.9	0.47	0.18-1.26	.75
3rd Quartile	510	1.5	1.67	0.47-5.89		558	1.7	0.90	0.39-2.03	
4th Quartile	600	1.5	1.67	0.49-5.72		499	1.6	0.84	0.35-2.01	
Microaneurysms										
Systolic*										
1st Quartile	413	3.9	1.00	—		683	2.7	1.00	—	
2nd Quartile	525	6.9	1.77	1.00-3.41	.02	573	4.2	1.56	0.86-2.82	.03
3rd Quartile	527	6.0	1.54	0.86-2.76		534	4.3	1.59	0.87-2.91	
4th Quartile	446	6.6	1.69	0.94-3.06		609	6.0	2.22	1.28-3.85	
Diastolic†										
1st Quartile	385	3.9	1.00	—		711	3.3	1.00	—	
2nd Quartile	416	5.2	1.33	0.70-2.54	.04	631	4.0	1.21	0.70-2.11	.04
3rd Quartile	510	5.2	1.33	0.71-2.48		558	6.1	1.85	1.11-3.09	
4th Quartile	600	7.2	1.85	1.04-3.27		499	5.0	1.52	0.87-2.63	
More severe nonproliferative retinopathy										
Systolic*										
1st Quartile	413	0.8	1.00	—		683	0.1	1.00	—	
2nd Quartile	525	1.0	1.25	0.32-4.92	.06	573	0.5	5.00	0.36-69.85	< .0001
3rd Quartile	527	0.9	1.13	0.28-4.56		534	0.8	8.00	0.62-102.63	
4th Quartile	446	2.2	2.75	0.80-9.50		609	2.1	23.67	1.85-238.94	
Diastolic†										
1st Quartile	385	1.8	1.00	—		711	0.7	1.00	—	
2nd Quartile	416	1.4	0.78	0.27-2.32	.16	631	0.6	0.86	0.23-3.20	.01
3rd Quartile	510	0.6	0.33	0.09-1.27		558	1.1	1.57	0.48-5.10	
4th Quartile	600	2.1	1.17	0.47-2.92		499	2.4	3.43	1.21-9.69	

Any retinopathy										
Systolic°										
1st Quartile	413	4.9	1.00	—		683	4.1	1.00	—	
2nd Quartile	525	9.9	2.02	1.23-3.32	.004	573	5.7	1.39	0.85-2.28	< .0001
3rd Quartile	527	8.1	1.65	0.99-2.76		534	6.4	1.56	0.96-2.54	
4th Quartile	446	11.2	2.29	1.39-3.76		609	10.6	2.59	1.68-3.97	
Diastolic†										
1st Quartile	385	6.6	1.00	—		711	6.0	1.00	—	
2nd Quartile	416	8.3	1.26	0.77-2.06	.03	631	5.7	0.95	0.62-1.46	.01
3rd Quartile	510	7.4	1.12	0.69-1.82		558	8.9	1.48	1.00-2.20	
4th Quartile	600	10.8	1.64	1.05-2.54		499	8.9	1.48	0.99-2.22	
Arteriolar narrowing										
Systolic°										
1st Quartile	413	5.7	1.00	—		683	9.9	1.00	—	
2nd Quartile	525	7.9	1.39	0.85-2.26	< .0001	573	13.4	1.35	1.00-1.84	< .0001
3rd Quartile	227	11.6	2.04	1.20-3.46		534	16.9	1.71	1.27-2.29	
4th Quartile	446	16.3	2.86	1.83-4.46		609	22.4	2.26	1.73-2.97	
Diastolic†										
1st Quartile	385	6.5	1.00	—		711	9.0	1.00	—	
2nd Quartile	416	8.6	1.32	0.81-2.16	< .0001	631	14.0	1.56	1.15-2.11	< .0001
3rd Quartile	510	11.3	1.74	1.11-2.73		558	13.5	1.50	1.10-2.05	
4th Quartile	600	16.9	2.60	1.71-3.95		499	25.2	2.80	2.12-3.70	
Arteriovenous nicking										
Systolic°										
1st Quartile	413	0.5	1.00	—		683	1.2	1.00	—	
2nd Quartile	525	1.3	2.60	0.55-12.27	< .0001	573	1.8	1.50	0.60-3.73	.01
3rd Quartile	227	2.3	4.60	0.93-22.86		534	3.1	2.58	1.13-5.92	
4th Quartile	446	3.9	7.80	1.86-32.80		609	3.7	3.08	1.40-6.81	
Diastolic†										
1st Quartile	385	1.6	1.00	—		711	1.8	1.00	—	
2nd Quartile	416	2.1	1.31	0.47-3.65	.39	631	1.8	1.00	0.45-2.21	.02
3rd Quartile	510	1.3	0.81	0.27-2.41		558	2.4	1.33	0.63-2.85	
4th Quartile	600	2.6	1.63	0.65-4.09		499	3.5	1.94	0.95-3.96	

°1st quartile, < 118 mm Hg; 2nd quartile, 118-129 mm Hg; 3rd quartile, 130-143 mm Hg; 4th quartile, ≥ 144 mm Hg.
†1st quartile, < 71 mm Hg; 2nd quartile, 71-77 mm Hg; 3rd quartile, 78-84 mm Hg; 4th quartile, ≥ 85 mm Hg.

most of the lesions increased with increasing systolic blood pressure. The relationships of the retinal lesions to increasing diastolic blood pressure were less consistent.

The relationships between retinal lesions, hypertension and age are presented in Table III. In persons younger than 65 years of age, higher frequencies of retinal lesions were more likely in those with hypertension than in those without hypertension. Thereafter the differences in prevalence of retinopathy by hypertensive status were somewhat less marked in women and virtually absent in men. Age-adjusted frequencies of most of the lesions were generally higher in persons with hypertension compared with those without hypertension. Prevalence of focal arteriolar narrowing increased threefold to tenfold across the four age groups in both men and women, with systemic hypertension and without.

Retinal lesions, focal arteriolar narrowing, and arteriovenous nicking were also more frequent in those whose blood pressure was elevated despite use of antihypertensive medications compared with those whose blood pressure was controlled with use of antihypertensive medications or those who were normotensive (Table IV). There was no relationship between any of the retinal lesions and self-reported duration of hypertension (data not shown).

The positive predictive value of blot hemorrhages when they were present alone for hypertension was 48.5% (32 of 66); for retinal microaneurysms only it was 44.8% (99 of 221), for more severe nonproliferative retinopathy it was 57.1% (28 of 49), for arteriolar narrowing it was 48.8% (284 of 582), and for arteriovenous nicking it was 52.6% (50 of 95).

DISCUSSION

Most information about the prevalence of retinal abnormalities in people with hypertension has been derived from studies of select groups attending specific clinics where patients with severe disease may be overrepresented. The Beaver Dam Eye Study provides data on the prevalence of specific retinal lesions by using standardized protocols for recording of the lesions by stereoscopic fundus photographs and for grading them.[18-21]

Variations in the composition and size of the groups previously studied, in the times relative to the advent of antihypertensive medication use in which the studies took place, and in the methods used to detect and evaluate the presence of retinal lesions make it difficult to compare our findings (ie, retinopathy in 11%, focal arteriolar narrowing in 19%, and arteriovenous nicking in 3% of the nondiabetic population with systemic hypertension) to findings of other studies. In the Framingham Eye Study, ophthalmoscopic screening examinations revealed that 0.8% (19 of 2375) of those without a

TABLE III: RELATIONSHIP OF RETINOPATHY LESIONS AND VASCULAR CHANGES TO HYPERTENSION BY AGE AND SEX IN THE NONDIABETIC POPULATION IN THE BEAVER DAM EYE STUDY (1988-1990)

LESION	FREQUENCY (%)								AGE-ADJUSTED PREVALENCE (%)	
	43-54 YR		55-64 YR		65-74 YR		75+ YR			
	NORMO	HYPER	NORMO	HYPER	NORMO	HYPER	NORMO	HYPER	NORMO	HYPER
Males	(n=512)	(n=168)	(n=359)	(n=182)	(n=267)	(n=193)	(n=144)	(n=86)*	(n=1282)	(n=629)
Blot hemorrhages alone	0.6	0.0	0.8	1.1	3.0	2.1	3.5	4.6	1.6	1.4
Microaneurysms alone	5.3	8.3	3.9	12.1	5.6	5.7	5.6	4.6	5.0	8.3
More severe retinopathy†	0.4	0.0	0.6	2.8	3.0	3.1	0.7	1.2	1.1	1.7
Any retinopathy‡	6.3	8.3	5.3	15.9	11.6	10.9	9.7	10.3	7.7	11.3
Arteriolar narrowing	2.2	4.2	5.6	12.1	16.9	17.1	28.2	32.2	9.8	13.1
Arteriovenous nicking	0.4	1.2	2.2	1.7	0.4	5.2	5.6	5.8	1.5	2.8
Females	(n=616)	(n=133)	(n=417)	(n=202)	(n=349)	(n=282)	(n=167)	(n=233)	(n=1549)	(n=850)
Blot hemorrhages alone	0.2	0.8	1.0	2.0	0.9	4.3	4.2	2.2	1.2	2.2
Microaneurysms alone	3.4	3.8	4.1	6.9	4.3	5.0	3.0	6.4	3.7	5.3
More severe retinopathy†	0.2	1.5	0.5	2.0	1.2	1.1	0.6	3.0	0.6	1.8
Any retinopathy‡	3.7	6.0	5.5	10.9	6.3	10.3	7.8	11.6	5.5	9.3
Arteriolar narrowing	2.9	9.8	11.0	15.8	17.2	24.2	35.2	35.1	14.1	19.4
Arteriovenous nicking	0.7	3.0	1.9	2.0	1.7	4.3	4.8	4.3	1.9	3.3

*One person's hypertension status could not be determined.

†Presence of hemorrhage and blot hemorrhages with or without other, more severe lesions (hard exudates, intraretinal microvascular abnormalities, soft exudates, and/or venous beading).

‡Presence of blot hemorrhages alone, microaneurysms alone, or more severe nonproliferative retinopathy.

TABLE IV: GENDER-SPECIFIC AGE-ADJUSTED PREVALENCE OF DIFFERENT LESIONS BY HYPERTENSIVE STATUS IN THE BEAVER DAM EYE STUDY (1988-1990)

	MALES				FEMALES			
	NO. AT RISK	AGE-ADJUSTED PREVALENCE (%)	RR	95% CI	NO. AT RISK	AGE-ADJUSTED PREVALENCE (%)	RR	95% CI
Blot hemorrhage alone								
Normotensive	1282	1.6	1.00	—	1549	1.2	1.00	—
Hypertensive								
Antihypertensive medication, controlled	382	0.8	0.50	0.15-1.65	557	2.5	2.08	1.05-4.15
No antihypertensive medication, uncontrolled	149	2.2	1.38	0.43-4.36	153	1.6	1.33	0.36-5.00
Antihypertensive medication, uncontrolled	98	2.7	1.69	0.48-5.97	140	2.0	1.67	0.48-5.79
Microaneurysms alone								
Normotensive	1282	5.0	1.00	—	1549	3.8	1.00	—
Hypertensive								
Antihypertensive medication, controlled	382	8.7	1.74	1.16-2.60	557	4.2	1.11	0.69-1.77
No antihypertensive medication, uncontrolled	149	5.2	1.04	0.50-2.15	153	7.0	1.84	0.98-3.46
Antihypertensive medication, uncontrolled	98	10.6	2.12	1.14-3.95	140	8.9	2.34	1.30-4.21
More severe nonproliferative retinopathy°								
Normotensive	1282	1.1	1.00	—	1549	0.6	1.00	—
Hypertensive								
Antihypertensive medication, controlled	382	1.3	1.18	0.43-3.27	557	1.3	2.17	0.82-5.70
No antihypertensive medication, uncontrolled	149	2.9	2.64	0.91-7.64	153	3.1	5.17	1.73-15.42
Antihypertensive medication, uncontrolled	98	1.7	1.55	0.31-7.60	140	1.8	3.00	0.75-11.94

Any retinopathy†								
Normotensive	1282	7.7	1.00	—	1549	5.5	1.00	—
Hypertensive								
Antihypertensive medication, controlled	382	10.8	1.40	0.99-1.98	557	8.0	1.46	1.03-2.06
No antihypertensive medication, uncontrolled	149	10.3	1.34	0.80-2.23	153	11.7	2.13	1.31-3.44
Antihypertensive medication, uncontrolled	98	15.0	1.95	1.17-3.24	140	12.6	2.29	1.41-3.71
Arteriolar narrowing								
Normotensive	1282	9.8	1.00	—	1549	14.2	1.00	—
Hypertensive								
Antihypertensive medication, controlled	382	19.6	2.00	1.54-2.60	557	14.9	1.05	0.83-1.33
No antihypertensive medication, uncontrolled	149	19.5	1.99	1.38-2.87	153	32.1	2.26	1.74-2.94
Antihypertensive medication, uncontrolled	98	23.2	2.37	1.59-3.52	140	22.2	1.56	1.12-2.18
Arteriovenous nicking								
Normotensive	1282	1.5	1.00	—	1549	2.0	1.00	—
Hypertensive								
Antihypertensive medication, controlled	382	2.0	1.33	0.58-3.06	557	2.7	1.35	0.74-2.48
No antihypertensive medication, uncontrolled	149	4.2	2.80	1.16-6.79	153	5.4	2.70	1.28-5.71
Antihypertensive medication, uncontrolled	98	4.0	2.67	0.92-7.75	140	3.4	1.70	0.66-4.39

*Presence of hemorrhages and blot hemorrhages with or without other, more severe lesions (hard exudates, intraretinal microvascular abnormalities, soft exudates, and/or venous beading).
†Presence of blot hemorrhages alone, microaneurysms alone, or more severe nonproliferative retinopathy.

previous history of diabetes had signs of retinopathy, of which 14 had a history of hypertension, 3 had a branch vein occlusion, 1 had diabetes mellitus discovered at the time of follow-up examination, and 1 had no other cause ascertained.[25] No other population-based prevalence estimates of retinopathy in nondiabetic hypertensive groups are available for comparison.

In two other population-based studies, both of which included people with diabetes, the relation of blood pressure to signs of retinopathy, arteriolar narrowing, and arteriovenous nicking was studied.[3,26] Signs of retinopathy (exudates and flame-shaped hemorrhages) were detected by ophthalmoscopy in 0.8% of white males and 2.3% of white females, and arteriovenous nicking was detected in 11.5% of white males and 14.2% of white females in a population-based study in Evans County, Georgia.[26] Retinopathy was present in 2.3% of white males and 4.9% of white females, and arteriovenous nicking was present in 15.5% of white males and 23.2% of white females whose diastolic blood pressure was greater than 100 mm Hg in that study. In a population-based study of 855 50-year-old men in Gothenburg, Sweden, in which both ophthalmoscopy and fundus photographs were used to detect retinopathy, hemorrhages were found in 0.4%, focal arteriolar narrowing was found in 6.0% and arteriovenous nicking was found in 8.9% of the population.[3] Mean systolic and diastolic blood pressures were significantly higher in those with these signs than in those without these signs. Four years later, there were no significant changes in the frequency of these lesions in the population.

The predictive value for systemic hypertension when specific retinal lesions were present varied from 45% when only microaneurysms were present to 57% when more severe nonproliferative retinopathy was present. Thus, only 43% to 55% of people with retinopathy, arteriolar narrowing, or arteriovenous nicking do not have hypertension. Clearly, routine blood pressure measurements remain a better method of detecting systemic hypertension.

In our study, the highest frequencies of retinopathy (15%) and arteriolar narrowing (28%) were found in persons being treated with antihypertensive medications whose blood pressure was poorly controlled. If these retinal lesions reflect systemic abnormalities in the kidney, heart, or central nervous system, then ophthalmoscopy may add further information about potential systemic complications associated with hypertension. In support of this are earlier observations, prior to widespread use of antihypertensive medications, which showed that in the presence of retinopathy, persons with hypertension had a significantly poorer 10-year survival rate (those with only retinal hemorrhages, without exudates, 20%; those with retinal hemorrhages

and exudates, 18%) than an age- and sex-matched normotensive population (86%).[8] More recently, in the Gothenburg population, after controlling for systolic blood pressure and other risk factors, persons with focal arteriolar narrowing or arteriovenous nicking were found to have increased 8-year mortality.[3] Dahlöff and associates[27] recently reported significant positive correlations between retinal vascular changes and left ventricular wall thickness as detected on echocardiography in a group of 28 untreated men with mild to moderate essential hypertension. However, not all data from other studies are consistent with these findings.[9,10]

The overall rate of retinopathy in the Beaver Dam nondiabetic population was 7.8%. This is nearly 10 times higher than the frequency previously reported in the Framingham nondiabetic population.[25] The differences may be due to the increased sensitivity of the methods of detection and the grading of fundus photographs used in the Beaver Dam Study, as compared with ophthalmoscopy used in the Framingham Study.[28,29] The prevalence of retinopathy in 43- to 54-year-old men in Beaver Dam (6.8%) was also higher than in a study of 50-year old men in Gothenburg (0.4%), but was significantly lower than in previous histopathologic studies in which microscopy was used to study the entire retina.[3,30,31]

The high frequency of retinal lesions found in the nondiabetic Beaver Dam population may be due to atherosclerotic disease of the internal carotid arteries affecting retinal blood vessels and flow.[32] These signs have been reported in eyes of persons with venous stasis retinopathy secondary to occlusion of the internal carotid artery.[33] It was not possible to evaluate the relationship of atherosclerotic vascular disease to retinopathy, arteriolar narrowing, or arteriovenous nicking in our study.

Any conclusions or explanations regarding associations described herein must be made with caution. For example, a possible reason for not finding a stronger relation between diastolic blood pressure and the prevalence of retinal lesions is that persons with high diastolic blood pressure who developed retinal lesions may have died before their examination was performed.

Second, the retinal lesions might have resulted from conditions in nondiabetic persons that were not asked about or determined in the study, such as atherosclerotic vascular disease, acquired immune deficiency syndrome, or aplastic anemia.[34] With the exception of atherosclerotic vascular disease, these conditions are rare in this population and would not be expected to account for the frequency of the retinal lesions found in the nondiabetic group.

Third, misclassification of hypertension status may have occurred, because the classification was based, in part, on two measurements of the blood pressure during a single examination. This type of misclassification

would probably weaken the significant relationship found between hypertensive status and the presence of retinal lesions in nondiabetic persons.

SUMMARY

This study provides precise estimates of the prevalence of retinal lesions in nondiabetic persons with and without hypertension. The findings suggest that retinopathy (6% in normotensives and 11% in people with hypertension), and retinal arteriolar narrowing (11% in normotensives and 19% in people with hypertension) are common. Further longitudinal study is necessary to evaluate the public health significance of these findings.

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DISCUSSION

DR ARNALL PATZ. It is a great pleasure to discuss the excellent paper of Dr Klein and colleagues from the University of Wisconsin. The authors have examined data from the large population-based Beaver Dam Eye Study. Very careful history taking and general screening of the patients, including special measurements of blood pressure and plasma glycosylated hemoglobin, were performed. Bilateral stereoscopic color fundus photographs of the posterior fundus and a nonstereophoto temporal to, but including the fovea, were taken. More peripheral areas were photographed if lesions were found elsewhere. Analysis of data was based on 4,311 individuals, approximately two thirds of whom had normal blood pressure and one third high blood pressure.

It was of interest that the relationships of the retinal lesions increased in frequency with increasing systolic blood pressure and were less consistent with increases in diastolic pressure. The authors raise the possibility that increased mortality in those patients with high diastolic pressures may have died before examination. Retinal arteriolar narrowing was noted in approximately 20% of those with hypertension.

The relationship of retinopathy and hypertension applied mostly to those patients under 65 years of age. After age 65, the prevalence of retinopathy by hypertensive status was less marked, especially in men.

The authors have pointed out that since only approximately 50% of persons with hypertension have characteristic retinal lesions such as microaneurysms, hemorrhages, focal narrowing, and arteriovenous nicking, routine blood pressure measurements remain a better method of detecting systemic hypertension.

Since the Beaver Dam Eye Study population was primarily white, I would be very interested in hearing Dr Klein's comments on what he might predict in an American black population in view of the increased prevalence of hypertension in these patients.

The authors refer to an AOS committee report on classification of retinal lesions in hypertension that was presented at the 1945 annual meeting (see Ref 7). Dr Clay, who prepared the major part of this committee report, was chief of ophthalmology at Emory University during my senior year in medical school. I had spent elective time working in the department and had the privilege of hearing his discussion, with illustrations, of this important committee report. It is noteworthy that there was only the most primitive treatment available for hypertension at that time. Dr Clay was unable to attend the 1945 meeting because of illness, and he died the following year. I am confident that he and other pioneer authorities on this topic would have appreciated Dr Klein's excellent contribution.

I want to congratulate the authors on this superbly organized study. These findings represent a major step forward in our understanding of the retinal vascular complications of systemic hypertension. This study takes on special importance because there are no other population-based prevalence estimates of retinopathy in nondiabetic hypertensive populations available.

I wish to take this opportunity to recognize the tremendous contributions of Drs Ronald and Barbara Klein to our knowledge of the epidemiology of diabetic retinopathy. These investigators, with their colleagues in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, have added significantly to our understanding of risk factors and other epidemiologic findings in diabetic retinopathy. I am confident that their more recent studies on the nondiabetic population will again provide additional valuable information.

DR THOMAS P. KEARNS. I would like to congratulate the authors on this superb paper. I believe that 40 years from now people will refer to this paper just as Dr Patz referred to the paper by Drs Wagner and Clay. I have a couple of things to add. It is difficult to study the retinopathy of hypertension now as we do not see the hypertension as in the past. When I started in ophthalmology in the 1940s there was little or no effective treatment for hypertension. We therefore saw many patients with severe hypertension that was not controlled. Effective drug therapy was introduced in the 1950s and since then hypertension has been mostly controlled. The severe retinopathies are now rarely seen and it is difficult to teach the residents this aspect of medical ophthalmology.

One should not overlook papilledema as part of hypertensive retinopathy. Of course I realize that the patients in the Beaver Dam Eye Study did not have severe uncontrolled hypertension. The blood pressure is usually in the 120 plus range diastolic when papilledema is present. I have seen residents as well as many senior ophthalmologists not recognize the true significance of papilledema in hypertension and refer the patient to a neurologist or neurosurgeon. This mistake is usually corrected but valuable time may be lost if this dangerous situation is misdiagnosed. The last thing I would like to mention is a point I learned while working under Dr Wagener at the Mayo Clinic. Hypertensive sclerosis, the copper wire and silver wire appearance of the retinal arterioles, is due to hypertension and hypertension alone. After seeing many thousands of patients being treated at the Mayo Clinic for hypertension I have found that Dr Wagener was correct. If the patient has hypertensive sclerosis he either has systemic hypertension or has had such in the past.

DR WILLIAM GLEW. I would just like to make a comment about focal arteriolar restrictions. Dr Klein referred strictly to them. I would like to ask him if he could analyze them further, as a subset of fundus findings that he talked about. Having trained at the Mayo Clinic where I fell under the influence of Drs Wagener, Hollenhorst, and Kearns with regard to hypertension and fundoscopic findings, I found during a study of patients with hypertension in Washington, DC, that focal constrictions were associated with diastolic pressure of 105 to 110 or more. This was

almost 100%. But you had to put a few qualifications on it. The focal constrictions had to be further away from the disc than about 1 disc diameter; also over 65 years of age the correlation fell down a little bit. What this means is that if you are in your office seeing patients and you see two focal constrictions or more you are going to find the diastolic elevated. That is very significant because these are the patients where the morbidity is great. The other thing that Dr Kearns mentioned was that we don't see as much hypertension anymore. That is true but there are two types of patients in whom you will see uncontrolled hypertension. One is the patient who is not compliant because he is not following his doctor's instructions. The patient saw the doctor and was given the proper prescription but has not taken the medications or has not returned to be checked. So the ophthalmologist seeing these patients can play an important role. He will also be able to diagnose in many cases hypertension and was previously undiagnosed. I would urge ophthalmologists to make good use of the blood pressure cuff. I think this is an important part of our role as primary physicians as well as referral specialists. Thank you.

DR W. BANKS ANDERSON. I just have a question. Some years ago tortuosity and/or straightening of the retinal vascular tree were said to be part of hypertension and other retinopathies. I think there is a study in Israel that shows there was no correlation with hypertension. Have you looked at tortuosity and/or straightening?

DR MARK O. M. TSO. I wish to congratulate Dr Klein for his stimulating paper and for reviving our interest in hypertensive retinopathy. As Dr Kearns pointed out, the study of hypertensive retinopathy has changed its tenor since the time of Keith and associates. In 1939 systemic hypertension had no treatment. The classification of Keith and associates provided important clues to the prognoses of patients and ratio of survival. In 1990 our patients had a number of options of therapy. A new classification was much needed for providing clues to the efficacy of treatment regimens. Dr Jampol and I proposed a new classification for hypertensive ocular diseases into three categories, namely (1) hypertensive retinopathy, (2) hypertensive choroidopathy, and (3) hypertensive optic neuropathy (*Hypertension: Pathophysiology, Diagnosis, and Management*, Vol I. New York, Raven Press, 1990, pp 433-465). This classification provides a yardstick for monitoring of the progression of hypertension affecting the retina, choroid, and optic nerve as well as the efficacy of antihypertensive therapy.

As to the relationship of systemic hypertension and age-related maculopathy, Sperduto and Hiller reanalyzed the data of the Framingham heart and eye studies. They noted a small, but consistent significant association between age-related maculopathy and systemic hypertension. Furthermore, they noted that the prevalence of age-related maculopathy progressively increases with increasing duration of systemic hypertension.

Last year we further explored the relationship of systemic hypertension and photoreceptor degeneration in the laboratory and noted that light-induced photoreceptor degeneration was significantly worse in the spontaneously hypertensive rats

when compared with controls. Our observation provided further support to a positive relationship between hypertension and age-related macular degeneration.

I would like to ask Dr Klein a few questions. How did you examine the macular functions in your population? Besides visual acuity, did you perform photo-stress test, Amsler grid study, or contrast sensitivity examination? In your study, can you provide further support to the relationship between age-related macular degeneration and systemic hypertension?

DR J. DONALD M. GASS. I too would like to add my congratulations to Dr Klein. I would like to ask a couple of questions. The major ocular complications that we see from hypertension are branch vein occlusion, central retinal vein occlusion, ischemic optic neuropathy, or arterial macroaneurysm. In your study, I believe that you excluded people who had any sort of retinal vascular complications. I would like to know how often you encountered these complications? Also, if you excluded these patients, how would this also affect the incidence of arteriovenous crossing defects, and focal arterial narrowing in your population?

DR RONALD BURDE. I would like to offer the following observation and I would like to solicit comments. I have noted that with the advent of the halogen bulb ophthalmoscope one can rarely see silver wiring or copper wiring and that is because the light source is too bright. If you really want to teach the medical students how to match what they see in the classic textbook and what they see with their ophthalmoscopes you have to have them turn down the rheostat. Under ordinary viewing conditions the students will see varying degrees of sclerosis and sheathing, if they then reduce the illuminating source they will see copper and silver wiring. I have not seen that written before and I just wondered if you found this to be true?

DR RONALD KLEIN. I wanted to thank Dr Patz for his comments regarding our paper. He asked why we found differences in the relationships of retinal lesions with systolic and diastolic blood pressure? I do not know the reason. It is possible that people with high diastolic blood pressure and retinal lesions were more likely to die prior to the study and not be examined compared to people with high systolic blood pressure and retinal lesions. This might weaken the relationship of retinal lesions with diastolic blood pressure. In addition, it is possible that systolic blood pressure is more strongly related than diastolic blood pressure to conditions associated with retinal lesions, such as atherosclerotic vascular disease of the internal carotid artery and venous stasis retinopathy. Dr Patz also asked whether the findings in our study, which is almost entirely in whites, can be generalized to other racial groups. It is difficult to extrapolate to other racial groups because of the variability of other factors besides hypertension, which may be associated with retinal lesions. There are few studies which have directly compared retinal lesions in a group of whites and African-Americans. Data from one such study, done in Evans County, Georgia, using ophthalmoscopy, suggest that after controlling for diastolic blood pressures, African-Americans had significantly higher prevalences of these retinal lesions than whites in

the study (see their Table 8). The Baltimore Eye Study may offer an opportunity to compare the prevalence of retinal lesions in a biracial population.

Dr Kearns describes severe retinal lesions, such as papilledema, associated with "uncontrolled" hypertension, especially prior to the use of antihypertensive medications. We arbitrarily chose 160/95 mm Hg as our definition of hypertension, and uncontrolled hypertension was defined as having a systolic blood pressure of ≥ 160 mm Hg or a diastolic blood pressure of ≥ 95 mm Hg with or without use of antihypertensive medications. We found a strong relationship of prevalence of the retinal lesions with uncontrolled hypertension. However, we found no individuals with papilledema in the population. Dr Anderson asked whether we examined tortuosity of the retinal arterioles. We did not examine tortuosity of the retinal arterioles. Dr Glew asked whether we counted the number of "focal narrowings" of the retinal arterioles. We did not.

Dr Tso asked what functional studies, such as visual acuity, contrast sensitivity, etc we examined. Although we measured visual acuity, contrast sensitivity, and thresholds we have not examined their relationship to blood pressure. Mark also asked whether we had examined the relation between high blood pressure and age-related macular degeneration. Others have reported a significant relationship between higher blood pressure and age-related macular degeneration. We have not found a significant relationship. The re-examination of this cohort will be important in understanding this relationship.

In response to the question asked by Dr Gass, we have not examined the relationship between retinal branch vein occlusion, retinal macroaneurysms, and other retinal conditions and blood pressure as yet. We will examine these relationships in further analyses.