THE RELATION OF SYSTEMIC HYPERTENSION TO CHANGES IN THE RETINAL VASCULATURE: The Beaver Dam Eye Study*

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ABSTRACT

Background Purpose: The objective was to investigate the relationship of systemic hypertension to the incidence of various retinal vascular lesions in the population-based Beaver Dam Eye Study.

Methods: Subjects aged 43 through 86 years who lived in Beaver Dam, Wisconsin between 1987 and 1988 were examined between 1988 and 1990 and 5 years later, 1993-1995. Blood pressure was measured using standardized protocols. Stereoscopic color fundus photographs were graded in a masked fashion using standardized protocols to determine the presence of retinopathy (blot hemorrhages, microaneurysms, hard and soft exudates, intraretinal microvascular abnormalities, and venous beading), retinal arteriolar narrowing, and arterio-venous nicking. People with diabetes or retinal vascular occlusions were excluded from the analyses.

Results: Among those examined, 2,151 (69.1%) were normotensive and 963 (30.9%) were hypertensive at baseline. Over the five-year period, retinopathy developed in 175 (6.0%), arteriolar narrowing in 282 (9.9%) and arterio-venous nicking in 201 (6.5%) nondiabetic subjects. After adjusting for age, hypertension was associated with the incidence of retinopathy (in men: relative risk [RR] 2.31, 95% confidence interval [CI] 1.54 to 3.48; in women: RR 1.61, 95% CI 1.07 to 2.43) and with arteriolar narrowing (in men: RR 1.82, 95% CI 1.25 to 2.66; in women: RR 1.36, 95% CI 1.05 to 1.77), but not with arterio-venous nicking (in men: RR 1.01, 95% CI 0.69 to 1.48; in women: RR 1.37, 95% CI 0.95 to 1.97). The five-year incidence of retinopathy and of arteriolar narrowing was higher in those subjects whose blood pressure was elevated despite use of antihypertensive medications compared with those subjects whose blood pressure was controlled with antihypertensive medications or those who were normotensive.

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Conclusions: These data show a relation of hypertension to an increased incidence of retinopathy and arteriolar narrowing. Furthermore, these data suggest that pharmacologic control of blood pressure is related to a lower incidence of these anatomic retinal lesions relative to uncontrolled blood pressure.

INTRODUCTION

Systemic hypertension is associated with an increased risk of both macrovascular and microvascular disease.[1,2] Retinopathy, retinal arteriolar narrowing, and arteriovenous nicking have been attributed to high blood pressure, and in the past these lesions were used to indicate the severity of hypertension.[2-9] However, data from some studies suggest that these retinal lesions may be no more common in people with systemic hypertension than in those without.[7,10] The purpose of this report is to describe the relationships of blood pressure and systemic hypertension to the 5-year incidence of retinopathy, focal arteriolar narrowing, and arteriovenous nicking 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

POPULATION

The Beaver Dam Eye Study population has been described in detail in previous reports.[11,12] A private census of the population of Beaver Dam, Wisconsin, was performed from September 15, 1987, to May 4, 1988, to identify all residents in the city or township of Beaver Dam who were 43 to 84 years of age. Of the 5,924 eligible individuals, 4,926 participated in the baseline examination between March 1, 1988, and September 14, 1990. Ninety-nine percent of the population was white. Nonparticipants consisted of 226 persons (3.8%) who died before the examination, 18 (0.3%) who could not be located, 337 (5.7%) who permitted an interview only (of these, 61 had moved), and 417 (7.0%) who refused to participate (of these, 39 had moved). Comparisons between participants and nonparticipants at the time of the baseline examination have appeared elsewhere.[11]

Before the start of the 5-year follow-up examination on March 1, 1993, 385 (7.8%) of the original participants had died. Of the 4,541 survivors in the baseline examination, 3,684 (81.1%) participated in the follow-up examination between March 1, 1993, and June 14, 1995. Four participants could not be located, 259 (5.7%) permitted an interview only (of these, 48 had moved out of the area), 423 (9.3%) refused to participate (of these, 44

had moved out of the area), and 171 died during the 5-year follow-up examination period. Both the mean and median times between the baseline and 5-year follow-up examinations were 4.8 years, and the standard deviation was 0.4 years.[12]

Comparisons between participants and nonparticipants at follow-up have been presented in detail elsewhere.[12] Briefly, persons who were alive and did not participate in the follow-up eye examination (n=686) were older at baseline than those who did (62.7 versus 60.4 years, $P<0.0001$). After adjusting for age, those who were alive during the study period and did not participate were more likely to have had fewer years of education, lower income, poorer visual acuity, a history of cardiovascular disease, a history of never drinking alcohol, more pack-years smoked, higher serum cholesterol levels, and higher systolic and diastolic blood pressure measurements, and more likely to be retired at baseline than persons who participated.

PROCEDURES

Similar procedures were used at both the baseline and follow-up examinations and have been described in detail elsewhere.[11,12] 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?"[13,14] 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.

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 using the hexokinase method,[16] and plasma glycosylated hemoglobin was determined using affinity chromatography (Isolab Inc, Akron, Ohio).[17]

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

Retinopathy was defined using a classification derived from studies of diabetic retinopathy but herein used to describe the presence of such lesions in the absence of diabetes. The presence of retinal microaneurysms only, blot and/or flame 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 was graded in a masked fashion using an abbreviation of the modified Airlie House classification scheme.[19,20] Focal arteriolar narrowing was graded 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 one-third disc diameter.[9,21] Arteriolar narrowing was graded as absent, questionable, less than the standard, and greater than or equal to the standard for all arterioles more than one-half disc diameter from the disc in all 3 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, 2 categories were used: (1) absent or questionably present and (2) present. Arteriovenous nicking was graded for all arteriovenous crossings that were more than one-half disc diameter from the disc in all 3 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 2 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 arteriolar narrowing was present in 1 eye but not the other, the participant would be considered to have arteriolar narrowing. When lesions could not be graded in 1 eye, the participant was assigned a score equivalent to that in the other eye.

Incidence was determined for retinopathy, arteriolar narrowing, and arteriovenous nicking. Incidence of a specific type of lesion for a participant was defined by the development of such a lesion in one or both eyes when it was not present at baseline in either eye.

Definitions

Current age was defined as the age at the time of the baseline examination. The mean systolic blood pressure was the average of the 2 systolic blood pressure determinations, and the mean diastolic blood pressure was the average of the 2 diastolic blood pressures at baseline. The pulse pressure was computed by taking the difference between the mean systolic and the mean diastolic blood pressure at baseline. Hypertension was defined as a mean systolic blood pressure of 160 mm Hg or greater and/or a mean diastolic blood pressure 95 mm Hg or greater and/or history of hypertension with use of antihypertensive medication at the time of the baseline examination. Uncontrolled hypertension was defined as a systolic

blood pressure of 160 mm Hg or greater and/or a diastolic blood pressure of 95 mm Hg or greater. A person was defined as having a positive history if he or she responded positively to the questions regarding cardiovascular disease and stroke at baseline. Diabetes was defined as a previous history of diabetes mellitus, treated with either insulin, oral hypoglycemic agents, and/or diet. Newly diagnosed diabetes mellitus was defined as no previous medical history of diabetes mellitus or use of hypoglycemic medications for diabetes mellitus and a glycosylated hemoglobin value that was greater than 2 standard deviations above the mean for a given age-sex group (43 to 54 years of age, men >9.5% and women >9.6%; 55 to 64 years of age, men >9.4% and women >10.0%; 65 to 74 years of age, men >9.6% and women >9.6%; and 75 years of age or older, men >9.5% and women >9.6%) and a random blood glucose level of greater than 200 mg/dL. Primary care physicians were consulted whenever there was doubt about the diagnosis.

Cigarette smoking status was defined as follows: subjects were classified as having never smoked if they reported having smoked fewer than 100 cigarettes in their lifetime; as ex-smokers if they had smoked more than this number of cigarettes in their lifetime but had stopped smoking before the baseline examination; and a current smoker if they had not stopped.

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 incidences were calculated by the direct method.[24] Relative risks and 95% confidence intervals were also calculated. Multivariable analyses were performed by logistic regression.[25] Hypertension status was coded as a set of indicator variables with normotension as the reference group. The attributable risk was defined as the "relative risk - 1/relative risk" in people with the risk factor, uncontrolled hypertension.

RESULTS

Of the 3,684 persons examined at both the baseline and the 5-year follow-up, we excluded 281 persons with a history of diabetes mellitus at baseline, 117 newly diagnosed to have diabetes at follow-up, and 72 persons suspected to have diabetes at either examination, leaving 3,214 persons. Of these, 52 were excluded because the photographs could not be graded for retinal lesions, and 47 were excluded because of central or branch retinal venous or arterial occlusions, retinal detachments, or macular edema due to a condition other than diabetes at the baseline or follow-up. Of the

remaining 3,115 persons, 2,151 (69.1%) were normotensive and 963 (30.9%) were hypertensive at baseline; the presence of hypertension could not be determined in 1 person at baseline.

The frequency of hypertension at baseline rose with increasing age for both men and women (Fig 1). Among those less than 65 years of age, hypertension was more frequent in men; after that, it was more frequent in women.

Over the 5-year period, retinopathy developed in 6.0% of subjects (175/2,921), arteriolar narrowing in 9.9% of subjects (282/2,839), and arteriovenous nicking in 6.5% (201/3,080) of subjects in the population. For men and women, the 5-year incidence of focal arteriolar narrowing and arteriovenous nicking rose significantly with age (Table I).

After controlling for age, men were found to have a 34% lower incidence of focal arteriolar narrowing and a 30% higher incidence of arteriovenous nicking than women (Table II). Although the incidence of retinopathy was higher in men than in women, this difference was not statistically significant.

The relationships between systolic blood pressure, diastolic blood pressure, and pulse pressure and the incidences of retinal lesions are pre-

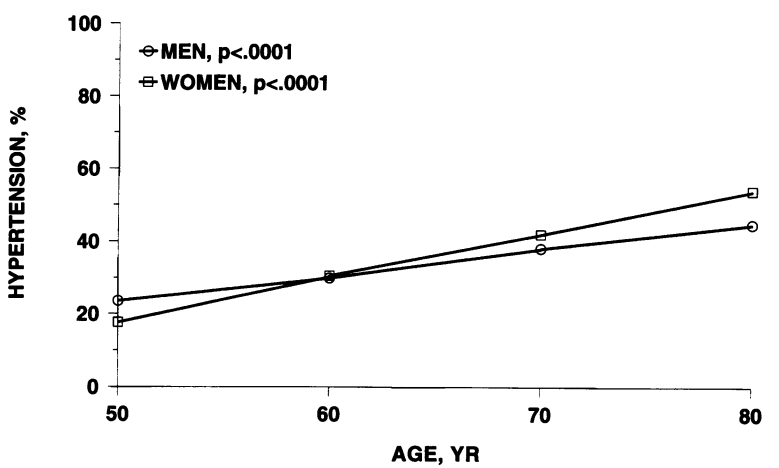

FIGURE 1
Relation of hypertension to age by sex at baseline in Beaver Dam Eye Study (*P*-value is for test of trend).

TABLE I. FIVE-YEAR INCIDENCE OF RETINAL ARTERIOLAR NARROWING, ARTERIOVENOUS NICKING, AND ANY RETINOPATHY BY AGE AND SEX IN THE BEAVER DAM EYE STUDY

END POINT	MEN			WOMEN			TOTAL		
AGE AT BASELINE	NO. AT RISK	%	P-TEST OF TREND	NO. AT RISK	%	P-TEST OF TREND	NO. AT RISK	%	P-TEST OF TREND
Arteriolar narrowing									
45-54 yr	521	2.9		615	4.9		1136	4.0	
55-64 yr	384	7.0	<0.0001	443	10.8	<0.0001	827	9.1	<0.0001
65-74 yr	269	11.2		399	20.8		668	16.9	
75-86 yr	78	25.6		130	22.3		208	23.6	
All	1,252	7.3		1,587	12.0		2,839	9.9	
Arteriovenous nicking									
45-54 yr	530	4.5		626	2.2		1156	3.3	
55-64 yr	407	6.9	<0.0001	479	6.1	<0.0001	886	6.4	<0.0001
65-74 yr	303	10.6		460	9.1		763	9.7	
75-86 yr	94	13.8		181	10.5		275	11.6	
All	1,334	7.3		1,746	6.0		3,080	6.5	
Any retinopathy									
45-54 yr	503	6.2		605	4.3		1108	5.1	
55-64 yr	384	6.0	0.15	447	6.0	0.10	831	6.0	<0.05
65-74 yr	282	5.7		435	6.4		717	6.1	
75-86 yr	88	13.6		177	6.8		265	9.1	
All	1,257	6.5		1,664	5.6		2,921	6.0	

Table II. Age-adjusted Incidence and Relative Risk by Sex for Arteriolar Narrowing, Arteriovenous Nicking, and any Retinopathy in the Beaver Dam Eye Study

End point	Sex	No. at Risk	Age-adjusted Rate %	Relative Risk (95% Confidence Interval)
Arteriolar narrowing	Women	1,587	12.6	1.00
	Men	1,252	8.6	0.66 (0.52, 0.83)
Arterio-venous nicking	Women	1,746	6.0	1.00
	Men	1,334	7.8	1.30 (1.00, 1.70)
Any retinopathy	Women	1,664	5.6	1.00
	Men	1,257	6.8	1.20 (0.90, 1.60)

sented in Table III. The incidence of focal arteriolar narrowing and arteriovenous nicking increased with increasing systolic blood pressure, diastolic blood pressure, and pulse pressure. There was a suggestion of a threshold effect for systolic blood pressure and for pulse pressure at baseline and of the incidence of retinopathy in men whose blood pressures fell above the third quartile cut point being higher than that of men whose pressures fell below this cut point.

After adjusting for age, systemic hypertension at baseline was associated with an increased incidence of focal arteriolar narrowing and retinopathy in both men and women (Fig 2). In women, the incidence of focal arteriolar narrowing and retinopathy was also more frequent in persons not taking antihypertensive medications whose blood pressures were elevated and 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).

Multivariable analyses were conducted to examine the relation of blood pressure and hypertension to the incidence of retinopathy, arteriolar narrowing, and arteriovenous nicking after controlling for other factors besides age associated with the incidence of these lesions (Table V). Higher systolic blood pressure, higher diastolic blood pressure, and higher pulse pressure at baseline were associated with a higher incidence of

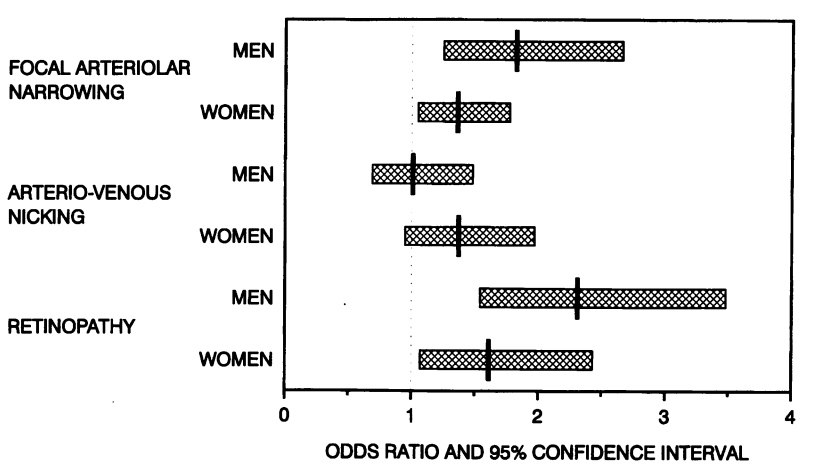

FIGURE 2

Relation of hypertension at baseline to 5-year age-adjusted incidence of focal arteriolar narrowing, arteriovenous nicking, and retinopathy in Beaver Dam Eye Study.

TABLE III. AGE-ADJUSTED INCIDENCE OF ARTERIOLAR NARROWING, ARTERIOVENOUS NICKING, AND RETINOPATHY BY SYSTOLIC BLOOD PRESSURE, DIASTOLIC BLOOD PRESSURE, AND PULSE PRESSURE AT BASELINE IN MEN AND WOMEN IN THE BEAVER DAM EYE STUDY

	MEN				WOMEN			
END POINT	NO. AT RISK	CRUDE RATE (%)	AGE-ADJUSTED RATE (%)	RR (95% CI)	NO. AT RISK	CRUDE RATE (%)	AGE-ADJUSTED RATE (%)	RR (95% CI)
Arteriolar narrowing								
Systolic blood pressure (mm Hg)								
87-116	268	3.0	3.5	1.00	502	5.4	6.8	1.00
117-128	364	5.5	8.2	1.95 (0.90, 4.22)	410	12.0	13.6	1.84 (1.17, 2.90)
129-142	352	7.7	8.2	2.30 (1.09, 4.86)	348	12.6	12.2	1.87 (1.18, 2.98)
143-226	267	13.5	13.1	3.67 (1.84, 7.30)	327	21.4	18.4	2.83 1.84, 4.34)
P test of trend			<0.0005				<0.0001	
Diastolic blood pressure (mm Hg)								
42-70	227	6.2	5.7	1.00	464	11.4	11.0	1.00
71-77	287	5.2	6.4	1.03 (0.52, 2.02)	420	10.7	10.9	0.97 (0.67, 1.41)
78-84	356	8.7	10.9	1.86 (1.04, 3.33)	395	12.2	13.1	1.19 (0.82, 1.72)
85-117	381	8.1	12.9	1.99 (1.10, 3.62)	308	14.3	16.8	1.55 (1.06, 2.27)
P test of trend			<0.005				<0.05	
Pulse pressure (mm Hg)								
16-40	318	3.8	5.8	1.00	473	5.1	5.7	1.00
41-50	381	5.2	6.2	1.22 (0.61, 2.41)	403	10.2	11.6	1.78 (1.09, 2.90)
51-62	330	8.5	9.2	1.54 (0.81, 2.94)	383	13.8	12.3	1.84 (1.10, 3.09)
63-135	222	14.0	10.6	1.81 (0.90, 3.63)	328	22.0	17.6	2.68 (1.61, 4.45)
p test of trend			<0.05				<0.0005	

TABLE III. (CONTINUED) AGE-ADJUSTED INCIDENCE OF ARTERIOLAR NARROWING, ARTERIOVENOUS NICKING, AND RETINOPATHY BY SYSTOLIC BLOOD PRESSURE, DIASTOLIC BLOOD PRESSURE, AND PULSE PRESSURE AT BASELINE IN MEN AND WOMEN IN THE BEAVER DAM EYE STUDY

	MEN				WOMEN			
END POINT	NO. AT RISK	CRUDE RATE (%)	AGE-ADJUSTED RATE (%)	RR (95% CI)	NO. AT RISK	CRUDE RATE (%)	AGE-ADJUSTED RATE (%)	RR (95% CI)
Arteriovenous nicking								
Systolic blood pressure (mm Hg)								
87-116	274	4.4	4.7	1.00	515	3.5	5.1	1.00
117-128	379	6.3	6.9	1.43 (0.74, 2.77)	442	5.2	5.6	1.18 (0.65, 2.14)
129-142	379	7.9	8.2	1.61 (0.85, 3.07)	384	4.7	4.3	0.86 (0.44, 1.64)
143-226	301	10.3	9.8	2.07 (1.08, 3.95)	405	11.1	9.8	2.02 (1.20, 3.39)
P test of trend			<0.05				<0.01	
Diastolic blood pressure (mm Hg)								
42-70	241	5.4	4.9	1.00	499	5.2	5.0	1.00
71-77	304	6.2	7.0	1.36 (0.70, 2.66)	465	6.2	6.0	1.25 (0.76, 2.07)
78-84	375	8.5	9.0	1.83 (0.96, 3.49)	426	4.9	5.0	1.00 (0.57, 1.77)
85-117	413	8.0	10.2	2.02 (1.08, 3.80)	356	7.9	8.4	1.71 (1.01, 2.89)
P test of trend			<0.05				<0.07	
Pulse pressure (mm Hg)								
16-40	323	6.5	7.3	1.00	490	2.7	6.0	1.00
41-50	403	4.5	5.2	0.60 (0.32, 1.11)	433	5.1	5.9	1.48 (0.75, 2.95)
51-62	354	8.2	8.3	1.02 (0.57, 1.81)	414	7.2	6.7	2.01 (1.03, 3.90)
63-135	253	11.5	11.2	1.41 (0.78, 2.54)	409	9.5	7.2	2.11 (1.01, 4.41)
p test of trend			<0.17				<0.05	

TABLE III. (CONTINUED) AGE-ADJUSTED INCIDENCE OF ARTERIOLAR NARROWING, ARTERIOVENOUS NICKING, AND RETINOPATHY BY SYSTOLIC BLOOD PRESSURE, DIASTOLIC BLOOD PRESSURE, AND PULSE PRESSURE AT BASELINE IN MEN AND WOMEN IN THE BEAVER DAM EYE STUDY

	MEN				WOMEN			
END POINT	NO. AT RISK	CRUDE RATE (%)	AGE-ADJUSTED RATE (%)	RR (95% CI)	NO. AT RISK	CRUDE RATE (%)	AGE-ADJUSTED RATE (%)	RR (95% CI)
Retinopathy								
Systolic blood pressure (mm Hg)								
87-116	265	3.8	4.4	1.00	500	4.8	5.2	1.00
117-128	353	5.9	5.3	1.65 (0.78, 3.49)	427	3.0	3.0	0.64 (0.34, 1.22)
129-142	357	4.2	4.2	1.14 (0.52, 2.48)	362	6.9	6.6	1.23 (0.69, 2.21)
143-226	281	12.8	12.6	3.06 (1.61, 5.80)	375	8.3	8.1	1.55 (0.89, 2.71)
p test of trend			<0.0005				<0.05	
Diastolic blood pressure (mm Hg)								
42-70	233	6.4	6.0	1.00	480	5.4	5.5	1.00
71-77	286	5.6	6.6	1.04 (0.54, 2.02)	447	5.1	5.0	0.94 (0.54, 1.64)
78-84	352	6.0	6.4	1.05 (0.54, 2.03)	401	4.5	4.8	0.89 (0.50, 1.58)
85-117	385	7.8	7.5	1.30 (0.67, 2.51)	336	7.7	7.6	1.42 (0.82, 2.44)
P test of trend			<0.21				<0.22	
Pulse pressure (mm Hg)								
16-40	305	5.2	4.3	1.00	483	5.0	7.5	1.00
41-50	380	4.7	4.6	1.04 (0.55, 1.97)	407	3.9	3.8	0.78 (0.43, 1.42)
51-62	338	4.4	4.5	0.79 (0.36, 1.74)	395	5.3	5.0	0.93 (0.51, 1.70)
63-135	233	14.2	13.4	2.93 (1.45, 5.94)	379	8.4	8.4	1.35 (0.74, 2.44)
P test of trend			<0.001				<0.11	

TABLE IV. AGE-ADJUSTED INCIDENCE OF ARTERIOLAR NARROWING, ARTERIOVENOUS NICKING, AND RETINOPATHY BY HYPERTENSION STATUS AT BASELINE IN MEN AND WOMEN IN THE BEAVER DAM EYE STUDY

	MEN				WOMEN			
END POINT	NO. AT RISK	CRUDE RATE (%)	AGE-ADJUSTED RATE (%)	RR (95% CI)	NO. AT RISK	CRUDE RATE (%)	AGE-ADJUSTED RATE (%)	RR (95% CI)
Arteriolar narrowing								
Normotensive	885	5.3	6.9	1.00	1,109	9.6	11.4	1.00
Untreated hypertensive	84	13.1	15.2	2.39 (1.31, 4.38)	69	21.7	23.1	1.97 (1.21, 3.21)
Treated, normal blood pressure	227	11.9	11.2	1.64 (1.05, 2.54)	346	15.3	13.4	1.14 (0.84, 1.55)
Treated, high blood pressure	55	10.9	12.1	1.80 (0.81, 3.98)	63	25.4	21.1	1.80 (1.13, 2.88)
Arteriovenous nicking								
Normotensive	932	7.0	8.4	1.00	1,201	4.7	5.4	1.00
Untreated hypertensive	92	5.4	5.9	0.77 (0.33, 1.80)	97	13.4	12.2	2.23 (1.27, 3.92)
Treated, normal blood pressure	245	9.0	9.7	1.08 (0.70, 1.65)	374	6.7	6.4	1.05 (0.67, 1.63)
Treated, high blood pressure	64	7.8	8.8	0.95 (0.41, 2.24)	74	12.2	10.3	1.65 (0.84, 3.24)
Retinopathy								
Normotensive	885	4.6	4.9	1.00	1,154	4.6	4.7	1.00
Untreated hypertensive	87	18.4	19.3	3.82 (2.27, 6.42)	90	10.0	10.0	2.13 (1.08, 4.18)
Treated, normal blood pressure	225	8.4	8.3	1.74 (1.02, 2.97)	355	6.5	6.0	1.32 (0.80, 2.16)
Treated, high blood pressure	59	10.2	10.7	2.16 (0.96, 4.86)	65	12.3	10.1	2.46 (1.18, 5.10)

TABLE V. LOGISTIC REGRESSION ANALYSIS CONTROLLING FOR AGE AND SEX* IN THE BEAVER DAM EYE STUDY.

END POINT	CHARACTERISTIC†	ODDS RATIO (95% CI)	P
Arteriolar narrowing	Systolic blood pressure, 10 mm Hg	1.21(1.13, 1.29)	<0.0001
	Diastolic blood pressure, 10 mm Hg	1.32 (1.15, 1.50)	<0.0001
	Pulse pressure, 10 mm Hg	1.20 (1.11, 1.30)	<0.0001
	Hypertension status		<0.0001
	Untreated hypertension‡	2.47 (1.54, 3.96)	
	Treated - normal blood pressure‡	1.32 (0.97, 1.78)	
	Treated - high blood pressure‡	2.04 (1.22, 3.42)	
Arteriovenous nicking	Systolic blood pressure, 10 mm Hg	1.16 (1.08, 1.25)	<0.0001
	Diastolic blood pressure, 10 mm Hg	1.29 (1.11, 1.49)	<0.001
	Pulse pressure, 10 mm Hg	1.13 (1.04, 1.24)	<0.01
	Hypertension status - Men§		<0.92
	Untreated hypertension‡	0.75 (0.29, 1.93)	
	Treated - normal blood pressure‡	1.08 (0.65, 1.82)	
	Treated - high blood pressure‡	1.01 (0.39, 2.62)	
	Hypertension status - Women§		<0.05
	Untreated hypertension‡	2.51 (1.30, 4.83)	
	Treated - normal blood pressure‡	1.03 (0.62, 1.70)	
	Treated - high blood pressure‡	1.88 (0.88, 4.05)	

TABLE V. (CONTINUED) LOGISTIC REGRESSION ANALYSIS CONTROLLING FOR AGE AND SEX* IN THE BEAVER DAM EYE STUDY

ENDPOINT	CHARACTERISTIC†	ODDS RATIO (95% CI)	P
Retinopathy	Systolic blood pressure, 10 mm Hg	2.14 (1.54, 2.97)	<0.0001
	Diastolic blood pressure, 10 mm Hg	1.54 (1.10, 2.16)	<0.05
	Pulse pressure, 10 mm Hg	2.31 (1.62, 3.29)	<0.0001
	Hypertension status		<0.0001
	Untreated hypertension‡	3.29 (2.05, 5.27)	
	Treated - normal blood pressure‡	1.51 (1.02, 2.22)	
	Treated - high blood pressure‡	2.43 (1.34, 4.43)	

*Total cholesteral, HDL cholesterol, Total/HDL ratio, hematocrit, glycosylated hemoglobin, and history of cardiovascular disease were also examined for confounding effects. None were found.

† Each variable (systolic blood pressure, diastolic blood pressure, pulse pressure, and hypertension status) was included in a separate logistic regression model.

‡ Reference group is normotension.

§ Separate models were developed for men and women because there is a significant interaction between sex and hypertension.

focal arteriolar narrowing, arteriovenous nicking, and retinopathy. For every 10-mm Hg increase in systolic blood pressure at baseline, there was a 21% increase in the odds ratio of developing arteriolar narrowing and a 16% increase in development of arteriovenous nicking in the population. Hypertension at baseline was also associated with the incidence of focal arteriolar narrowing and retinopathy. The relationship between hypertension and the incidence of arteriovenous nicking was significant in women only.

In Beaver Dam, among those with uncontrolled hypertension, 60% of the incidence of retinopathy, 49% of the incidence of focal arteriolar narrowing, and 37% of the incidence of arteriovenous nicking is attributable to the uncontrolled hypertension and the remainder is attributable to other factors.

DISCUSSION

Our data show a relation of uncontrolled systemic hypertension to an increased incidence of retinopathy and focal arteriolar narrowing in persons without diabetes. After adjusting for other risk factors, nondiabetic persons with treated but uncontrolled hypertension were twice as likely to develop focal arteriolar narrowing and 2.4 times as likely to develop retinopathy as normotensive persons. Persons with treated but controlled hypertension had lower risks of developing focal arteriolar narrowing and retinopathy than persons whose hypertension was not controlled. These data are consistent with the higher prevalence of these retinal changes in persons with hypertension reported at baseline in Beaver Dam and in other studies.[3,9,26] In Evans County, Georgia, retinopathy was present in 2.3% of white males and 4.9% of white females whose diastolic blood pressure was greater than 100 mm Hg.[26] In a population-based study of 855 men 50 years of age in Göteborg, Sweden, mean systolic and diastolic blood pressures were significantly ($P<.05$) higher in those subjects with arteriolar narrowing and retinopathy than in those without these signs.[8] However, not all data from other studies are consistent with these findings.[7,10]

If focal retinal arteriolar narrowing and retinopathy reflect an adverse effect of systemic hypertension on the microvasculature of the kidney, heart, or central nervous system, ophthalmoscopy may add further information about potential systemic complications associated with hypertension. Before the widespread use of antihypertensive medications, data from one study showed that the presence of retinopathy in persons with hypertension was associated with a higher 10-year cardiovascular disease mortality than that of an age- and sex-matched normotensive population.[27] In the Göteborg population, after controlling for systolic blood pressure and other risk factors, people with arteriolar narrowing or arteriovenous

nicking had increased 8-year mortality rates.[8] More recently, Dahlof and associates[28] 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.

The incidence of arteriovenous nicking was higher in women but not in men with uncontrolled hypertension. The reason for this finding is not known. It is possible that other conditions, such as arteriolar sclerosis, which are postulated to be causally related to the development of arteriovenous nicking, may have different frequencies in men and women.

The high incidence of retinal lesions found in our nondiabetic Beaver Dam population may be due to atherosclerotic disease of the internal carotid arteries affecting retinal blood vessels and flow.[6,29,30] Leishman[6] hypothesized that retinal arteriolar sclerosis, which may be associated with aging and hypertension, is important in the pathogenesis and appearance of the retinal lesions associated with the direct effects of systemic hypertension. The findings of a strong relationship between pulse pressure, which has been suggested as an indicator of large-vessel atherosclerosis and the incidence of arteriovenous nicking, focal arteriolar narrowing, and retinopathy in our population is consistent with this hypothesis.

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 incidence of retinal lesions is that persons with high diastolic blood pressure who developed retinal lesions may have died before their follow-up examination was performed.

The retinal lesions might have resulted from conditions in a nondiabetic person that were not asked about or determined in the study, such as atherosclerotic vascular disease or acquired immune deficiency syndrome. Except for 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.

Misclassification of hypertension status as derived from the clinical examinations may have occurred because the classification was based, in part, on two measurements of the blood pressure during a single examination. When we analyzed the data for hypertension status based on the second examination findings, however, we found no differences in the relationships reported (Klein R., unpublished data).

SUMMARY

This study provides precise estimates of the incidence of retinal lesions in nondiabetic persons by blood pressure levels and hypertension status. The

findings suggest that the incidence of retinopathy (4.6% in normotensives and 9.2% in people with hypertension) and retinal arteriolar narrowing (7.7% in normotensives and 15.2% in people with hypertension) was common. The relationship of these signs in people with systemic hypertension to cardiovascular disease morbidity and mortality needs to be determined.

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DISCUSSION

WILLIAM TASMAN, MD. It is a pleasure for me to discuss yet another Beaver Dam Study, this one on the relationship of systemic hypertension to retinopathy and changes in the retinal vasculature. Before I reviewed the paper, I was curious to know how many previous Beaver Dam studies there had been. I gave up my search at 23 and called Dr Ronald Klein, who told me that the number was in the neighborhood of 70, although not all are in the ophthalmic literature.

In this most recent investigation, carefully done as are all of the studies from Beaver Dam, patients between the ages of 43 and 86 were examined initially, and then again after 5 years. Stereoscopic photographs were graded in a masked fashion to determine the presence or absence of retinopathy, retinal arteriolar narrowing, and arteriovenous nicking.

The incidence of hypertensive retinopathy was 6%, arterial narrowing 9.9%, and arteriovenous nicking 6.5%. The authors concluded that hypertension was associated with an increased incidence of retinopathy and arteriolar narrowing, and that pharmacologic control of blood pressures was related to a lower incidence of these lesions.

As with any study of this nature, the question of assessing good control is vital because of the wide swings in blood pressure that may occur over a 24-hour period. For example, a 76-year-old man taking Tenormin and Cardene, who was examined by us, had the following blood pressures at different times of the day: 240/120 at 8 AM, 210/105 at 10:30 AM, 150/90 at 12:30 PM, and 180/110 at 2:30PM. If the 12:30 PM window were the only one measured, it is easy to see how one could be misled as to the degree of control. So we are governed by practical limitations in establishing whether or not the blood pressure is at a satisfactory level.

Despite this, it is important to recognize that in this protocol, uncontrolled hypertensives were twice as likely to develop focal arteriolar narrowing and 2.4 times as likely to develop retinopathy as normotensive individuals. This highlights the importance of checking our patients' blood pressures. We have all seen those who claim to be controlled, such as the example presented earlier, who, when checked, clearly are not.

Beaver Dam, as pointed out by the authors is a 99% white community. One wonders whether the authors might find a higher incidence of retinopathy, arteriolar narrowing, and arteriovenous nicking in a population of African Americans, where hypertension is frequently more devas-

tating than in Caucasians, again often because of poor control.

The authors mention intraretinal microvascular abnormalities (IRMA) as one of the retinopathy changes noted in the study. In our experience, this is an exceedingly rare occurrence in hypertension, and I wondered what the frequency of this finding was in the Beaver Dam population. Finally, although vein occlusions and macroaneurysms were excluded from the study, I would like to ask if the authors have any information that may have been recorded about these occurrences.

Once again, the Drs Klein and coworkers have provided us with additional helpful information that is clinically relevant to the management of our patients. I congratulate them on another excellent Beaver Dam Study, and thank the Program Committee for allowing me to discuss this paper.

THOMAS P. KEARNS, MD. I would like to thank the Drs Klein for this fine paper. This is the first paper today that I can understand, and it is the first subject that I know anything about. My discussion is much the same as I made following your 1993 AOS presentation on hypertension, but I do believe it is important and bears repetition. None of your subjects had papilledema. This is understandable, because papilledema is only a part of the retinopathy of hypertension when the diastolic pressure is about 120 or more. Since the advent of effective hypertensive therapy in the 1950s, we do not see such papilledema as we did in the days before effective therapy was available. Dr Klein, I wonder if you have ever seen papilledema as a part of hypertensive retinopathy. Most younger ophthalmologists have not seen this, but it must be kept in mind. If it is not properly identified, much valuable time can be lost before the patient receives the proper treatment.

JOSE PULIDO, MD. I would like to congratulate Dr Klein. I have learned so much from all of the papers the Kleins have written over the years. My concern in this paper is that considering 50% of persons with type II diabetes are undiagnosed, were glycosolated hemoglobin levels evaluated in every patient to be sure the reported incidences of retinopathy did not actually include some cases of undiagnosed type II diabetes?

JONATHAN WIRTSCHAFTER, MD. I want to congratulate the Kleins on their paper. I have one question in terms of the take-home message. What happens to the patient who assures us that their blood pressure is normal but in whom we identify findings that suggest systemic hypertension? Do we ask them to go home and ask for more careful blood pressure monitoring? Do we tell them their doctor isn't paying enough attention to their blood pressure even though the numbers are normal? Is there some reason that we should be talking about antiplatelet-aggregation therapy?

RONALD KLEIN, MD. I want to begin by thanking Dr Tasman for his remarks. In answer to the specific questions, none of the individuals developed intraretinal microvascular abnormalities (IRMAs) during the 5-year period. I agree completely with Dr Tasman that ambulatory blood pressures are very important, and misclassification can occur with persons who have high blood pressures in the evening and low blood pressures at other times of the day. In our study, the lack of measurements of ambulatory blood pressures might lead to misclassification of the actual hypertension status that would probably weaken the association with retinal arteriolar changes that we report. Thus, our findings are conservative. We did have a second blood pressure measurement at the time of the second eye exam. When we reanalyzed the data using the blood pressure value and hypertension status at the second examination, there were no changes in any of the relationships that we report.

The question of higher rates of retinal vascular changes in blacks compared with whites is important, since hypertension is more prevalent in blacks than in whites. We had very few blacks in the Beaver Dam population. Data from the Evans County Heart Study, a biracial study in the 1960s, showed a higher rate of retinal vascular abnormalities in blacks than in whites. We are currently examining these relationships in the Atherosclerosis Risk Study.

In response to Dr Kearns, we did not see a single person in the entire population develop disc edema associated with hypertension at baseline or follow-up. I have observed a patient with blood pressure of 240/130 who had papilledema. It was the first time in nearly 20 years that I had seen this finding in a person with hypertension.

In response to Dr Pulido's concern, we did measure glycosolated hemoglobin in both Beaver Dam examinations and used classification criteria to categorize people as having "suspect" or "newly diagnosed" diabetes. We feel confident that we excluded people who did not know that they had diabetes in our study.

Finally, Dr Wirtschafter, I'm not sure whether hypertension is one of the "success" stories actually in terms of achieving good control through treatment. In Beaver Dam, for example, there are still many people who have uncontrolled hypertension despite taking antihypertensive medication. I'm not sure that our data suggest antihypertensive intervention is necessary to minimize the incidence of these retinal vascular complications. I think the importance of our data is whether the development of these retinal vascular complications adds additional information to the ambulatory blood pressures regarding cardiovascular disease mobidity and mortality. If so, such patients showing these retinal signs should be treated more aggresively with antihypertensive medications.