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Relation of Blood Pressure to Retinal Vessel Diameter in Type 1 Diabetes Mellitus

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Abstract

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Objective—To examine the relationship of blood pressure (BP) and use of angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACEI) to retinal vessel diameter in normotensive, normoalbuminuric persons with type 1 diabetes mellitus (T1DM).

Design—Randomized controlled clinical trial.

Participants—Persons with T1DM and gradable fundus photographs both at baseline (n=147) and 5-year follow-up (n=124).

Methods—Clinic and 24-hour ambulatory BPs (ABP) were measured. Retinal arteriolar and venular diameters were measured using a computer-assisted technique. Individual arteriolar and venular measurements were combined into summary indices that reflect the average retinal arteriolar (central retinal arteriolar equivalent [CRAE]) and venular (central retinal venular equivalent [CRVE]) diameter of an eye, respectively.

Main Outcome Measures—CRAE and CRVE.

Results—While controlling for age, study site, glycosylated hemoglobin and ambulatory pulse rate, daytime ambulatory systolic (-0.29 μm effect per 1mmHg, *P*=.02) and daytime ambulatory diastolic (-0.44 μm effect per 1mmHg, *P*=.04), nighttime ambulatory systolic (-0.27 μm effect per 1mmHg, *P*=.03), and 24-hour ambulatory systolic BP (-0.31 μm effect per 1mmHg, *P*=.03) were cross-sectionally associated with a smaller CRAE. While controlling for age, study site, glycosylated hemoglobin, ambulatory pulse rate and baseline CRAE, no BP measure was associated with a change in CRAE or CRVE over 5 years of follow-up. Treatment with losartan or enalapril was not associated with a statistically significant change in CRAE or CRVE.

Conclusions—ACEI or ARB therapy does not affect retinal arteriolar or venular diameter in normotensive persons with T1DM.

Higher mean arterial blood pressure (MABP) has been consistently shown to be related to narrower retinal arterioles.1-6 Most studies showing this relation have been cross-sectional and involved general populations of middle to older-aged persons and individuals with hypertension. There are few studies which have examined whether increases in blood pressure (BP) over time are related to a subsequent decrease in the retinal arteriolar diameter and whether antihypertensive treatment affects retinal arteriolar and venular diameters.7-11 In a cross-sectional study in a general population, a history of use of an angiotensin-receptor-converting enzyme inhibitor (ACEI) was not related to retinal arteriolar or venular caliber.7 In the Anglo-Scandinavian Cardiac Outcomes Trial, involving 712 hypertensive individuals, despite similar blood pressure levels, persons randomized to a calcium channel blocker, amlodipine had a smaller arteriolar length to diameter ratio, a measure of retinal arteriolar narrowing, compared to those randomized to a beta blocker, atenolol.10 While the data suggest that blood pressure lowering is associated with a decrease in retinal arteriolar narrowing due to hypertension, it is not certain whether drugs, such as amlodipine, alters small artery structure independent of BP reduction during antihypertensive treatment. There were no differences in venular measures between treatment groups in this study. In another study involving non-diabetic hypertensive patients, treatment with losartan, an angiotensin-receptor blocker (ARB) led to an increase in the retinal arteriolar but did not affect the venular diameter.8 In a randomized controlled clinical trial in men with untreated hypertension, an ACEI, enalapril, but not a diuretic, hydrochlorothiazide, was shown to reduce narrowing of retinal arterioles.9 In a small study of 25 men with untreated hypertension randomized to treatment with an amlodipine or lisinopril over a one year period, blood pressure reduction using both treatments were associated with a reduction in arteriolar narrowing but had no effect on venular diameter.11

There are no comparable data on the effect of ACEI or ARB on retinal arteriolar diameter in normotensive persons with type 1 diabetes mellitus (T1DM). Understanding the relation of these drugs to retinal arteriolar narrowing and venular widening is important because the latter

are thought to be markers of microvascular changes in the cerebral, coronary, peripheral, and renal circulations, and possibly of pathogenetic processes damaging to other targets of diabetic microvascular injury.[4,5,12-20] In this report, we examine the relation of ACEI or ARB treatment and blood pressure to changes in retinal vessel caliber in a randomized controlled clinical trial of normotensive normoalbuminuric (NA) persons with T1DM.[21]

Methods

Description of Cohort

The Renin-Angiotensin System Study (RASS) was a parallel, double-blind, placebo-controlled, multicenter, clinical trial of primary prevention of diabetic nephropathy conducted at three clinical centers in Minneapolis, Minnesota, United States and Montreal, Quebec and Toronto, Ontario, Canada. The study design and cohort description have been detailed elsewhere.[21,22] The study was conducted and data were collected with Institutional Review Board approval in conformity with all federal, state and provincial laws, and the study was in adherence with the tenets of the Declaration of Helsinki as revised in 1983. Informed consent was obtained. Subjects were 15 years of age or older with 2 to 20 years of T1DM and onset before their 45th birthday. All were normotensive, NA (albumin excretion rate [AER] <20 μg/min on at least 2 of 3 timed overnight urine collections) and had a normal or increased glomerular filtration rate ≥90 mL/min/1.73 m^2. Two hundred and eighty-five subjects were randomized into one of the following three treatment groups: losartan (an ARB), enalapril, or placebo.[22] We limited our analyses to only the 147 who had fundus photography before randomization into the trial and whose retinal vessels were measurable. Those included were older and after controlling for age, there were no statistically significant differences (P <0.05) in glycosylated hemoglobin, blood pressure, retinopathy severity and other characteristics in those included and excluded in the analyses (Table 1).

Blood Pressure, Weight, Height

The baseline and follow-up examinations included clinic measurement of BP and pulse rate (PR), with the participant in the seated position after resting for 5 minutes, using an automated BP device (DinaMap Vital Signs Monitor #18465X). Three readings of the systolic (S)BP and fifth phase diastolic (D)BP were recorded one minute apart, and the average of the second and third readings was used as the mean for each visit. This was labeled clinic BP.

Annual 24-hour ambulatory BP (ABP) and ambulatory pulse rate (APR) monitoring were performed using the SpaceLabs 90207 monitor (Redmond, WA). BP was recorded at 20 minute intervals day and night for a period of 24 hours and individual measurement values were analyzed on a Macintosh personal computer (Apple Computers, Cupertino, CA) using Mathematica 3.0 (Wolfram Research, Champagne, IL). Individual BP and PR values were excluded if any of the following criteria were met: DBP > SBP, DBP <49 or >150 mmHg, SBP <60 or >250 mmHg, SBP - DBP <10 mmHg, or PR <50 or >175 beats/minute. Individual records were discarded if >20% of measurements had been excluded or if a recording gap of > 4 hours was present. Mean systolic (S)ABP and diastolic (D)ABP and intra-individual standard deviation (SD) were calculated for the entire 24-hour record. Daytime values were calculated for the hours 10:00-20:00; nighttime values were calculated for the hours 00:00-06:00.[23] Participants were defined as nondippers if the night/day ratios for both systolic ABP and diastolic ABP were >0.9.[23,24]

Height and weight were measured according to standard anthropometric procedures.

Retinal Measurements

Pupils were dilated, and 30° color stereoscopic fundus photographs were taken of the seven standard fields as defined in the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol.25 The photographs were graded in a masked fashion by the University of Wisconsin Ocular Epidemiology Reading Center using the modified Airlie House Classification scheme and the ETDRS retinopathy severity scale. Grading protocols have been described in detail elsewhere.25,26 For each eye, the maximum grade in any of the seven standard photographic fields was determined for each of the lesions and used to define the "retinopathy levels". For purposes of classification, if the retinopathy severity could not be graded in an eye, it was considered to have a score equivalent to that in the other eye. Diabetic retinopathy (DR) severity, based on the more severe eye, was grouped as follows: None (Level 10), Mild DR (Levels 20-43) and Moderate to Severe DR (Levels ≥47).

Retinal vessel diameters were measured at the baseline and 5-year follow-up examinations using a computer-assisted technique based on the following standard protocol: retinal photographs of field 1 (centered at the optic nerve head) were converted to digital images by a high-resolution scanner using identical settings for all photographs.1 Retinal vessel measurements were done independently for each examination and each eye. Trained graders masked to participant characteristics measured the diameters of all arterioles and venules coursing through a specified area one-half to one disc diameter surrounding the optic disc using a computer software program. On average, between 7 and 14 arterioles and between 7 and 14 venules were measured per eye. Individual arteriolar and venular measurements were combined into summary indices that reflect the average retinal arteriolar (central retinal arteriole equivalent [CRAE]) and venular (central retinal venule equivalent [CRVE]) diameter of an eye, respectively, based on the Parr-Hubbard-Knudtson formula.27 Graders regularly participated in quality control exercises; the inter- and intra-grader variability was small (interclass and intraclass correlations >0.90 for CRAE and CRVE).

Statistics

Statistical analyses were conducted in SAS, version 9 (SAS Institute Inc., Cary, NC). Means were compared for statistically significant differences by the t-test and analysis of variance when two or more than two groups, respectively, were involved. Multivariable associations between clinic BP, ABP and APR (and changes in these measures) and ACEI, ARB, or control placebo status with changes in CRAE and CRVE were explored by multiple linear regression controlling age, site, glycosylated hemoglobin, and APR. In additional analyses, baseline CRAE was controlled for in models involving changes in CRAE and baseline CRVE was controlled for in models involving changes in CRVE.

Results

Description of Cohort

At baseline, the mean age was 31.3 ± 9.3 years, mean duration of T1DM was 11.2 ± 4.7 years, mean clinic SBP, DBP, MABP, and 24-hour ASBP and ADBP were 119.8 ± 12.0, 70.8 ± 8.2, 87.0 ± 8.6, 117.8 ± 8.8, and 71.4 ± 5.4 mmHg, respectively, mean glycosylated hemoglobin level was 8.5 ± 1.6%, mean CRAE was 158.4 ± 13.6 μm with a range of 123.8 to 194.4 μm and mean CRVE was 227.0 ± 21.2 μm with a range of 178.9 to 289.1 μm in the 147 RASS participants in whom retinal photography was done prior to randomization into the RASS. Eighty-eight percent of the cohort had no or mild DR (ETDRS severity score of 37/37 or less). Twenty-two percent of the cohort were nondippers.

Cross-Sectional Relationships with CRAE and CRVE

At baseline, older age, higher clinic SBP, DBP, and MABP, 24-hour ASBP and ADBP, and daytime ASBP and ADBP were inversely associated with CRAE (Table 2). Gender, glycosylated hemoglobin, body mass index, clinic pulse pressure, ambulatory pulse, nighttime ASBP and ADBP, smoking status, dipper status, DR severity, and treatment group were not statistically significantly associated with CRAE.

Age, clinic SBP, DBP, and MABP were inversely associated with CRVE while APR was directly associated with CRVE (Table 2). Gender, glycosylated hemoglobin, body mass index, clinic pulse pressure, 24-hour ASBP and ADBP, daytime or nighttime ASBP or ADBP, dipper status, smoking status, DR severity, and treatment group randomized to were not statistically significantly associated with CRVE.

Multivariate analyses, controlling for age, study site, glycosylated hemoglobin level, and APR, showed that higher baseline levels of 24-hour ASBP, daytime ASBP and ADBP, and nighttime ASBP were associated with smaller CRAE (Table 3). While controlling for the same factors, there were no statistically significant associations of clinic SBP, DBP or MABP, 24-hour ADBP, nighttime ADBP or dipper status with CRAE and no relation of any BP measure with CRVE (Table 3).

Relationships of Blood Pressure, Treatment Status and Other Factors at Baseline to Change in CRAE and CRVE Over 5 Years

There were 124 persons who had fundus photographs before randomization and who had both baseline and 5-year follow-up photographs gradable for retinal vessel measurements. The mean increase in CRAE over the 5-year period was 1.61 ± 8.14 μm with a range from -14.53 μm to 36.62 μm and for CRVE it was 4.08 ± 15.83 μm with a range from -29.28 μm to 63.60 μm.

The relationships of baseline characteristics to changes in retinal vessel measures are presented in Table 4. Higher baseline daytime ADBP was significantly associated with a 5-year increase in CRAE. Daytime ADBP remained significantly associated with an increase in CRAE while adjusting for age, study site, glycosylated hemoglobin, and APR (data not shown). However, when baseline CRAE (P=.08) was controlled for in the multivariate model, the association was no longer statistically significant (data not shown). Baseline age, gender, glycosylated hemoglobin level, smoking status, body mass index, clinic SBP, DBP, and MABP, 24-hour ADBP, daytime ASBP, nighttime ASBP and ADBP, dipper status, and DR severity were not related to change in CRAE. When the analyses were limited to the placebo group, none of the blood pressure measures were associated with an increase in CRAE.

Clinic SBP, DBP, and MABP at baseline were the only factors related to larger increase in the CRVE (Table 4). Age, sex, and none of the other baseline BP measures were associated with a change in CRVE. Clinic SBP and MABP remained significantly associated with an increase in CRVE while adjusting for age, study site, glycosylated hemoglobin, and APR (data not shown). When baseline CRVE was also controlled for in the model, the association of clinic SBP with change in CRVE remained statistically significant (P=.05) while clinic MABP (P=.08) was no longer associated with change in CRVE (data not shown). Clinic DBP (P=0.14) was no longer associated with CRVE after controlling for age, study site, glycosylated hemoglobin level, and APR (data not shown). Similar relationships were found when percentage instead of absolute change in CRAE or CRVE was used as the endpoint (data not shown).

There were no differences in the changes in the mean CRAE among the 3 treatment groups. The difference in the change in CRAE between enalapril and placebo groups was 1.49 ± 1.80

μm (P=0.99) and between losartan and placebo it was 1.15 ± 1.81 μm (P=0.99). Adjusting for age, site, and daytime ADBP did not change these relationships (data not shown).

While controlling for age and site, there were no statistically significant interactions of any of the BP medications by treatment status for change in CRAE (data not shown).

Relationships of Average Blood Pressure to Change in CRAE and CRVE

While controlling for age, study site, glycosylated hemoglobin, and APR, none of the 5-year average BP variables were significantly associated with change in CRAE or CRVE (data not shown). There was no change after further controlling for baseline CRAE or CRVE in the models (data not shown).

Discussion

We had hypothesized that higher BP at baseline would be associated with narrower retinal arteriolar diameters as measured by CRAE and that renin-angiotensin system blockade would result in larger CRAE and smaller CRVE compared to those assigned to placebo independent of BP level. The hypothesized relation of renin-angiotensin system blockade with retinal arteriolar diameter was based on observations that ACEI and ARB block the local renin system in the eye. The expected relation with retinal venular diameter was based on observations that ACEI and ARB may reduce inflammation and endothelial dysfunction, both previously shown to be related to larger CRVE.[18,28-37] While controlling for age and other factors, we found an inverse cross-sectional association of daytime ASBP and ASDP, nighttime ASBP, and 24-hour ASBP at baseline with CRAE, no relation of any BP measure with change in CRAE, and no relation of the 5-year average of any BP measure with change in CRAE. There was no statistically significant effect of enalapril or losartan when compared to placebo with changes in CRAE or CRVE in the normotensive NA patients with T1DM in our study.

Higher BP has been consistently found to be associated with smaller CRAE.[1-5] In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, in persons with type 1 and 2 diabetes which included those with hypertension, an increase in BP was cross-sectionally associated with a smaller CRAE.[2,6] It has been hypothesized that this was due to the damaging effect of higher levels of BP on arteriolar structure. In the RASS, higher 24-hour ASBP and daytime ASBP were all related to smaller CRAE at baseline, but no BP measure at baseline or averaged over the study was related to change in CRAE over the 5-year period. Thus, in normotensive NA patients with T1DM, higher baseline BP does not appear to be associated with a decrease in retinal arteriolar narrowing over a 5 year period.

Treatment with enalapril and losartan reduced the rate of 2-step or more progression of DR by approximately 65% in the RASS but had no effect on CRAE and CRVE.[21] The lack of an effect on CRAE and CRVE in our study is not consistent with findings of earlier studies that showed that ACEI or ARB treatment either reduced the amount of retinal arteriolar narrowing or increased retinal arteriolar width.[8,9] These studies involved treatment in older hypertensive patients and the effect of such treatment would be expected to be weaker and less apparent in younger normotensive individuals in which the retinal arterioles would unlikely be narrowed at baseline.[8-11]

DR severity was unrelated to CRAE or CRVE in the RASS. This was unexpected based on earlier observations in the WESDR.[2] In that study, increasing severity of retinopathy was associated with a gradual decrease in mean arteriolar diameter and an increase in venular diameter in people with T1DM. Differences in factors associated with CRAE and CRVE such as higher blood pressure, glycosylated hemoglobin, and lipid levels, and the frequency of renal

disease in the WESDR compared to the RASS may, in part, explain the differences between the studies.

There are several strengths to our study, namely, the objective determination of retinal vessel caliber using standardized protocols for photography and grading, the research protocol clinic measurements of SBP and DBP 4 times per year, and the annual measurement of ABP over a 5-year period. However, caution must be observed in interpreting the findings described herein. Factors associated with variability of measurements of CRAE and CRVE, e.g., variation in photograph quality, the time in the pulse cycle that the photographs were taken, and grader variability in measuring retinal vessels may have limited the ability to find associations with retinal vessel measurements in this cohort. Second, there was limited variability of change in blood pressure in this normotensive cohort. Third, the sample sizes were relatively small. Fourth, other measures of arteriolar changes, e.g., tortuosity, bifurcation angle, and optimality, that might be affected by blood pressure, were not measured in this study.[10]

In summary, use of ACEI or ARB, despite their beneficial effect in reducing the progression of DR, were not statistically significantly associated with changes in retinal blood vessel caliber in younger normotensive NA patients with T1DM.

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Table 1

Difference in Various Baseline Characteristics Between Those Included and Excluded from Analyses in the Renin-Angiotensin System Study

	Included			Excluded				
Characteristic	**N**	**Mean (%)**	**SD**	**N**	**Mean (%)**	**SD**	***P*-value***	**Age-adjusted *P*-value†**
Age (years)	147	31.33	9.33	138	27.88	9.89	0.003	
Male gender	67	45.8		65	47.1		0.80	0.38
Glycosylated hemoglobin (%)	147	8.49	1.55	137	8.65	1.59	0.39	0.67
Body mass index (kg/m2)	147	26.11	3.92	138	25.28	3.39	0.06	0.09
Clinic SBP (mmHg)	147	119.78	12.04	138	119.54	10.99	0.87	0.51
Clinic DBP (mmHg)	147	70.57	8.20	138	69.76	8.56	0.41	0.74
Clinic MABP (mmHg)	147	86.98	8.58	138	86.36	8.45	0.54	0.60
Clinic pulse pressure (mmHg)	147	49.20	9.38	138	49.78	8.92	0.59	0.61
Ambulatory pulse (beats/min)	115	77.38	9.30	100	80.52	8.68	0.01	0.06
Ambulatory 24-hour SBP (mmHg)	115	117.84	8.77	100	118.92	8.87	0.37	0.20
Ambulatory 24-hour DBP (mmHg)	115	71.41	5.41	100	72.22	5.95	0.30	0.09
Ambulatory daytime SBP (mmHg)	115	121.95	9.66	100	122.94	9.82	0.46	0.18
Ambulatory daytime DBP (mmHg)	115	75.44	6.16	100	76.39	7.12	0.30	0.08
Ambulatory nighttime SBP (mmHg)	115	111.17	9.66	100	111.65	8.85	0.71	0.60
Ambulatory nighttime DBP (mmHg)	115	65.34	6.94	100	65.13	7.11	0.83	0.81
CRAE (μm)	147	158.43	13.58	110	159.71	12.59	0.44	0.83
CRVE (μm)	147	227.03	21.22	110	229.47	23.29	0.38	0.81
Current smoker	37	25.2		35	25.4		0.97	0.99
Non-dipper status	32	21.8		25	18.1		0.44	0.55
Treatment								
Placebo	48	34.7		44	31.9		0.87	0.80
Enalapril	48	32.7		46	33.3			
Losartan	51	32.6		48	34.8			
Diabetic retinopathy								
None	54	36.8		35	31.8		0.37	0.38
Mild nonproliferative	75	51.0		67	60.9			
Moderate to severe nonproliferative	15	10.2		7	6.4			

	Included			Excluded				
Characteristic	**N**	**Mean (%)**	**SD**	**N**	**Mean (%)**	**SD**	***P*-value***	**Age-adjusted *P*-value†**
Proliferative	3	2.0		1	0.9			

*P-value is for t-test for difference in means between continuous variables and chi-square test for categorical variables.

†P-value is for t-test for differences in means between continuous variables, adjusted for age, and for the Cochran-Mantel-Haenszel test of general association for categorical variables.

Abbreviations: CRAE = central retinal arteriole equivalent; CRVE = central retinal venule equivalent; SBP=systolic blood pressure; DBP=diastolic blood pressure; MABP= mean arterial blood pressure.

Table 2

Relationship of Various Characteristics to Central Retinal Arteriolar Equivalent and Central Retinal Venular Equivalent at Baseline in the Renin-Angiotensin System Study

	Central Retinal Arteriolar Equivalent (μm)				Central Retinal Venular Equivalent (μm)			
Characteristic	**N**	**Mean**	**SD**	***P*-value***	**N**	**Mean**	**SD**	***P*-value***
Gender								
Male	67	156.861	13.08	0.20	67	226.38	20.74	0.74
Female	80	159.745	13.93		80	227.57	21.72	
Age								
15–29 yrs	64	163.31	13.27	<.0001	64	236.78	19.82	<.0001
30–58 yrs	83	154.66	12.65		83	219.51	19.19	
Glycosylated hemoglobin (%)								
5.5-7.8	46	157.43	14.19	0.10	46	225.48	18.18	0.32
7.9-8.8	57	158.57	14.52		57	228.42	24.28	
8.9-15.3	44	159.30	11.80		44	226.85	20.23	
Body mass index (kg/m^2)								
20.0-23.9	45	159.95	12.07	0.78	45	224.78	21.00	0.19
24.0-26.9	51	156.70	14.78		51	226.61	22.55	
27.0-43.9	51	158.82	13.66		51	229.43	20.18	
Clinic SBP (mmHg)								
90-113	47	161.45	12.49	0.001	47	230.95	18.00	0.03
114-124	51	160.11	14.39		51	226.32	24.88	
125-152	49	153.79	12.73		49	224.00	19.71	
Clinic DBP (mmHg)								
42-66	46	162.73	12.55	0.0002	46	229.93	18.14	0.005
67-73	53	157.86	12.44		53	229.66	20.61	
74-97	48	154.94	14.84		48	221.33	23.76	
Clinic MABP (mmHg)								
63-81	47	163.58	12.08	<.0001	47	231.76	16.41	0.01
82-90	50	157.30	13.21		50	225.89	24.32	
91-115	50	154.72	14.04		50	223.71	21.51	

Characteristic	Central Retinal Arteriolar Equivalent (μm)				Central Retinal Venular Equivalent (μm)			
	N	Mean	SD	*P*-value*	N	Mean	SD	*P*-value*
Clinic pulse pressure (mmHg)								
30-46	52	158.97	14.44	0.61	52	227.28	24.17	0.80
47-54	52	158.64	13.20		52	226.08	18.90	
55-81	43	157.52	13.24		43	227.86	20.49	
Ambulatory pulse (beats/min)								
59-74	44	154.39	14.45	0.10	44	222.23	20.98	0.03
75-82	42	158.95	11.44		42	224.15	20.93	
83-103	29	160.27	15.20		29	233.16	21.27	
Ambulatory 24-hour SBP (mmHg)								
97-112	40	161.44	14.51	0.005	40	223.29	22.19	0.93
113-121	38	157.62	13.70		38	227.94	22.37	
122-151	37	153.23	11.90		37	225.97	19.49	
Ambulatory 24-hour DBP (mmHg)								
59-68	40	161.99	14.27	0.04	40	227.44	22.44	0.62
69-72	43	156.34	11.99		43	225.23	20.10	
73-96	32	153.59	14.15		32	224.11	21.99	
Ambulatory daytime SBP (mmHg)								
98-116	44	162.20	13.76	0.001	44	225.43	21.60	0.48
117-125	39	157.03	13.76		39	227.36	22.54	
126-164	32	151.74	11.61		32	224.00	19.86	
Ambulatory daytime DBP (mmHg)								
62-72	39	162.65	11.71	0.002	39	230.44	19.46	0.14
73-77	43	157.06	14.24		43	225.47	22.63	
78-98	33	152.13	13.49		33	220.35	20.99	
Ambulatory nighttime SBP (mmHg)								
90-106	42	159.88	15.11	0.06	42	224.42	22.67	0.58
107-116	43	158.33	12.76		43	226.56	20.52	
117-152	30	153.12	12.46		30	226.22	21.12	
Ambulatory nighttime DBP (mmHg)								
51-61	37	160.88	12.67	0.25	37	226.82	21.76	0.75

	Central Retinal Arteriolar Equivalent (μm)				Central Retinal Venular Equivalent (μm)			
Characteristic	**N**	**Mean**	**SD**	***P*-value***	**N**	**Mean**	**SD**	***P*-value***
62-68	53	156.08	14.03		53	224.20	19.54	
69-97	25	155.69	14.33		25	227.18	24.74	
Smoking status								
Non-smoker	110	157.95	13.79	0.46	110	226.29	20.71	0.47
Smoker	37	159.85	13.02		37	229.21	22.82	
Dipping status								
Dipper	115	158.08	14.21	0.55	115	226.30	22.33	0.43
Non-dipper	32	159.70	11.13		32	229.64	16.64	
Treatment								
Placebo	51	158.93	14.65	0.24	51	225.43	23.38	0.50
Enalapril	48	155.87	14.08		48	225.74	19.33	
Losartan	48	160.47	11.64		48	230.01	20.73	
Diabetic retinopathy								
None	54	154.72	13.11	0.43	54	223.42	19.49	0.22
Mild nonproliferative	75	161.41	13.42		75	229.09	22.24	
Moderate to severe nonproliferative	15	157.43	12.81		15	230.39	18.09	
Proliferative	3	155.71	19.25		3	223.65	39.78	

**P*-value is for correlation between each continuous variable and CRAE or CRVE or for ANOVA test for difference between mean CRAE and CRVE for categorical variables.

Abbreviations: SD=standard deviation; SBP=systolic blood pressure; DBP=diastolic blood pressure; MABP= mean arterial blood pressure.

Table 3

Multivariate Models of the Association of Blood Pressure Measures with Baseline Central Retinal Arteriolar Equivalent (CRAE) Adjusting for Site, Baseline Age, Glycosylated Hemoglobin Level, and Ambulatory Pulse Rate

	Central Retinal Arteriolar Equivalent (μm)			Central Retinal Venular Equivalent (μm)		
Variable	**Effect**	**SE**	***P*-value**	**Effect**	**SE**	***P*-value**
Clinic SBP	-0.18	0.10	0.09	-0.003	0.16	0.99
Clinic DBP	-0.25	0.16	0.12	-0.26	0.24	0.29
Clinic MABP	-0.28	0.15	0.07	-0.15	0.23	0.49
Ambulatory 24-hour SBP	-0.31	0.14	0.03	0.24	0.21	0.26
Ambulatory 24-hour DBP	-0.35	0.25	0.17	0.33	0.37	0.37
Ambulatory daytime SBP	-0.29	0.13	0.02	0.17	0.20	0.38
Ambulatory daytime DBP	-0.44	0.21	0.04	0.03	0.32	0.93
Ambulatory nighttime SBP	-0.27	0.13	0.03	0.16	0.19	0.39
Ambulatory nighttime DBP	-0.23	0.19	0.21	0.23	0.28	0.40
Dipper status	0.33	2.71	0.90	1.53	4.03	0.71

Abbreviations: SE=standard error; SBP=systolic blood pressure; DBP=diastolic blood pressure; MABP= mean arterial blood pressure.

Table 4

Relationship of Various Characteristics to 5-year Change in Central Retinal Arteriolar Equivalent and 5-year Change in Central Retinal Venular Equivalent at Baseline in the Renin-Angiotensin System Study

	5-year Change in Central Retinal Arteriolar Equivalent (μm)				5-year Change in Central Retinal Venular Equivalent (μm)			
Characteristic	**N**	**Mean**	**SD**	***P*-value***	**N**	**Mean**	**SD**	***P*-value***
Gender								
Male	56	1.60	8.22	0.99	56	3.70	14.58	0.81
Female	68	1.62	8.13		68	4.39	16.90	
Age								
15-29 yrs	53	0.47	6.72	0.12	53	1.76	12.21	0.17
30-58 yrs	71	2.46	9.01		71	5.81	17.97	
Glycosylated hemoglobin (%)								
5.5-7.8	38	0.95	6.36	0.89	38	1.71	17.09	0.06
7.9-8.8	48	2.66	9.33		48	3.47	16.16	
8.9-15.3	38	0.95	8.17		38	7.21	13.91	
Body mass index (kg/m^2)								
20.0-23.9	37	2.61	8.44	0.62	37	5.18	15.11	0.44
24.0-26.9	45	2.06	7.75		45	4.80	16.64	
27.0-43.9	42	0.25	8.28		42	2.34	15.81	
Clinic SBP (mmHg)								
90-113	39	0.44	6.04	0.26	39	-1.77	10.59	0.01
114-124	44	1.71	7.86		44	4.81	15.48	
125-152	41	2.62	10.01		41	8.86	18.69	
Clinic DBP (mmHg)								
42-66	38	0.77	7.71	0.08	38	1.94	16.29	0.02
67-73	47	2.08	8.34		47	2.72	13.52	
74-97	39	1.87	8.45		39	7.81	17.63	
Clinic MABP (mmHg)								
63-81	37	0.72	5.72	0.09	37	1.14	14.52	0.01
82-90	45	0.94	8.83		45	2.55	14.68	
91-115	42	3.11	9.10		42	8.31	17.52	

Characteristic	5-year Change in Central Retinal Arteriolar Equivalent (μm)				5-year Change in Central Retinal Venular Equivalent (μm)			
	N	Mean	SD	*P*-value*	N	Mean	SD	*P*-value*
Clinic pulse pressure (mmHg)								
30-46	43	1.54	6.17	0.99	43	2.33	13.08	0.25
47-54	44	1.45	8.64		44	2.45	16.06	
55-81	37	1.88	9.62		37	8.05	18.05	
Ambulatory pulse (beats/min)								
59-74	38	4.25	10.17	0.29	38	6.78	18.41	0.49
75-82	35	0.46	7.51		35	2.92	17.25	
83-103	24	0.28	7.82		24	5.01	14.65	
Ambulatory 24-hour SBP (mmHg)								
97-112	34	1.03	8.10	0.22	34	4.35	17.04	0.86
113-121	31	0.88	7.95		31	3.58	17.41	
122-151	32	3.81	10.25		32	6.91	17.05	
Ambulatory 24-hour DBP (mmHg)								
59-68	33	-0.29	6.74	0.10	33	4.14	14.48	0.25
69-72	38	2.13	8.53		38	2.06	13.85	
73-96	26	4.34	11.01		26	10.20	22.81	
Ambulatory daytime SBP (mmHg)								
98-116	36	0.47	7.59	0.28	36	4.75	16.73	0.98
117-125	33	0.95	8.28		33	3.88	16.69	
126-164	28	4.85	10.42		28	6.47	18.32	
Ambulatory daytime DBP (mmHg)								
62-72	31	0.19	6.04	0.03	31	3.34	11.19	0.18
73-77	39	1.47	8.89		39	2.40	17.10	
78-98	27	4.48	10.95		27	10.48	21.34	
Ambulatory nighttime SBP (mmHg)								
90-106	37	1.56	8.10	0.15	37	2.99	16.62	0.56
107-116	33	0.58	8.77		33	5.42	19.02	
117-152	27	3.97	9.78		27	7.06	15.29	
Ambulatory nighttime DBP (mmHg)								
51-61	32	1.21	8.79	0.14	32	1.92	14.28	0.20

	5-year Change in Central Retinal Arteriolar Equivalent (μm)				5-year Change in Central Retinal Venular Equivalent (μm)			
Characteristic	**N**	**Mean**	**SD**	***P*-value***	**N**	**Mean**	**SD**	***P*-value***
62-68	43	1.78	8.24		43	6.10	19.73	
69-97	22	3.14	10.23		22	7.11	15.03	
Smoking status								
Non-smoker	94	1.40	8.23	0.60	94	4.08	16.81	0.99
Smoker	30	2.28	7.92		30	4.07	12.52	
Dipping status								
Dipper	99	1.56	8.14	0.90	99	3.95	16.48	0.85
Non-dipper	25	1.79	8.28		25	4.61	13.26	
Diabetic retinopathy								
None	54	223.42	19.49	0.35	54	223.42	19.49	0.56
Early	75	229.09	22.24		75	229.09	22.24	
Moderate to severe	15	230.39	18.09		15	230.39	18.09	
Proliferative	3	223.65	39.78		3	223.65	39.78	

**P*-value is for correlation between each continuous variable and CRAE or CRVE or for ANOVA test for difference between mean CRAE and CRVE for categorical variables.

Abbreviations: SD=standard deviation; SBP=systolic blood pressure; DBP=diastolic blood pressure; MABP= mean arterial blood pressure.