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Parallel Cardiac and Vascular Adaptation in Hypertension

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Background. Although vascular damage in the noncoronary circulation is a major cause of complications in hypertension, relatively little is known of the in vivo geometry and function of the arterial circulation in patients with uncomplicated hypertension or of their relation to left ventricular hypertrophy, a marker of enhanced risk of cardiovascular complications.

Methods and Results. Wall thickness and internal diameter of the common carotid artery and the presence of atherosclerosis within the extracranial carotid arteries were determined by ultrasound in 43 asymptomatic hypertensive patients and 43 normotensive subjects matched for sex, age, and body size. Vascular stiffness was estimated from simultaneous superimposed carotid pressure waveforms obtained with an external solid-state transducer. Left ventricular size and function were determined echocardiographically. Compared with normal subjects, hypertensive patients had greater left ventricular absolute and relative wall thicknesses, left ventricular mass, and carotid absolute and relative wall thicknesses ($p < 0.005$). Carotid intimal-medial thickness exceeded the 95th percentile of normal values in 28% of hypertensive patients ($p < 0.01$). Carotid atherosclerosis was equally prevalent within the two blood pressure groups and was associated with older age, larger left ventricular and carotid wall thicknesses, and carotid diameter. Despite similar carotid pulse pressures, vascular stiffness was significantly increased in the hypertensive patients. Among the population as a whole, significant relations existed between cardiac and vascular wall thicknesses and internal dimensions. In multivariate analyses, these relations were statistically independent of age and blood pressure.

Conclusions. The present study documents the presence of geometric and functional changes within the common carotid artery in uncomplicated hypertension that parallel findings within the left ventricle. The potential contribution of these changes to the cardiovascular complications of hypertension, particularly in the setting of left ventricular hypertrophy, is unknown. (*Circulation* 1992;86:1909-1918)

KEY WORDS • carotid arteries • atherosclerosis • left ventricle • hypertrophy • hypertension

The presence of left ventricular hypertrophy detected by the echocardiogram significantly magnifies the risk of cardiovascular complications in both hypertensive patients^{1,2} and a sample of the general population.^{3,4} Potential mechanisms that might account for this observation include increased vulnerability of hypertrophied myocardium to ischemic damage⁵ and enhanced arrhythmogenesis.⁶⁻⁹ The relative contributions of atherosclerosis, myocardial fibrosis, and alterations in coronary vascular reserve to these abnormalities are unresolved.^{10,11}

Left ventricular hypertrophy may also be associated with an increased likelihood of concomitant noncoronary vascular disease and consequent morbidity. Thus,

more severe degrees of retinopathy and proteinuria have been reported in hypertensive patients with concentric left ventricular hypertrophy,¹² the ventricular geometric pattern associated with the highest risk of adverse outcome.² In addition, reduction in brachial artery compliance has been associated with increased left ventricular mass.^{13,14} Although extracranial carotid atherosclerosis has been reported to be independently related to the level of systolic blood pressure in women¹⁵ and to the presence of hypertension in patients with symptomatic heart disease,^{16,17} this association has not been confirmed in a population-based study¹⁸ or in patients with symptomatic cerebrovascular disease.¹⁹ Furthermore, estimates of the prevalence of structural abnormalities of the carotid artery in asymptomatic hypertensive patients are quite variable.²⁰⁻²⁴ Most studies have reported no relation of carotid artery diameter to blood pressure²⁴ or the presence of hypertension.²⁰⁻²² Although Salonen and Salonen^{25,26} have reported that both pulse pressure and systolic blood pressure are important determinants of carotid intimal-medial thickness,²⁵ they found that progressive increases in carotid wall thickness were unrelated to the presence of hypertension or the level of blood pressure.²⁶ Finally, the

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relation of structural changes within the carotid arteries to cardiac hypertrophy is unknown.

Preliminary data from our laboratory have indicated significant increases in common carotid artery diameter and wall thickness in asymptomatic hypertensive patients that parallel cardiac hypertrophic changes.²⁷ In addition, the presence of asymptomatic carotid atherosclerosis appears to be associated with left ventricular hypertrophy independent of age, blood pressure, or serum lipids.²⁸ Thus, the present study was designed to evaluate the presence of structural changes within the carotid artery and their relation to left ventricular structure in patients with established hypertension without clinical evidence of cardiovascular disease.

Methods

Study Population

The study population comprised 43 hypertensive patients and 43 control subjects matched for sex and age because of their known important effects on cardiac and vascular anatomy, respectively. The hypertensive population consisted of ambulatory patients referred for study from the Hypertension Center of The New York Hospital. All patients were studied off medications; 12 patients (28%) had never received antihypertensive drugs. The diagnosis of essential hypertension was established by the presence of a sustained increase in blood pressure (>140 mm Hg systolic or >90 mm Hg diastolic pressure) and the absence of clinical or laboratory evidence suggestive of secondary forms of hypertension. Isolated systolic hypertension (systolic pressure ≥ 160 mm Hg and diastolic blood pressure <90 mm Hg) was present in three patients. Normotensive control subjects were derived from an employed population participating in an ongoing longitudinal study ($n=30$)²⁹ and from medical personnel ($n=13$). Thirty-five percent of patients and control subjects were women; 26% of the control subjects and 19% of the patients were black. All 86 subjects were free of clinical evidence of coronary artery or cerebrovascular disease. The presence of valvular heart disease was excluded by Doppler echocardiography. The study was performed in accordance with protocols approved by the Committee on Human Rights in Research of Cornell University Medical College.

Echocardiography

All subjects underwent standard M-mode and two-dimensional echocardiography performed by a highly skilled research technician using a commercially available echocardiograph equipped with 2.5- and 3.5-MHz imaging transducers. Left ventricular dimensions were obtained from two-dimensionally guided M-mode tracings according to recommendations of the American Society of Echocardiography.³⁰ Measurements were performed on up to six cycles by use of a digitizing tablet and were averaged. Left ventricular mass was calculated by the Penn convention.³¹ Whenever M-mode tracings were considered technically inadequate, left ventricular dimensions were measured from the two-dimensional study by the method recommended by the American Society of Echocardiography.³² Left ventricular hypertrophy was considered present if the left ventricular mass indexed by body surface area exceeded 125 g/m^2 in

men² or 110 g/m^2 in women.³³ Relative wall thickness, a measure of left ventricular geometry, was calculated as two times posterior wall thickness divided by end-diastolic dimension. Concentric hypertrophy was defined as the presence of left ventricular hypertrophy with an increased relative wall thickness (≥ 0.45) and eccentric hypertrophy as the presence of left ventricular hypertrophy with a normal relative wall thickness. Concentric remodeling was defined as the presence of a normal left ventricular mass with an increased relative wall thickness.³⁴ Fractional shortening, a measure of left ventricular performance, was calculated from the formula [(end-diastolic dimension minus end-systolic dimension) divided by end-diastolic dimension] times 100. End-systolic stress was calculated by the method of Reichek et al.³⁵ Cardiac output was calculated according to the formula aortic annular cross-sectional area times time velocity integral of left ventricular outflow times heart rate.³⁶ Total peripheral resistance was calculated as (mean arterial pressure times 80) divided by cardiac output.

Carotid Ultrasonography

Imaging of both carotid arteries was performed in all subjects by use of a Biosound Genesis II system (OTE Biomedica, Florence, Italy) equipped with a 7.5-MHz imaging transducer. With the subject in the supine position with slight hyperextension of the neck, the common carotid artery, carotid bulb, and extracranial internal and external carotid arteries were identified. Two-dimensionally guided M-mode tracings of the distal common carotid artery approximately 1 cm proximal to the carotid bulb were obtained with simultaneous ECG and carotid pressure waveform (described below) and recorded on $\frac{1}{2}$ -in. super VHS videotape. The videotape was subsequently reviewed, and suitable frames for measurement of M-mode images were obtained in real time by use of a frame grabber (Imaging Technology, Inc., Woburn, Mass.) interfaced with a high-resolution (640×640 -pixel) video monitor and stored on diskettes. The axial resolution of the M-mode system is 0.2 mm.

All carotid measurements were performed on stored images by use of a mouse-driven computer program after calibration for depth and time. The simultaneous carotid pressure waveform was used to time carotid artery measurements at end diastole (minimum arterial pressure) and at the time of peak systolic carotid pressure. Measurements included end-diastolic wall thickness (defined as the combined intimal-medial thickness of the far wall³⁷) (Figure 1) and end-diastolic and peak-systolic internal dimensions obtained by continuous tracing of the intima-lumen interface of the near and far walls. All measurements were performed on several cycles and averaged. Systolic expansion (strain) was calculated according to the formula [(peak-systolic minus end-diastolic dimension) divided by end-diastolic dimension] times 100. Relative wall thickness of the artery was calculated according to the formula (two times wall thickness) divided by end-diastolic dimension. Ultrasound characterization of carotid wall layers and measurement of wall thicknesses has been validated by Pignoli et al.³⁷ by use of gross and histopathological reference standards. Intraobserver ($r=0.98$, $\text{SEE}=0.04$ mm for both) and interobserver ($r=0.97$,

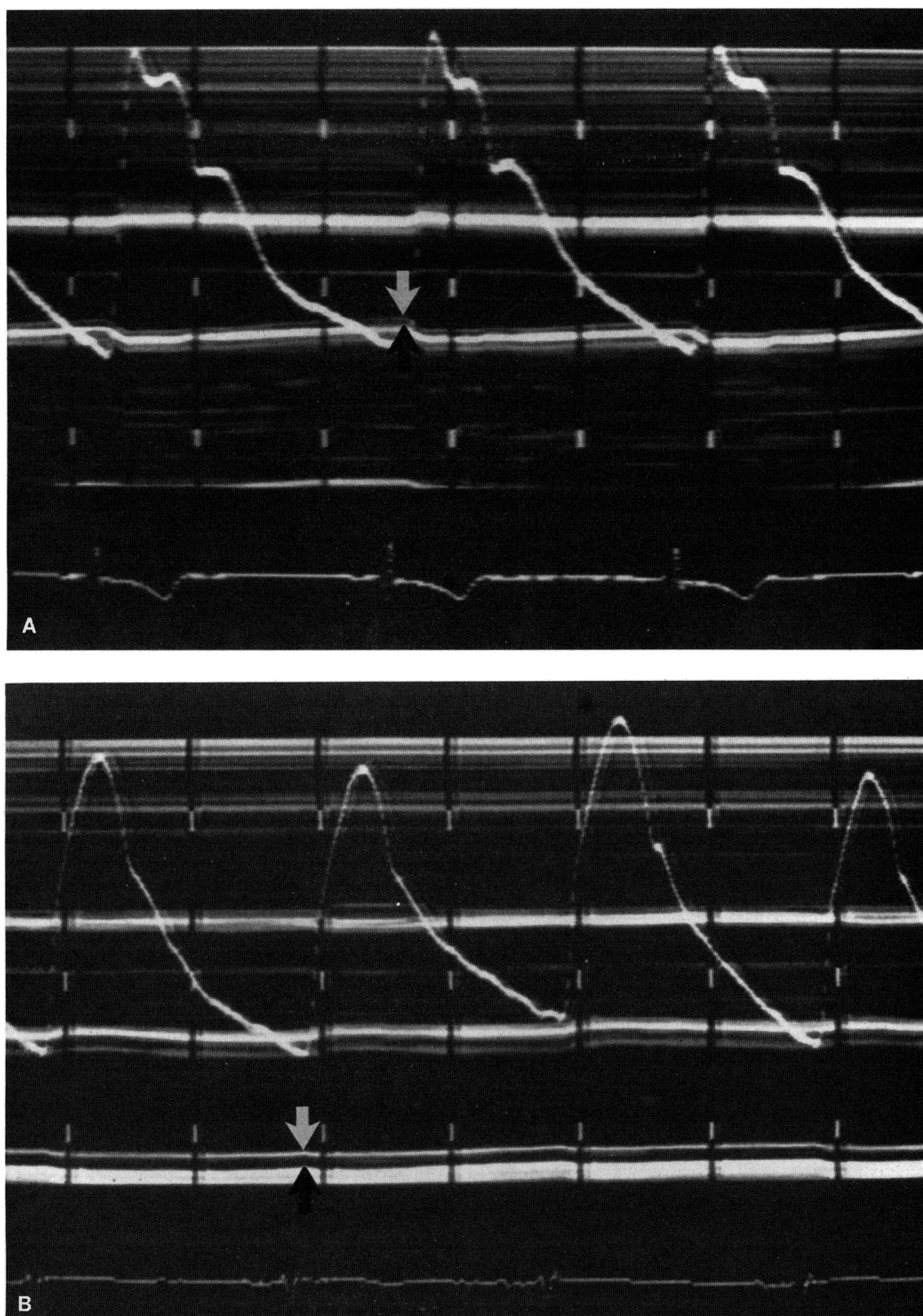


FIGURE 1. *M-mode* tracing of common carotid artery with superimposed pressure waveform. The intimal-medial thickness is indicated between the two arrows at end-diastole in (panel A) a 30-year-old normotensive man and (panel B) a 71-year-old hypertensive man.

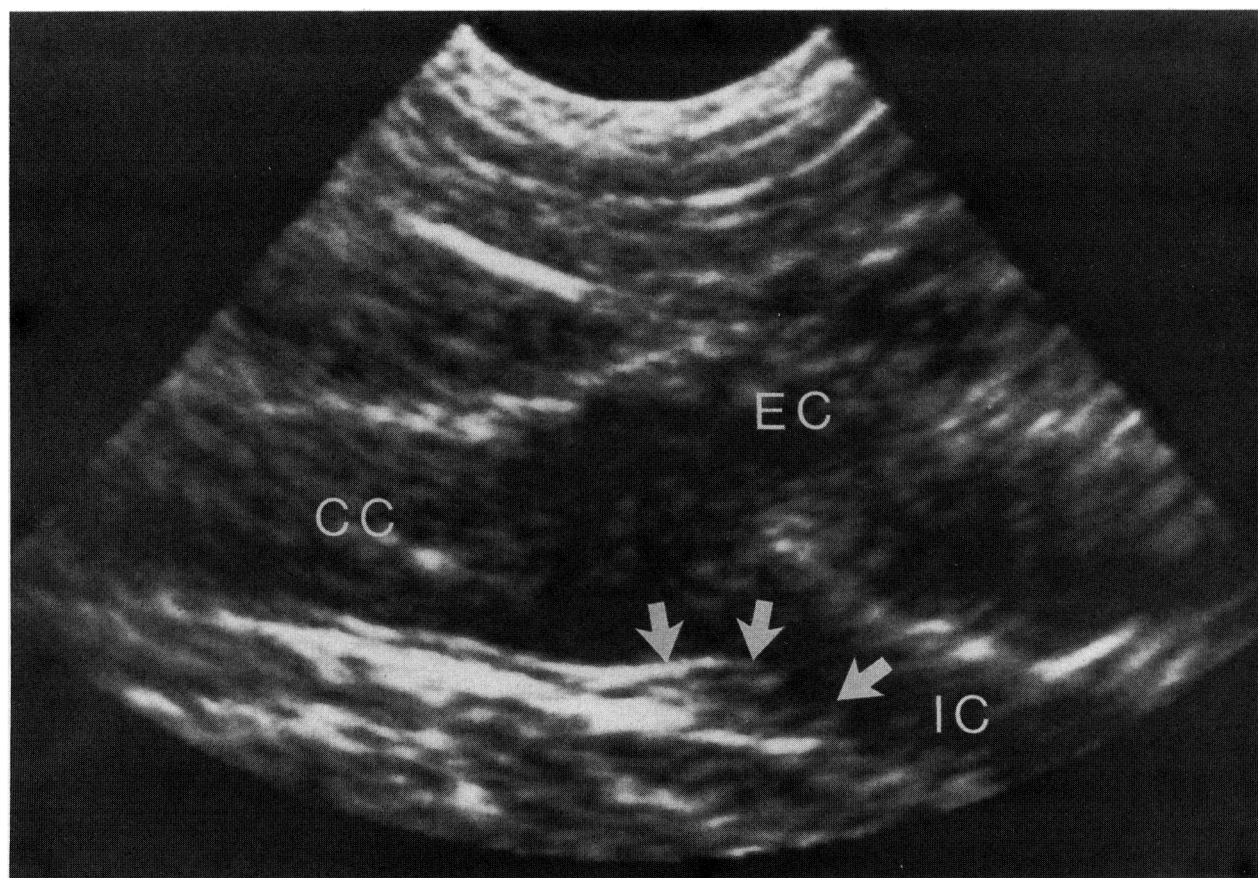


FIGURE 2. Two-dimensional ultrasound image of the distal common carotid artery (CC) and bifurcation into the external (EC) and internal (IC) carotid arteries. The presence of a plaque within the carotid bulb and proximal internal carotid artery is indicated by the arrows.

SEE=0.05 mm) reproducibility of blinded wall thickness measurements was quite high. These results compare favorably with those reported in Salonen et al³⁸ and in the Asymptomatic Carotid Artery Plaque study.³⁹ Intraobserver ($r=0.99$, SEE=0.10 mm and $r=0.98$, SEE=0.18 mm) and interobserver ($r=0.99$, SEE=0.15 mm) reproducibility for carotid diastolic dimensions were likewise high.

Both carotid arteries were scanned for evidence of atherosclerosis. Discrete atherosclerosis (plaque) was defined as the presence of wall thickening at least 50% greater than the surrounding wall.⁴⁰ Carotid plaque size was quantified by computer-assisted measurement of plaque thickness on grabbed two-dimensional frames (Figure 2). Intimal-medial thickening, which may be a measure of diffuse atherosclerosis,^{40,41} was defined as the presence of diffuse thickening of the far wall of the common carotid artery (≥ 1.2 mm).⁴⁰ Standard wall thickness measurements were never obtained at the level of a discrete plaque.

Arterial Pressure Waveform

The regional compliance characteristics of the carotid artery were calculated by methods that incorporate simultaneous superimposed carotid artery waveforms with carotid imaging. The carotid pressure waveform was obtained with a high-fidelity external solid-state strain-gauge transducer (Millar Instruments, Inc.,

Houston, Tex.) that functions as an applanation tonometer. Waveforms and modulus and phase of harmonic components⁴² obtained with this external transducer closely resemble those derived from intra-arterial recordings. Previous validation studies in human subjects⁴³⁻⁴⁵ have shown close relations between the carotid pulse pressure and waveform morphology assessed by applanation tonometry and pressures recorded by a Millar catheter in the central aorta.

The transducer registers absolute changes in blood pressure over a range of 300 mm Hg but requires external calibration to a known level of arterial pressure to avoid errors caused by variability in the force needed to be applied to the tonometer to achieve applanation. On the basis of the observation that, although systolic and diastolic pressures may change significantly from central to peripheral arteries with pressure wave amplification, mean blood pressure remains the same within the conduit arteries,^{46,47} systolic and diastolic brachial artery pressures were measured with a cuff and mercury sphygmomanometer at the end of the study with the subject in the supine position. Mean blood pressure was calculated according to the formula (0.33 times pulse pressure) plus diastolic blood pressure. The level of mean blood pressure of the carotid pressure waveform was determined electronically and set equal (in millimeters of mercury) to the mean brachial pressure. From this mean pressure and the deviations (in millimeters of

TABLE 1. Clinical Characteristics of Normal Subjects and Hypertensive Patients

	Control subjects (n=43)	Hypertensive patients (n=43)	p
Age (years)	53±13	54±12	NS
(range)	(29–76)	(28–76)	
Male sex (%)	65	65	NS
Body surface area (m ²)	1.83±0.22	1.89±0.24	NS
Body mass index (kg/m ²)	25.0±3.9	26.5±4.6	NS
Brachial BP (mm Hg)			
Systolic	120±10	163±20	<0.00005
Diastolic	72±9	96±11	<0.00005
Carotid BP (mm Hg)			
Systolic	116±12	147±15	<0.00005
Diastolic	69±12	97±12	<0.00005
Total cholesterol (mg/dl)	228±44	225±41	NS
HDL cholesterol (mg/dl)	54±14	61±18	NS
Serum creatinine (mg/dl)	1.0±0.2	1.1±0.3	NS
Positive smoking history (%)	26	45	NS

BP, blood pressure; HDL, high density lipoprotein.

mercury) from the mean of the arterial waveform recorded by the Millar tonometer, the carotid peak-systolic and end-diastolic pressures were electronically calculated by computer. Intraobserver and interobserver variability of blood pressures determined by this method from calibrated waveforms in our laboratory was identical for both systolic and diastolic pressures ($r=0.99$, $SEE=1$ mm Hg for all comparisons).

Peterson's elastic modulus (E_p),⁴⁸ an estimate of vascular stiffness that does not take into account differences in distending pressure, was calculated according to the formula

$$E_p = [(P_s - P_d) / (D_s - D_d)] \times D_d$$

where P_s and P_d are systolic and diastolic pressures, respectively, and D_s and D_d are systolic and diastolic dimensions, respectively.

Statistical Analyses

Data were stored and analyzed with the Crunch Statistical Package (Crunch Software Corp., Oakland, Calif.). Mean values in the control and hypertensive populations were calculated and compared by Student's t test. Differences in prevalences between two populations were compared by a χ^2 test. The relation between continuous variables was evaluated by linear regression. Independence of association was assessed by stepwise multiple regression.

Results

Study Population

Characteristics of the control and hypertensive groups are presented in Table 1. The two groups were similar with regard to mean age and age range, sex, and body size assessed by body surface area and body mass index, a measure of obesity. Highly significant differences were found in brachial and carotid systolic and diastolic blood pressures ($p<0.00005$ for all comparisons). Average pressure wave amplification, as mea-

TABLE 2. Comparison of Left Ventricular Structure and Function in Normal Subjects and Hypertensive Patients

	Normal subjects (n=43)	Hypertensive patients (n=43)	p
Interventricular septum (cm)	0.85±0.15	0.97±0.13	<0.0005
Posterior wall (cm)	0.81±0.14	0.93±0.12	<0.0001
End-diastolic dimension (cm)	4.88±0.47	5.05±0.54	NS
Relative wall thickness	0.33±0.06	0.37±0.05	<0.005
Mass (g)	139±44	175±52	<0.001
Mass index (g/m ²)	75±19	92±21	<0.0005
End-systolic stress (dynes/cm ² ×10 ³)	62±13	76±21	<0.0005
Fractional shortening (%)	37±5	37±6	NS
Total peripheral resistance (dynes·sec·cm ⁻⁵)	1,547±362	1,802±397	<0.005

sured by the increase in pulse pressure between carotid and brachial arteries, was 27%, similar to previously reported values.⁴⁹ Total cholesterol, high density lipoprotein (HDL) cholesterol, and serum creatinine were similar in the two groups, as was the likelihood of being a current or former smoker.

Left Ventricular Structure

Echocardiographic results are presented in Table 2. Interventricular septal and posterior wall thicknesses were significantly greater in the hypertensive patients than in control subjects. There was no significant difference in left ventricular end-diastolic dimension; hence, relative wall thickness was also significantly greater in the hypertensive patients. However, the mean increase in wall thickness of about 15% was less than the average increase of 36% in systolic blood pressure, as a result of which end-systolic stress was significantly increased in the hypertensive patients (76±21 versus 62±13 dynes/cm²×10³, $p<0.0005$).

Although both indexed and nonindexed left ventricular masses were significantly larger in the hypertensive patients, frank hypertrophy was uncommon. Left ventricular hypertrophy was present in six hypertensive patients (14.0%) and in two control subjects (4.7%). Concentric hypertrophy was present in both control subjects and three hypertensive patients, whereas eccentric hypertrophy was present in three hypertensive patients.

Carotid Artery Structure and Physical Properties

Results of carotid ultrasonography are presented in Table 3. The far wall of the common carotid artery was significantly thicker in the hypertensive patients than in control subjects, by a mean of 25%. Although end-diastolic artery diameter was on average 8% larger in the hypertensive patients, relative wall thickness remained statistically greater, by a mean of 15%, in the hypertensive patients, suggesting a disproportionate impact of hypertension upon carotid wall thickening. The distribution of carotid far wall thicknesses is presented in Figure 3. When the 95th percentile of normal values (0.96 mm) was used as a partition value, 12 hypertensive patients (28%) had abnormal increases in carotid wall thickness ($p<0.01$).

TABLE 3. Comparison of Carotid Structure in Normal Subjects and Hypertensive Patients

	Normal subjects (n=43)	Hypertensive patients (n=43)	p
Far wall (mm)	0.71±0.15	0.89±0.21	<0.00005
End-diastolic dimension (mm)	5.59±0.69	6.04±0.87	<0.01
Peak-systolic dimension (mm)	6.34±0.69	6.64±0.89	NS (0.09)
Relative wall thickness	0.26±0.06	0.30±0.07	<0.005
Systolic expansion (%)	13.6±4.1	10.8±3.5	<0.005
Carotid atherosclerosis (n)			
Discrete	6	4	
Diffuse	0	3	
Both	0	1	
Total (n)	6 (14.0%)	8 (19.0%)	

Systolic expansion, or vascular strain, was significantly reduced among the hypertensive patients. The elastic modulus was likewise significantly different between the two groups (0.50 ± 0.24 versus 0.67 ± 0.38 dynes/cm² × 10⁻⁶, $p < 0.05$), indicating that the arterial tree was stiffer in our hypertensive patients.

When the hypertensive patients who had never been medicated were compared with those who had previously taken medication, there were no differences in age, blood pressure, or measures of carotid and vascular structure.

Carotid Atherosclerosis

Carotid artery plaques were similarly prevalent among control subjects (14%) and hypertensive patients (12%) (Table 3). Mean plaque thickness was 2.90 mm

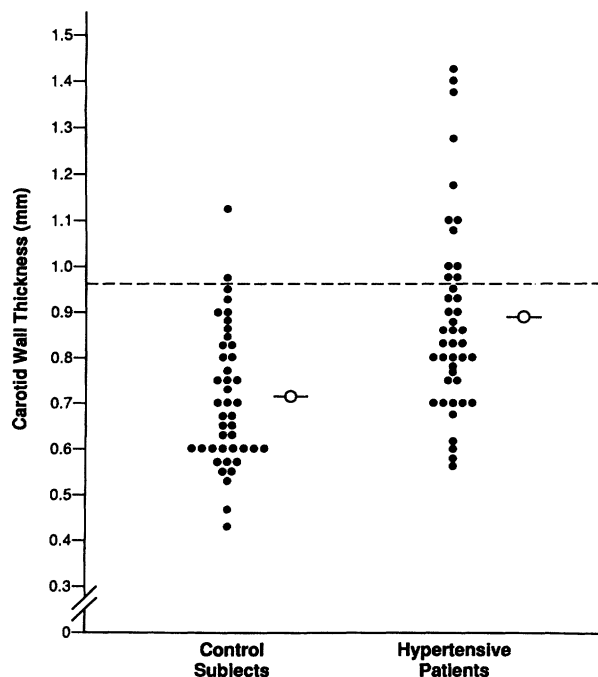


FIGURE 3. Scatterplot showing comparison of end-diastolic carotid artery wall thickness measurements in normal subjects and hypertensive patients. Dashed line indicates the 95th percentile of normal values.

TABLE 4. Univariate Relations of Risk Factors and Left Ventricular Structure to Carotid Artery Geometry

	Absolute wall thickness	Relative wall thickness	Internal dimension
Systolic blood pressure	0.49*	0.29†	0.40‡
Diastolic blood pressure	0.47*	0.31‡	0.34‡
Age	0.41*	0.31‡	0.23†
Body mass index	0.38*	0.38*	0.07
Total cholesterol	0.07	0.08	-0.04
HDL cholesterol	0.20	0.18	0.02
LV posterior wall thickness	0.40*		
LV relative wall thickness		0.24†	
LV end-diastolic dimension			0.33‡
LV mass	0.37*	0.18	0.36‡

HDL, high density lipoprotein; LV, left ventricular.

* $p < 0.0005$; † $p < 0.05$; ‡ $p < 0.005$.

and ranged from 1.70 to 4.41 mm. A diffuse increase in intimal-medial thickness was present in four hypertensive patients, one of whom additionally had a discrete plaque. When the entire population was subdivided according to the presence or absence of atherosclerosis, the 14 subjects with atherosclerosis were significantly older (61 ± 9 versus 52 ± 12 years, $p < 0.005$) and had significantly larger left ventricular posterior wall thickness (0.92 ± 0.09 versus 0.86 ± 0.15 cm, $p < 0.05$), carotid absolute (1.00 ± 0.27 versus 0.76 ± 0.17 mm, $p < 0.01$) and relative (0.32 ± 0.09 versus 0.27 ± 0.06 , $p < 0.05$) wall thicknesses, and carotid diameter (6.27 ± 0.84 versus 5.73 ± 0.78 mm, $p < 0.05$) than the 72 subjects without atherosclerosis. There were no statistically significant differences between the two groups in body surface area (1.97 ± 0.25 versus 1.83 ± 0.22 m²), blood pressures ($146 \pm 25/84 \pm 13$ versus $141 \pm 27/84 \pm 16$ mm Hg), or total serum cholesterol and HDL or their ratio (227 ± 43 versus 226 ± 42 mg/dl, 64 ± 18 versus 56 ± 16 mg/dl, and 3.9 ± 2.0 versus 4.3 ± 1.3 , respectively). Similar results were obtained when analyses excluded the three hypertensive patients with a diffuse increase in carotid wall thickness.

Of the five plaques that occurred in the hypertensive patients, three (25%) were in the 12 patients with increased carotid wall thicknesses, whereas two (6%) were in the 31 patients with normal wall thickness of carotid segments removed from the plaques.

Relation of Risk Factors to Arterial Structure

Univariate relations of risk factors to carotid artery geometry are presented in Table 4. Carotid systolic blood pressure bore the strongest univariate relation to carotid artery wall thickness ($r = 0.49$, $p < 0.00005$) and internal dimension ($r = 0.40$, $p < 0.0001$). Age also bore significant relations to carotid structure (far wall thickness [$r = 0.41$, $p < 0.0001$], relative wall thickness [$r = 0.31$, $p < 0.005$], and internal dimension [$r = 0.23$, $p < 0.05$]). Body mass index, a measure of obesity, was related to both absolute and relative carotid wall thicknesses ($r = 0.38$, $p < 0.0005$ for both) but not to internal dimension.

In multivariate analyses (Table 5) including smoking and a single blood pressure variable (whichever was stronger), carotid wall thickness was independently pre-

TABLE 5. Multivariate Relations of Risk Factors to Carotid Artery Geometry

Dependent variable	Independent variable	Multiple	
		<i>R</i>	<i>p</i>
Absolute wall thickness	Systolic blood pressure	0.48	0.00005
	Age	0.57	0.00009
	Body mass index	0.62	0.007
Relative wall thickness	Body mass index	0.39	0.0001
	Age	0.46	0.009
	Diastolic blood pressure	0.52	0.02
Internal dimension	Systolic blood pressure	0.41	0.0001

dicted by systolic pressure, age, and body mass index, with a multiple *R* of 0.62. Relative wall thickness was predicted by body mass index, age, and diastolic blood pressure, with a multiple *R* of 0.52. Carotid diameter was predicted only by systolic pressure. Serum lipids and smoking history were not significantly related to carotid artery structure.

Both age and systolic but not diastolic blood pressure were related to regional vascular stiffness (Peterson's elastic modulus versus age, $r=0.39$, $p<0.0005$ and versus systolic pressure, $r=0.50$, $p<0.00005$). Total peripheral resistance bore no relation to vascular structure.

Relations Between Cardiac and Carotid Structure

Among the population as a whole, significant relations existed between comparable cardiac and vascular structures (Table 4): left ventricular posterior wall and carotid far wall thicknesses ($r=0.40$, $p<0.0005$), left ventricular and carotid relative wall thicknesses ($r=0.24$, $p<0.05$), and left ventricular and carotid internal dimensions ($r=0.33$, $p<0.005$). Left ventricular mass was positively related to carotid arterial wall thickness ($r=0.37$, $p<0.0005$) and luminal diameter ($r=0.33$, $p<0.005$). In multivariate analyses, the relations between carotid and cardiac wall thicknesses and internal dimensions remained significant after consideration of age and blood pressure (Table 6). The relation of relative wall thicknesses was not independent of blood pressure.

Discussion

Although vascular damage in the cerebral, renal, and other peripheral circulations represents common complications of hypertension, relatively little is known of the in vivo structure or function of the arterial circulation in patients with uncomplicated hypertension. The present study documents the existence of highly significant structural remodeling characterized by both wall thickening and luminal dilatation of the common carotid artery in patients with essential hypertension. Furthermore, the increases in both carotid wall thickness and diameter parallel similar changes in the left ventricle. These findings are especially notable because of the relatively young age of these otherwise healthy hypertensive patients and the matching of control subjects for age, sex, and body size, factors known to influence normal variability of cardiac and vascular structure.

Arterial Structure in Hypertension

Carotid wall thickness was significantly increased on average in the hypertensive group and fell above the 95th percentile of values in normal subjects in 28% of the patients. The increase in wall thickness was disproportionate to that in internal dimension such that carotid relative wall thickness was also significantly increased. Systematic in vivo measurements of carotid wall thickness in hypertensive patients have not previously been reported. Indirect data from population studies have been inconsistent with regard to the influence of hypertension on carotid wall thickness. Crouse et al¹⁶ and Rubens et al¹⁷ found hypertension to be independently and positively related to a score that summated maximal wall thicknesses of the internal, external, and common carotid arteries in patients hospitalized to undergo coronary angiography. Salonen and Salonen²⁶ compared intimal-medial thickness in 100 Finnish men at baseline and after 24 months. The mean increase of 0.12 mm between studies was most strongly related to age, low density lipoprotein (LDL) concentration, white blood cell count, and platelet aggregability, whereas hypertension, current level of blood pressure, and HDL concentration were unrelated to the

TABLE 6. Multivariate Relations of Carotid and Cardiac Structure

	Univariate relations			Multivariate relations		
	Coefficient (B)	Standard error	<i>p</i>	Coefficient (B)	Standard error	<i>p</i>
Carotid absolute wall thickness						
Systolic blood pressure	0.005	0.001	0.0000	0.003	0.001	0.003
Age	0.007	0.002	0.0001	0.005	0.002	0.003
LV wall thickness	0.573	0.145	0.0002	0.291	0.144	0.05
Carotid relative wall thickness						
Age	0.002	0.001	0.005	0.001	0.001	0.02
Systolic blood pressure	0.001	0.000	0.01	0.001	0.000	0.04
LV relative wall thickness	0.285	0.124	0.05			NS
Carotid internal dimension						
Systolic blood pressure	0.016	0.004	0.0001	0.014	0.004	0.0005
LV internal dimension	0.521	0.164	0.003	0.417	0.156	0.01
Age	0.015	0.007	0.05			NS

LV, left ventricular.

change in wall thickness. Likewise, hypertension was not associated with the presence of increased intimal-medial thickness (>1.0 mm) or plaque in 720 men examined in the Kuopio Ischaemic Heart Disease Risk Factor Study.¹⁸ However, a subsequent report from the same authors involving a sample of 1,224 men did detect significant relations between intimal-medial thickness and both pulse pressure and systolic blood pressure.²⁵

The diameter of the carotid artery lumen was also increased in our hypertensive patients. One previous preliminary study²³ comparing 16 normotensive subjects with 14 treated hypertensive patients demonstrated a significant increase in carotid artery diastolic dimension in the hypertensive group (7.86 versus 7.03 mm, $p<0.005$). Subsequent results from the same authors, published on a larger population,⁵⁰ indicated that carotid diastolic dimensions were significantly greater in untreated hypertensive patients than in control subjects (7.4 versus 6.9 mm, $p<0.01$), whereas arterial diameter values were intermediate in treated hypertensive patients (7.2 mm). Three other studies, however, found no significant difference in carotid internal dimension between hypertensive subjects and age-matched control subjects.²⁰⁻²² A potential explanation for the discrepancy between the present findings and those of previous reports²⁰⁻²² might be differences in measurement methodology. Most previous studies used a pulsed Doppler system to measure arterial dimensions indirectly by determining which of successive sample volumes exhibited arterial flow rather than by direct visualization as in the current study. The increment in depth between sample volumes with the Doppler system is reportedly 0.4 mm,²² and additional ambiguity may be introduced when Doppler sample volumes straddle both flowing blood and arterial wall. Resolution is substantially better with our technique, which uses direct visualization. Additional differences from the present study include small sample size²² and less-well-established hypertension²¹ in some previous reports.

Relation Between Arterial and Cardiac Structure

We also observed a parallelism between cardiac and vascular structural changes. Although hemodynamic factors, particularly systolic blood pressure, are the best-characterized stimuli for cardiac and vascular hypertrophy, relatively little of the variability in arterial or cardiac dimensions could be attributed to the level of blood pressure as measured clinically in our population ($r^2=0.04-0.24$ for various measures of arterial structure and $0.05-0.24$ for left ventricular dimensions), raising the possibility of other influences. Genetic factors appear to be important in determining ventricular size in humans^{51,52} and cardiac and vascular hypertrophy in experimental forms of hypertension.^{53,54} Non-pressure-related increases in wall thicknesses of conduit vessels distal to experimental coarctation in rats have been reported.⁵⁵ In addition, ventricular hypertrophy may precede the development of hypertension.^{29,53}

An additional hemodynamic abnormality that might contribute to the observed parallelism between cardiac and vascular hypertrophy is increased stiffness of the arterial tree in hypertensive patients. This is supported by the lesser arterial distension in systole despite a similar central pulse pressure, as a result of which Peterson's elastic modulus is higher in hypertensive

patients. This finding indicates greater effective stiffness of the carotid artery in hypertensive patients under their usual conditions of arterial pressure and geometry.

Vascular stiffness varies directly with arterial chamber dimension because of a shift of the primary tension-bearing element from elastin to collagen fibers.⁵⁶ Thus, passive distension by increased blood pressure may increase arterial stiffness independent of structural changes within the vessel walls. The increase in carotid internal dimension among our hypertensive patients may be a result of their increased level of distending pressure but might also reflect chronic structural remodeling resulting from hemodynamic or nonhemodynamic stimuli. Whereas previous authors have inferred the existence of structural changes within the arteries to account for increases in vascular stiffness in hypertension,⁵⁷ rather than differences in distending pressure,⁵⁸ the present study demonstrates structural abnormalities and differences in distending pressure that may account for the alterations in vascular stiffness. The strong association of common carotid artery stiffness with age noted by earlier investigators^{59,60} was also seen in our population. Systolic expansion, or vascular strain, was significantly reduced in hypertensive patients, in agreement with most previous reports^{21,23} but not all.⁵⁰

Hypertension, Cardiovascular Structure, and Atherosclerosis

Although no difference was found in the prevalence of atherosclerosis between the control and hypertensive groups in the present study, other authors have noted an increased frequency of in vivo carotid atherosclerosis in hypertensive patients^{61,62} and a strong association of blood pressure with cerebral (including carotid) atherosclerosis at autopsy.^{63,64} Lusiani et al⁶¹ found an increased prevalence of atherosclerosis within the internal carotid arteries of 49 asymptomatic hypertensive patients compared with matched control subjects (24.5 versus 10.2%, $p<0.01$), although the accompanying stenosis was mild ($<20\%$) in most instances. In an expanded study of 146 hypertensive patients,⁶² the same authors noted a 43% prevalence of internal carotid atherosclerosis, which correlated strongly with age but not duration of hypertension or serum cholesterol. This finding is in agreement with the analysis of our entire population wherein the presence of atherosclerosis was most strongly related to age. The observed association of atherosclerosis with an increase in arterial lumen has been described previously,⁶⁵ although in our population this association was not independent of age. The newly observed association of carotid atherosclerosis with increased left ventricular wall thickness is particularly intriguing in view of the known association between carotid and coronary atherosclerosis.^{16,66,67}

Summary

In conclusion, the present study documents the presence of structural changes in the common carotid artery, a vessel that is both a common target of hypertensive disease and also a representative of the conduit or capacitance portion on the circulation, in patients with uncomplicated hypertension. Abnormal carotid intimal-medial thickness was present in 28% of patients. Parallel findings were noted in left ventricular structure, i.e., an increase in absolute and relative wall

thickness as well as left ventricular mass. Although atherosclerosis was not more prevalent among hypertensive patients than their age-matched control subjects, the subjects with carotid atherosclerosis were found to have increased carotid wall thickness and lumen diameter as well as increased left ventricular wall thickness. The potential contribution of these vascular changes to the increased cardiovascular morbidity associated with hypertension, particularly in the setting of ventricular hypertrophy, requires prospective evaluation.

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