

Regression of Radial Artery Wall Hypertrophy and Improvement of Carotid Artery Compliance After Long-Term Antihypertensive Treatment in Elderly Patients

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Objectives. The present study was designed to assess whether a diuretic- or an angiotensin-converting enzyme inhibitor-based treatment can reduce arterial wall hypertrophy of a distal muscular medium-sized artery—the radial artery—and the stiffness of a proximal large elastic artery—the common carotid artery.

Background. Large-artery wall thickness and stiffness are increased during sustained essential hypertension and contribute to the increased risk of complications. Whether antihypertensive treatment can normalize the wall hypertrophy of conducting arteries has not yet been determined.

Methods. Seventy-seven elderly hypertensive patients were randomized to receive 9 months of double-blind treatment with perindopril (2 to 8 mg/day) or the diuretic combination of hydrochlorothiazide (12.5 to 50 mg/day) plus amiloride (1.25 to 5 mg/day) after a 1-month placebo washout period. If systolic blood pressure remained at >160 mm Hg after 5 months, chlorthalidone or atenolol was added, respectively. Arterial variables, including radial artery mass and common carotid artery compliance, were calculated from noninvasive measurements of internal diameter and wall thickness with the use of high resolution echo-tracking systems at baseline and after 5 and 9 months.

Results. During treatment, blood pressure and arterial variables changed to the same extent in both groups. After a 9-month treatment, systolic, diastolic and pulse pressures and radial artery wall thickness, mass and thickness/radius ratio decreased significantly ($p < 0.01$), whereas carotid compliance increased ($p < 0.001$). The decrease in radial artery thickness/radius ratio after a 9-month treatment was significantly related to the reduction in pulse pressure ($p < 0.01$), whereas the improvement in carotid compliance was related to the reduction in mean arterial pressure ($p < 0.01$). In healthy subjects and untreated hypertensive patients, radial artery diameter, wall thickness and thickness/radius ratio and carotid artery compliance did not change significantly during a 9-month observation period.

Conclusions. These results indicate that in elderly hypertensive patients, both angiotensin-converting enzyme inhibitor- and diuretic combination-based treatments can reduce radial artery wall hypertrophy and improve carotid artery compliance.

(J Am Coll Cardiol 1998;31:1064-73)

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During sustained essential hypertension, structural changes in the cardiovascular system are associated with an independent increased risk of cardiovascular disease and death. Most evidence concerns left ventricular hypertrophy (1,2). Increased arterial wall thickness, which is influenced not only by elevated mean blood pressure but also by high pulse pressure (3-6), contributes to the normalization of circumferential wall stress in patients with hypertension (7,8), parallels the development of left ventricular hypertrophy (9) and could potentiate the

development of atherosclerosis at some arterial sites, like the carotid artery (6,10).

Experimental studies in rats have shown that the reversibility of structural vascular changes during antihypertension treatment may be obtained in the larger (11-13) as well as the smaller (14,15) arteries. Although long-term antihypertension treatment may correct in part the structural abnormalities present in the subcutaneous arteries of patients with mild hypertension (16), there is little evidence for extrapolation to large arteries in humans. Investigations of large arteries have shown that the reverse may be very difficult to obtain (17). Because angiotensin-converting enzyme (ACE) inhibitors have been shown to induce a significant regression in large artery wall hypertrophy in animals with hypertension (11-13), perindopril, which was demonstrated to have efficacy in animals (11), was used in the present study and compared with the use of a combination of a thiazide diuretic plus amiloride. The thiazide diuretic hydrochlorothiazide (HCTZ) was selected because it is commonly used in the management of hypertension

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Manuscript received July 14, 1997; revised manuscript received December 29, 1997, accepted January 9, 1998.

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
CCA	=	common carotid artery
DBP	=	diastolic blood pressure
HCTZ	=	hydrochlorothiazide
RF	=	radiofrequency
SBP	=	systolic blood pressure

in the elderly and has been used in intervention trials in the elderly with (18) and without (19,20) isolated systolic hypertension. In addition, ACE inhibitors and thiazide diuretics have demonstrated efficacy in decreasing left ventricular mass (21). Because pulse pressure is an important factor of vascular hypertrophy (3-6) and large-artery distensibility is one of the main determinants of pulse pressure, in addition to wave reflections (22-24), we also investigated the effects of antihypertension treatment on the elastic properties of the common carotid artery (CCA).

The objective of the present study was to determine whether drug treatment of hypertension, with either a diuretic or an ACE inhibitor is able to obtain the reverse of functional and structural arterial changes in elderly patients with hypertension. Two arterial sites were considered: a proximal, predominantly elastic, large artery, the CCA, for assessment of the effects of long-term antihypertension treatment on arterial distensibility, and a distal, medium-sized, predominantly muscular artery, the radial artery, for evaluation of the regression of arterial wall hypertrophy during treatment.

Methods

Patients. The study was conducted in two centers, one in France and one in Italy, and was named PERICLES (PERIn-dopril and hydrochlorothiazide + amiloride for the Control at Long term of wall thickness in ESsential hypertension). One hundred three patients with hypertension between 60 and 80 years old with or without isolated systolic hypertension (systolic blood pressure [SBP] >160 mm Hg regardless of diastolic pressure [DBP]) were selected for participation in the study. The diagnosis of essential hypertension was established by the absence of clinical evidence of secondary hypertension. Patients were included in the study if they had normal serum electrolyte and creatinine levels. Exclusion criteria were congestive heart failure, myocardial infarction or cerebrovascular accident within the past 3 months, unstable angina pectoris, overt atherosclerotic lesions, diabetes mellitus treated with insulin or oral antidiabetic agents or serum creatinine of >200 μ mol/liter.

Patients entered a single-blind, placebo-controlled washout period that lasted 1 week for patients not previously treated with antihypertensive agents and 4 weeks for patients receiving antihypertensive agents. Placebo was administered once daily in the morning. After the placebo washout period, patients with an SBP between 160 and 230 mm Hg and a DBP of

<120 mm Hg were included in the study. The upper limits of SBP of 230 mm Hg and DBP of 120 mm Hg were chosen for safety, like in the STOP-Hypertension trial (19). Blood pressure was recorded as the mean value of three consecutive measurements obtained with a standard mercury sphygmomanometer after 15 min of rest in the sitting position. Korotkoff phases 1 and 5 were taken as SBP and DBP, respectively. Patients were excluded if the fall in SBP was >30 mm Hg between sitting and standing measurements.

After inclusion, patients were stratified at each center and randomized to receive a 9-month treatment with either perindopril (2 mg/day) or HCTZ (12.5 mg/day) plus amiloride (1.25 mg/day) each morning in a double-blind fashion. After 1 month, the dosage was doubled. After the 1-month follow-up visit, drugs were titrated during follow-up to achieve goal blood pressure. The goal was a decrease in sitting SBP of >30 mm Hg in patients with an initial SBP of >200 mm Hg or a decrease in sitting SBP of >20 mm Hg in patients with initial SBP between 160 and 200 mm Hg. At 3 months, the dosage was doubled if patients had not achieved goal blood pressure. At 5 months, chlorthalidone was added at a dosage of 12.5 mg once daily for patients randomized to receive perindopril, and atenolol was added at a dosage of 50 mg once daily for patients randomized to receive hydrochlorothiazide plus amiloride. At 7 months, these dosages were doubled. Weight, blood pressure, heart rate, clinical acceptability and patient adherence to therapy were assessed at each visit during the active treatment period (months 1, 3, 5 and 7). During the follow-up, patients were withdrawn from the study if they had an SBP of >230 mm Hg or a DBP of >120 mm Hg (at the maximal dose). Treatment was discontinued in patients who experienced serious adverse effects or major intercurrent disease or in the case of poor patient adherence. Patients were asked about their adherence to therapy at each visit, and the number of capsules returned at the end of each treatment period was counted and compared with the number of days of treatment. Patients having taken <70% of their capsules were excluded from study analysis. Routine laboratory tests were obtained at inclusion, and arterial measurements were made at inclusion and after 5 and 9 months of active treatment.

Of the 103 patients who were initially eligible, 84 were randomized to receive treatment. Three patients were excluded due to orthostatic hypotension, and 16 were excluded because their SBP was not high enough after the wash-out period to meet the inclusion criteria. Of the 84 patients randomized to receive treatment, 77 completed the study. Among the 7 patients withdrawn before the end of the study, 2 were excluded due to poor compliance with drug treatment, 1 because of a minor side effect (cough), 3 because of severe intercurrent medical problems (cirrhosis decompensation, intermittent leg claudication, pulmonary embolism) and 1 due to protocol violation (unauthorized treatment). The 7 patients withdrawn before the end of the study were compared with the 77 patients who completed the study; no significant difference was observed between the two groups with regard to baseline biologic characteristics. No serious side effects related to

treatments occurred during the study in the remaining 77 patients. Thirty-eight patients were included in the perindopril group, and 39 were included in the HCTZ-plus-amiloride group. Thirty-two patients in the perindopril group and 27 in the HCTZ-plus-amiloride group had previously been treated with antihypertensive agents. The protocol was approved by the ethical committee of each participating center. Written informed consent to participate in the study was obtained from each subject.

Repeatability study. Thirteen healthy subjects and patients with hypertension (mean age \pm SD 45 ± 7 years) were included in a long term (9 ± 1 months) repeatability study of carotid and radial artery measurements. The 8 healthy subjects included in the study had a normal physical examination and SBP and DBP of <140 and <85 mm Hg, respectively. They were untreated during the follow-up. Five patients with hypertension, who were followed at the Hypertension Clinic of Broussais Hospital, had essential hypertension and remained hypertensive despite treatment.

Measurements. The investigation was performed in a controlled environment maintained at $22 \pm 1^\circ\text{C}$. Blood pressure and arterial measurements were made between 2 and 5 h after the treatment and at the same time of the day for each patient during the study. Blood pressure measurements were made with the standard mercury sphygmomanometer and auscultatory method. Blood pressure and arterial measurements were performed by two senior physicians, in Paris (X.G.) and Milan (C.G.), who followed the training sessions and were certified.

Radial artery variables. *Internal diameter and wall thickness.* Radial artery internal diameter and wall thickness were measured with a high resolution pulsed ultrasound echo-tracking device (NIUS 02; SMH, Bienne, Switzerland; marketed by Capital Medical Services, Paris, France) described and validated previously (25-29). Briefly, a 10-MHz probe was used to acquire backscattered radiofrequency (RF) data from the radial artery at the wrist. The transducer is placed perpendicular to the arterial axis, in its largest cross-sectional dimension, with a stereotactic arm, so its focal zone is located in the center of the artery and the backscattered echoes from both the anterior and posterior walls can be visualized. To measure the internal diameter and intima-media wall thickness of the posterior wall, electronic trackers are positioned on specific peaks of the RF ultrasound signal, as described previously (25,28). All data processing was performed with software developed by Asulab (Neuchatel, Switzerland). The pulse length of this 10-MHz ultrasound system was $0.1 \mu\text{s}$ at 6 dB and corresponded to a practical axial resolution of 0.16 mm for absolute internal diameter or wall thickness measurements and 0.0025 mm for these parameters during systolic-diastolic changes.

Mean internal diameter and wall thickness were calculated by integrating the time course of the systolic-diastolic variations over ≥ 20 consecutive cardiac cycles. At the end of the study, tracings obtained for the radial artery were cross-checked by the two physicians (X.G. and C.G.), who were unaware of treatment, clinical data, date of acquisition and

rank of study visit for the patients. If the quality of a tracing was found to be nonacceptable for analysis, the tracing was reanalyzed by the two readers to reach a consensus. With these criteria, 13 of 231 tracings were rejected, and only patients with acceptable tracings obtained at the three visits were included in the statistical analysis. Thus, radial artery variables were analyzed in 33 patients of the perindopril group and 33 patients of the HCTZ-plus-amiloride group.

Thickness/radius ratio (%) was calculated as follows:

$$2h/D_i, \quad [1]$$

where h = mean wall thickness and D_i = mean internal diameter. Mean circumferential wall stress (kPa) was calculated according to Lamé's equation as follows:

$$\sigma\theta = \text{MBP} \cdot 2h/D_i, \quad [2]$$

where MBP = mean blood pressure, calculated as $\text{DBP} + \frac{1}{3}(\text{SBP} - \text{DBP})$.

Because wall thickness is influenced by instantaneous variations in blood pressure level, radial artery mass is a more appropriate variable due to the incompressibility of the arterial mass (8). Radial artery mass was calculated as follows:

$$\text{RAM} = \rho L(\pi R_e^2 - \pi R_i^2), \quad [3]$$

where ρ = arterial wall density ($\rho = 1.06$), L = length of the arterial segment and R_e and R_i = values of mean internal and external radii, respectively. Radial artery mass was normalized to the length of the arterial segment and expressed as mg/cm (length). The calculation of the radial artery mass has been described and validated previously (7,28).

Long-term repeatability. Long-term repeatability of radial artery diameter, wall thickness, thickness/radius ratio and radial artery mass measurements was investigated in a group of 13 healthy subjects and patients with hypertension through calculation of the absolute difference, variation coefficient and repeatability coefficient (RC). The repeatability coefficient was defined by the British Standard Institution (30) according to the formula $\text{RC}^2 = \sum D_i^2/N$, where RC = the repeatability coefficient, N = sample size and D_i = relative difference within each pair of measures. This coefficient is the SD of the estimated difference between two repeated measurements. The 95% confidence interval of the expected difference was calculated as $\pm 1.96 \text{ RC}$. Repeated measurements are expected to differ by more than the confidence interval with a probability of only 5%. This long-term intraobserver repeatability study compared two determinations obtained by the same observer at a 9 ± 1 -month interval.

Carotid artery variables. The CCA measurements were performed after radial artery measurements, with the patient in the recumbent position. The measurement site was the right CCA, 2 cm beneath the carotid bifurcation. Very few patients (four in the HCTZ-plus-amiloride group and three in the perindopril group) had atherosclerotic plaques at the site of the CCA. In these patients, the contralateral carotid artery was devoid of atherosclerotic plaque and was used for compliance measurements on the repeat study.

Internal diameter. The vessel wall properties of the right CCA were assessed with a pulsed ultrasound echo-tracking system (Wall-Track System; Neurodata, Maastricht, The Netherlands) developed to measure the wall motion of superficial large arteries after B-mode echographic localization. This system has been described in detail (31) and has been used in clinical studies (32,33). Because of the accurate determination of the Doppler frequency (phase-locked echo-tracking system), a stereotactic device is not necessary to obtain reliable measurements. Briefly, this system allows the transcutaneous assessment of arterial wall displacement during successive cardiac cycles and hence of the time-dependent changes in arterial wall diameter relative to its initial diameter at the start of the cardiac cycle. Based on the two-dimensional B-mode image, an M line perpendicular to the longitudinal and transverse axes of the artery is selected 2 cm below the CCA bifurcation. The RF signal over four to eight cardiac cycles is digitized and stored temporarily; the device has large memory capability. Two sample volumes, selected under cursor control, are positioned on the anterior and posterior walls, respectively. The vessel walls are continuously tracked by sample volume according to phase. Then the displacement of the arterial walls is obtained by autocorrelation processing of the Doppler signal originating from the sample volumes. The accuracy of the system is 30 μm for diastolic diameter measurement and $<1 \mu\text{m}$ for the pulsatile change in diameter (systolic diameter minus diastolic diameter).

Distensibility and compliance. Arterial stiffness parameters were derived from analysis of the pressure-volume relationship. Compliance and volume distensibility were defined as compliance = $\Delta V/\Delta P$ and distensibility = $\Delta V/(V \times \Delta P)$, where V = arterial volume, ΔV = change in volume and ΔP = change in pressure. It is assumed that the increase in volume of an arterial segment is almost exclusively caused by an increase in radius because elongation is negligible in vivo at this site (8,34). Thus, arterial compliance and distensibility can be estimated on the basis of the variations in arterial cross-sectional area (ΔA) and blood pressure (ΔP) during systole (31). Cross-sectional distensibility coefficient is defined as

$$DC = \Delta A/A \cdot \Delta P, \quad [4]$$

where A = diastolic lumen area. Cross-sectional compliance can be defined as

$$CC = \Delta A/\Delta P. \quad [5]$$

Carotid pulse pressure was estimated as the difference between SBP and DBP, as measured with an oscillometric recorder (Dinamap Model 845; Critikon) at the site of the brachial artery; the amplification of the pressure wave between the aortic arch and brachial artery decreases with age and blood pressure (35,36), leading to similar amplitudes of carotid and brachial pulse pressures in patients 60 to 70 years old (36). Measurements were obtained automatically every 3 min. Several studies have documented the close correlation between peak Dinamap SBP and DBP readings and corresponding

Table 1. Baseline Characteristics of Patients

	Perindopril (n = 38)	HCTZ + A (n = 39)
Clinical variables		
Age (yr)	67 \pm 6	69 \pm 7
Men/women	12/26	12/27
Height (cm)	160 \pm 7	162 \pm 7
Weight (kg)	70 \pm 11	68 \pm 12
SBP (mm Hg)	180 \pm 16	178 \pm 13
DBP (mm Hg)	99 \pm 9	95 \pm 8
Heart rate (beats/min)	84 \pm 11	78 \pm 11
Biologic variables		
Total cholesterol (mmol/liter)	6.02 \pm 0.94	6.22 \pm 1.04
LDL cholesterol (mmol/liter)	4.03 \pm 0.92	4.14 \pm 1.01
HDL cholesterol (mmol/liter)	1.45 \pm 0.37	1.43 \pm 0.39
Triglycerides (mmol/liter)	1.4 \pm 0.9	1.3 \pm 0.5
Fasting glycemia (mmol/liter)	5.8 \pm 1.2	5.7 \pm 1.1
Creatinine ($\mu\text{mol/liter}$)	84 \pm 19	85 \pm 23

Data presented are mean value \pm SD or number of patients. A = amiloride; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; HDL = high density lipoprotein; LDL = low density lipoprotein; SBP = systolic blood pressure.

central aortic pressures in adults with and without hypertension (37-39).

Statistical analysis. The primary goal of this study was to analyze the arterial changes after 9 months of follow-up. All results are reported according to an efficacy sample analysis. Data are expressed as mean values \pm SD, unless otherwise stated. The homogeneity of the randomized groups at baseline was determined with an unpaired Student *t* test for continuous variables and a chi-square test for categorical variables. For comparison of serial changes in blood pressure and arterial parameters, repeated-measures analysis of variance (period and group) was performed to examine treatment differences and interactions (period \times group) (40). Because no "center effect" was significant, the two populations of the study were analyzed as a whole. The effects of biologically relevant variables (patient age, weight, baseline blood pressure and magnitude of SBP and DBP change with treatment and heart rate at baseline and after treatment) on the study end points were analyzed with multivariate regression analysis. To determine whether there were drug-specific effects, the group (either HCTZ-plus-amiloride or perindopril) was included in this analysis. Statistical analysis was performed with SAS software. Statistical significance was assumed for $p < 0.05$.

Results

Patient characteristics, blood pressure and heart rate.

Patient demographics are shown in Table 1. The 38 and 39 patients randomized to perindopril- and HCTZ-plus-amiloride-based treatments, respectively, were similar in age, gender ratio, height, weight, blood pressure before treatment and blood biochemistry values.

Perindopril- and HCTZ-plus-amiloride-based treatments produced similar reductions in SBP, DBP and mean and pulse

Table 2. Changes in Sitting Blood Pressure and Heart Rate During Treatment*

	Baseline	5 mo	9 mo	p Value (analysis of variance)		
				Group Effect	Period Effect	Group × Period Interaction
SBP (mm Hg)						
HCTZ + A†	178 ± 13	153 ± 16	146 ± 11	NS	< 0.01	NS
Perindopril‡	180 ± 16	159 ± 18	154 ± 15			
DBP (mm Hg)						
HCTZ + A†	95 ± 8	88 ± 7	84 ± 7	NS	< 0.01	NS
Perindopril‡	99 ± 9	89 ± 8	88 ± 7			
Mean BP (mm Hg)						
HCTZ + A†	123 ± 8	110 ± 10	105 ± 9	NS	< 0.01	NS
Perindopril‡	126 ± 10	112 ± 9	110 ± 10			
Pulse pressure (mm Hg)						
HCTZ + A†	83 ± 11	65 ± 10	62 ± 11	NS	< 0.01	NS
Perindopril‡	81 ± 13	70 ± 11	66 ± 12			
Heart rate (beats/min)						
HCTZ + A†	73 ± 9	73 ± 7	73 ± 9	< 0.05	NS	NS
Perindopril‡	79 ± 11	75 ± 7	75 ± 7			

*Sitting blood pressure (BP) was measured with a sphygmomanometer. †n = 39. ‡n = 38. Data presented are mean value ± SD. Other abbreviations as in Table 1.

pressures (Table 2). In both groups, the decreases in SBP, DBP and mean blood pressures were significant by 5 months. Sixteen patients among the perindopril group required the addition of chlorthalidone and 10 among the HCTZ-plus-amiloride group required the addition of atenolol to achieve the goal blood pressure. After 9 months of treatment, sitting SBP decreased by 26 mm Hg with perindopril and by 32 mm Hg with HCTZ-plus-amiloride. DBP decreased by 11 mm Hg in both groups. Heart rate remained unchanged with perindopril and HCTZ-plus-amiloride but was higher in the perindopril group than in the HCTZ-plus-amiloride group throughout the study. There was no significant decrease in heart rate between months 5 and 9 when the 10 patients who

required the addition of atenolol to HCTZ-plus-amiloride (from 76 ± 7 to 73 ± 10 beats/min) were compared with the 29 patients who remained under monotherapy (from 73 ± 9 to 74 ± 9 beats/min). The changes in laboratory values (including serum potassium level) were not statistically significant.

Radial artery variables. Table 3 shows the radial artery variables for both treatment groups at baseline and during follow-up. At baseline, mean values did not differ significantly between the groups. During antihypertension treatment with the perindopril- and the HCTZ-plus-amiloride-based regimens, the radial artery exhibited a significant decrease in wall thickness, mass and thickness/radius ratio (period effect). After 9 months, the wall thickness changes were ~7% ($-21 \mu\text{m}$) and

Table 3. Changes in Radial Artery Variables During Treatment

	Baseline	5 mo	9 mo	p Value (analysis of variance)		
				Group Effect	Period Effect	Group × Period Interaction
Internal diameter (mm)						
HCTZ + A*	2.35 ± 0.35	2.37 ± 0.36	2.38 ± 0.41	NS	NS	NS
Perindopril†	2.46 ± 0.37	2.46 ± 0.34	2.49 ± 0.42			
Wall thickness (μm)						
HCTZ + A*	298 ± 63	273 ± 63	264 ± 57	NS	< 0.01	NS
Perindopril†	282 ± 64	274 ± 66	261 ± 65			
Radial artery mass (mg/cm)						
HCTZ + A*	26.9 ± 9.1	24.5 ± 8.3	23.8 ± 8.2	NS	< 0.01	NS
Perindopril†	26.3 ± 10.0	25.4 ± 9.0	24.5 ± 9.3			
Thickness/radius (%)						
HCTZ + A*	0.25 ± 0.04	0.23 ± 0.05	0.23 ± 0.05	NS	< 0.01	NS
Perindopril†	0.23 ± 0.05	0.22 ± 0.05	0.21 ± 0.04			
Circumferential wall stress (kPa)						
HCTZ + A*	64 ± 13	61 ± 14	62 ± 14	NS	NS	NS
Perindopril†	70 ± 15	64 ± 13	67 ± 12			

*n = 33. †n = 33. Data presented are mean value ± SD. HCTZ + A = hydrochlorothiazide plus amiloride.

Table 4. Changes in Common Carotid Artery Variables During Treatment

	Baseline	5 mo	9 mo	p Value (analysis of variance)		
				Group Effect	Period Effect	Group × Period Interaction
Internal diameter (mm)						
HCTZ + A*	7.81 ± 0.79	7.58 ± 0.88	7.60 ± 0.88	NS	NS	NS
Perindopril†	7.93 ± 0.90	7.78 ± 0.76	7.78 ± 0.80			
Ds - Dd (μm)						
HCTZ + A*	354 ± 146	316 ± 112	351 ± 128	< 0.05	NS	NS
Perindopril†	294 ± 92	283 ± 77	304 ± 88			
(Ds - Dd)/Dd (%)						
HCTZ + A*	4.5 ± 1.7	4.2 ± 1.2	4.6 ± 1.5	< 0.05	NS	NS
Perindopril†	3.8 ± 1.2	3.7 ± 1.1	4.0 ± 1.2			
CS compliance (m ² ·kPa ⁻¹ ·10 ⁻⁷)						
HCTZ + A*	3.8 ± 1.9	4.4 ± 2.1	4.9 ± 1.8	< 0.05	< 0.01	NS
Perindopril†	3.2 ± 1.4	3.6 ± 1.2	4.1 ± 1.4			
CS distensibility (kPa ⁻¹ ·10 ⁻³)						
HCTZ + A*	7.7 ± 3.3	9.5 ± 3.2	10.7 ± 3.4	< 0.05	< 0.01	NS
Perindopril†	6.6 ± 2.8	7.9 ± 2.7	8.8 ± 3.2			

*n = 39. †n = 38. Data presented are mean value ± SD. HCTZ + A = hydrochlorothiazide + amiloride; CS = cross-sectional; Ds - Dd = absolute pulsatile change in diameter; (Ds - Dd)/Dd = relative pulsatile change in diameter.

-11% (-34 μm) in the perindopril and HCTZ-plus-amiloride groups, respectively. The corresponding changes in radial artery thickness/radius ratio were ~-9% (-0.02) and ~-8% (-0.02), and changes in radial artery mass were ~-7% (-1.8 mg/cm) and -11% (-3.1 mg/cm). No significant period × group interaction was observed, indicating radial artery wall thickness, mass and thickness/radius ratio decreased to the same extent in both groups.

The effects of biologically relevant variables (patient age, weight, baseline blood pressure and magnitude of SBP and DBP change with treatment and heart rate at baseline and during treatment) on the radial artery end points were analyzed using a multivariate regression analysis. To determine whether there were drug-specific effects, the group (either HCTZ-plus-amiloride or perindopril) was included in the analysis. There was a significant relation between the final (month 9) wall thickness and the percent decrease in pulse pressure between months 9 and 0 (p = 0.013) independent of gender (p < 0.001). Similarly, a significant relation was observed between the final (month 9) thickness/radius ratio and the percent (p = 0.001) or absolute (p = 0.014) decrease in pulse pressure between months 9 and 0. Group treatment, age, baseline SBP and DBP, magnitude of SBP and DBP change with treatment and heart rate at baseline and during treatment were not significantly related to final radial artery wall thickness or thickness/radius ratio when included in the multivariate analysis. These results indicate that the alterations in the radial artery end points (month 9) are simply dependent on efficacy of pulse pressure lowering and suggest there were no drug-specific effects. Among the population as a whole, the decrease in thickness/radius ratio after 9 months of treatment was significantly related to the reduction in pulse pressure (r = 0.411, p < 0.01) independent of age (r = 0.320, p < 0.01) and changes in mean blood pressure.

In both groups, internal diameter and circumferential wall stress remained unchanged throughout the study.

Carotid artery variables. Table 4 shows the mean values of carotid artery variables at baseline and during follow-up with each treatment. No significant change in internal diameter or absolute or relative pulsatile changes in diameter were observed for each group. Absolute and relative pulsatile changes in diameter were significantly lower in the perindopril group than in the HCTZ-plus-amiloride group (group effect).

During antihypertension treatment with the perindopril and HCTZ-plus-amiloride-based regimens, a significant increase in CCA distensibility and compliance was observed (period effect). After 9 months, the distensibility changes were ~+33% (+2.2 kPa⁻¹·10⁻³) and ~+38% (3.0 kPa⁻¹·10⁻³) in the perindopril and HCTZ-plus-amiloride groups, respectively. The corresponding CCA compliance changes were ~+28% (+0.9 m²·kPa⁻¹·10⁻⁷) and ~+29% (+1.1 m²·kPa⁻¹·10⁻⁷). No significant period × group interaction was observed, indicating CCA distensibility and compliance were improved to the same extent by treatment in each group. Compliance and distensibility remained lower in the perindopril group than in the HCTZ-plus-amiloride group throughout the study, including baseline values.

Among the cohort as a whole, the increases in CCA distensibility and compliance with treatment were significantly related to the reduction in mean arterial pressure (r = -0.397, p < 0.01; and r = -0.281, p < 0.05, respectively).

No significant difference in baseline characteristics (including radial and carotid artery variables) or responses to treatment was observed between the 51 patients who remained under monotherapy and the 26 patients who required bi-therapy.

Repeatability study in control subjects and patients. Table 5 summarizes the long term intraobserver repeatability of

Table 5. Long-Term Intraobserver Repeatability of Radial and Carotid Artery Variables Measurements in 13 Subjects and Patients With Hypertension

	Baseline Value	Absolute Difference*	Variation Coefficient†	Repeatability Coefficient‡
Radial artery				
Diameter (mm)	2.36 ± 0.34	0.13 ± 0.09	5.6%	0.16
Wall thickness (μm)	229 ± 48	13 ± 9	5.6%	15
Thickness/radius	0.19 ± 0.03	0.02 ± 0.02	9.2%	0.03
Radial artery mass (mg/cm)§	20.2 ± 6.9	1.0 ± 0.7	5.4%	1.4
Carotid artery				
Diameter (mm)	6.42 ± 0.90	0.48 ± 0.35	7.8%	0.36
Ds - Dd (μm)	381 ± 117	46 ± 35	13.9%	60
Compliance (m ² ·kPa ⁻¹ ·10 ⁻⁷)	5.2 ± 2.2	0.9 ± 0.7	19.2%	0.15

*Absolute change after 9 ± 1 months. †Absolute difference/Mean × 100. ‡(SD₂/n)^{1/2}. §Units of radial artery mass are mg/cm length of arterial segment (see text). Data presented are mean value ± SD. Ds - Dd = absolute pulsatile change in diameter.

radial and carotid artery variables in 13 healthy subjects and patients with hypertension. The repeatability coefficients of the various variables were small compared with the mean baseline values. In the 8 healthy subjects, radial artery diameter, wall thickness, thickness/radius ratio and mass remained unchanged after 9 months (2.26 ± 0.28 vs. 2.20 ± 0.21 mm, 196 ± 22 vs. 196 ± 23 μm, 0.17 ± 0.02 vs. 0.18 ± 0.02 and 16 ± 3 vs. 16 ± 3 mg/cm, respectively). In the 5 patients with hypertension, radial artery diameter, wall thickness, thickness/radius ratio and mass remained unchanged after 9 months (2.47 ± 0.40 vs. 2.62 ± 0.30 mm, 287 ± 26 vs. 281 ± 19 μm, 0.24 ± 0.05 vs. 0.22 ± 0.01 and 26 ± 5 vs. 27 ± 5 mg/cm, respectively).

In the eight healthy subjects, carotid artery diameter, stroke change in diameter and compliance did not change significantly after 9 months (6.22 ± 1.03 vs. 6.63 ± 1.11 mm, 458 ± 164 vs. 385 ± 137 μm and 6.2 ± 2.2 vs. 5.9 ± 2.2 m²·kPa⁻¹·10⁻⁷, respectively). In the five patients with hypertension, carotid artery diameter, absolute pulsatile change in diameter and compliance remained unchanged after 9 months (6.68 ± 0.37 vs. 6.40 ± 0.12 mm, 343 ± 140 vs. 340 ± 111 μm and 3.8 ± 2.3 vs. 3.9 ± 1.9 m²·kPa⁻¹·10⁻⁷, respectively).

Discussion

To our knowledge, the present study is the first controlled, blinded study of whether antihypertension treatment reduces intima-media thickness at the site of a medium-sized artery. The results indicate that in elderly patients with hypertension, the intima-media thickness of a peripheral muscular artery, the radial artery and the stiffness of a proximal elastic artery, the CCA, were reduced after 9 months of a perindopril- or HCTZ-plus-amiloride-based treatment. The reduction in the radial artery wall/lumen ratio was directly related to the decrease in pulse pressure, whereas the decrease in carotid

stiffness was directly related to the decrease in mean blood pressure.

Regression of radial artery wall hypertrophy. During sustained essential hypertension, large and medium-sized artery wall hypertrophy may represent target organ damage, like left ventricular hypertrophy or impaired renal function (1,6,17, 23,41). The increase in arterial wall thickness contributes to the normalization of circumferential wall stress (7,8), parallels the development of left ventricular hypertrophy (9) in patients with hypertension and could potentiate the development of atherosclerosis at some arterial sites, like the carotid artery (6,10).

One of the main results of the present study is that in elderly persons with essential hypertension, both ACE inhibitor- and diuretic-based treatments reduced radial artery intima-media thickness. This result is consistent with studies in animals with hypertension that have shown that the reversibility of structural vascular changes during antihypertension treatment can be obtained in the large arteries (11-13). Although in humans long-term antihypertension treatment has been reported to correct in part the structural abnormalities present in the small arteries with mild hypertension (16), to the best for our knowledge no study reported such findings at the site of medium-sized arteries. Whether one pharmacologic class of antihypertensive agents causes a greater normalization of the structure of small arteries (16) and left ventricle (21, 42, 43) than other classes for an equal antihypertension effect in humans remains a matter of debate. In the elderly patients with hypertension in the present study, the ACE inhibitor perindopril decreased radial artery intima-media thickness, as did the combination of HCTZ-plus-amiloride. Antihypertension treatments likely reduced wall thickness through a non-specific effect (i.e., the lowering of distending blood pressure) because circumferential wall stress did not change with treatment and the reduction in thickness/radius ratio was significantly related to the decrease in SBP or pulse pressure among patients as a whole.

Although the objective of the present study was not to compare the radial artery intima-media thickness of untreated persons with hypertension with that of persons without hypertension, it is noteworthy that the radial artery wall of elderly patients with untreated hypertension was thicker than that of the younger subjects without hypertension who were included in the repeatability study. In addition, radial artery wall thickness of persons with and without hypertension, as observed in the present study, were similar to those reported for untreated middle-aged persons with and without hypertension, respectively (7). Thus, the decrease in radial artery intima-media thickness that we observed in the patients with hypertension in the present study can be considered a regression of arterial wall hypertrophy.

Radial artery site for measurement of intima-media thickness. The radial artery site was selected for assessment of the reduction of intima-media thickness for various reasons. First, ultrasound examination is easy to perform because of its superficial rectilinear course and the absence of lateral move-

ment at the wrist (7,26,27). Second, in essential hypertension, structural changes in the large artery wall involve an increased amount of vascular smooth muscle, which is more susceptible to detection in a muscular than in an elastic artery. Because the radial artery is a muscular artery devoid of atherosclerotic lesions, even in patients with severe coronary disease (28), intima-media thickening should reflect morphological changes independent of atherosclerotic lesions. This is of particular relevance for any pathophysiologic study carried out in individuals with essential hypertension, because it is not possible to noninvasively differentiate the hypertension-induced wall thickening from atherosclerotic lesions at various arterial sites such as the carotid artery (9,44). Third, we had the unique opportunity of comparing *in vivo* and *in vitro* measurements in patients who were scheduled for coronary artery bypass graft surgery using the radial artery and to use *in vitro* ultrasonic and histologic measurements to validate *in vivo* measurements made with the high resolution echo-tracking system NIUS 02 (7).

Study limitations. Because the present study was not a placebo-controlled study, for obvious ethical reasons, and because no drug proved to be more efficacious than the other, one may question whether antihypertension treatment truly reduced radial artery intima-media thickness. However, several findings strongly suggest that a time effect is very unlikely and that true regression of radial artery wall hypertrophy occurred in these patients with hypertension. A major argument is that in the healthy subjects and patients with hypertension included in the repeatability study, wall thickness, thickness/radius and ratio and radial artery mass remained unchanged with time. Second, the repeatability coefficients of radial artery parameters were low compared with their respective baseline values (Table 5). Third, tracings were read by two physicians who were blinded to treatment, clinical data and study visit; thus, a sequence bias could not have occurred. Fourth, a multiple regression analysis showed that the final (month 9) thickness/radius ratio was related not only to the baseline value but also to the *in-treatment* reduction in pulse pressure. Fifth, the reduction in radial artery mass observed with treatment in the present study is close, in relative value, to those obtained in various long term studies showing a reduction in left ventricular mass (42,43,45). Therefore, our conclusion that the reduction in wall thickness represents a true regression of radial artery wall hypertrophy seems well founded.

The second important result of this study is the absence of significant period \times group interaction for the radial artery parameters. We can conclude that radial artery intima-media thickness, mass and thickness/radius ratio decreased to the same extent in the perindopril- and diuretic-based treatment groups. Could this result be a false negative? A power calculation ($\alpha = 0.05$) estimates that with the given number of subjects and the given SDs, we had an 84% likelihood of detecting a difference in intima-media thickness between groups at 9 months (regardless of whether patients remained on monotherapy) of $>29 \mu\text{m}$, a value that represents a 10%

reduction in baseline intima-media thickness. Any difference smaller than that may be considered of little relevance in view of the intersubject variability observed in the present study and previous studies (7,28).

Improvement of carotid compliance under treatment. Increased arterial stiffness in hypertension contributes to a further rise in SBP and pulse pressure at any given value of mean arterial pressure (22,23). The increase in pulse pressure has been shown to be independently associated with an increase in coronary and cardiac disease and death (46-48). Animal (3,4) and clinical (5) studies have shown that the increased load due to pulse pressure represented for small arteries a higher determinant of structural abnormalities than mean arterial pressure. In the present study, the significant relationship between the reduction in pulse pressure and the decrease in radial artery thickness/radius ratio suggests that for medium-sized conduit arteries, the increased load due to pulse pressure also represents a strong determinant of wall thickness.

We investigated the effects of antihypertension treatment on the elastic properties of the CCA. After 9 months of antihypertension treatment with the perindopril- or the HCTZ-plus-amiloride-based regimen, the CCA exhibited a significant increase in cross-sectional compliance and distensibility. Although improvement in large artery compliance with ACE inhibitors has been largely reported in patients with hypertension (22,33,49), the effects of diuretics are less consistent (33,50). No change was observed at the site of the brachial and common carotid and femoral arteries after treatment with hydrochlorothiazide or in dapamide in controlled studies (50). In a long-term controlled study, Kool et al. (33) observed that a 6-month treatment with perindopril significantly increased carotid artery distensibility and compliance, whereas HCTZ plus amiloride did not. The reasons for the discrepancy between the results of the study by Kool et al. (33) and those of the present study are unclear, but three hypotheses can be suggested. Although no significant difference in blood pressure reduction was observed between both treatments in the study by Kool et al. (33), blood pressure tended to be reduced to a greater extent in the perindopril-treated group, a change that may have contributed to the greater improvement in carotid compliance in these patients. A second possibility is that the pressure-independent effect of ACE inhibition on large arteries had been offset in elderly patients by the prevailing role of blood pressure reduction or by the lack of counterregulatory mechanisms (activation of the renin-angiotensin and sympathetic nervous systems) after treatment with diuretics in the elderly. Third, diuretics, which are effective in the reduction of pulse pressure and SBP in the elderly (18-20), very likely improved carotid compliance through their blood pressure-lowering effect. Thus, in the population of the present study (i.e., elderly patients with systolic hypertension), antihypertension treatments improved CCA compliance mainly through a pressure-dependent mechanism. In this context, the significant relationship that we observed between the reversibility of arterial hypertrophy and the reduction in the pulsatile (and not steady) component of blood pressure is of major interest.

The lack of reduction in radial and carotid artery diameters along with the decrease in blood pressure during treatment may be due to various mechanisms, including a direct vasodilating effect of the antihypertensive agents and a chronic remodeling process aimed at maintaining the circumferential wall stress as unchanged (8).

Conclusions. These results indicate that in elderly patients with hypertension both ACE inhibitor- and diuretic-based treatments can reduce radial artery wall hypertrophy and improve carotid artery compliance. They suggest that the pressure-dependent increase in carotid distensibility and compliance, which likely reflects the improvement in systemic distensibility and compliance, may lead to a reduction in pulse pressure and the subsequent reduction in radial artery wall thickness/radius ratio.

We are grateful to the physicians who participated in the study: Pierre Berger, MD, Daniel Delbecq, MD, Raphaël Sebbah, MD, Bernard Mage, MD, André Sebbah, MD, Jean Marie Halmenschlager, MD, Hugues-Henry Pujade, MD, Josué Ouaknine, MD, Christiane Fieyre, MD, Hai N'guyen Nhu, MD, André Fontaine, MD, Paul Brami, MD, François de Lamotte, MD, Hubert Khalfat, MD, and Guy Thuillier, MD.

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