Changes in Arterial Structure and Function Under Trandolapril-Verapamil Combination in Hypertension

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Background and Purpose—Converting enzyme inhibition and calcium blockade alter large arteries in hypertension. However, the heterogeneity of the response according to the site of cardiovascular measurements has never been investigated.

Methods—In a double-blind study, we compared for 180 days 3 hypertensive patient groups treated with verapamil, trandolapril, or their combination. Using echo-Doppler technique and applanation tonometry, we independently measured mean pressure, local pulse pressure, arterial diameter, and distensibility at 3 arterial sites (brachial and common carotid arteries and abdominal aorta), as well as cardiac and carotid wall structure.

Results—Mean and pulse pressure decreased significantly to a greater extent with the drug combination. Regarding arterial and cardiac hemodynamics, significant and similar changes were noted in the 3 groups: decreases in abdominal aorta and carotid but not brachial diameter; increases in carotid artery, abdominal aorta, and brachial distensibility even after adjustment to mean blood pressure reduction; and more substantial regression of cardiac mass than carotid wall thickness.

Conclusions—This study shows that both compounds and more significantly combination therapy decreased mean and pulse pressures measured independently and that the changes in diameter, thickness, and stiffness were influenced primarily by the site of cardiovascular measurements, resulting in a predominant increase in distensibility of muscular arteries, little change in carotid wall thickness, but a significant regression of cardiac hypertrophy. **(*Stroke*. 1999;30:1056-1064.)**

Key Words: antihypertensive therapy ■ arterial wall ■ hypertension

Increased pulse pressure is an independent predictor of cardiac mortality, primarily for myocardial infarction.[1,2] Because at a given ventricular ejection arterial stiffness is the principal factor influencing pulse pressure, it becomes important to develop methods that can routinely be applied to investigate large arteries in cardiovascular pharmacology, particularly hypertension.

Noninvasive determinations of arterial diameter and stiffness by echo-tracking techniques[3,4] and measurement of pulse pressure amplification by applanation tonometry[5,6] are suitable methods to evaluate the structure and function of large arteries. Nevertheless, when these methods are applied to the study of arterial segments, they raise 2 important points. First, central arteries, such as the aorta and the common carotid artery, are elastic or musculoelastic arteries, whereas peripheral medium-sized arteries are rather muscular. These 2 types of vessels are expected to respond differently to the same blood pressure reduction. Second, although mean arterial pressure is known to be identical along the entire arterial tree, pulse pressure increases markedly from central to peripheral arteries, rendering the level of pulsatile stress quite different from 1 artery to another.[6] Thus, when noninvasive determinations of pulse pressure and arterial stiffness are made, it is important to evaluate the arterial changes at different sites.

In a recent study,[7] we compared the long-term arterial effects of 2 antihypertensive agents, the converting enzyme inhibitor ramipril and the calcium entry blocker nitrendipine. We showed that despite substantial differences in their mechanisms of action, the 2 drugs did not differ significantly in their effects on the structure and function of the heart and vasculature. However, important differences were noted according to the site of cardiac and arterial measurements. For instance, the 2 drugs produced the same reduction in cardiac mass but did not significantly modify the hypertrophy of the hypertensive radial artery. These findings raised 2 possibilities that required further investigation. First, it is possible that the combination of the 2 drugs gives similar results, thus suggesting the predominant influence of measurement site over mechanism of action of each antihypertensive agent. Second, it is likely that the regression of vascular hypertrophy differs in a medium-sized muscular artery, such as the radial artery, compared with a central musculoelastic artery, like the

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common carotid artery. To the best of our knowledge, such a differential structural effect has never been explored.

The main objectives of this study were (1) to determine whether the combination of the converting enzyme inhibitor trandolapril[8–10] and the calcium entry blocker verapamil[11,12] has an antihypertensive effect superior to that of each drug given alone and (2) to evaluate whether the structural and functional cardiovascular changes produced by each antihypertensive agent or their combination were influenced by measurement site, independent of their mechanism of action. For this purpose, we studied, in addition to cardiac mass and carotid wall thickness, the diameter and the mechanical properties of 3 different arteries: the common carotid artery, brachial artery, and abdominal aorta.

Subjects and Methods

One hundred forty-nine patients were preincluded for hypertension by general practitioners working with the Institut de Recherche et Formation Cardiovasculaire (Paris, France). Sixty-nine patients (38 men and 31 women) were selected as having mild to moderate essential hypertension with a diastolic blood pressure between 95 and 114 mm Hg and thus fulfilled the primary inclusion criteria. Their mean age (±SD) was 53 years (range, 29 to 76 years). Weight and height were 79±15 kg and 168±9 cm, respectively. In all hypertensive subjects, treatments were discontinued 1 month before the study, and diastolic blood pressure as assessed by conventional sphygmomanometry remained >95 mm Hg and ≤114 mm Hg throughout this washout placebo period. Patients had no signs, symptoms, or history of strokes or major cardiac or renal diseases other than hypertension. No stenosis >30% of the lumen area of the common carotid, internal carotid, or iliofemoral artery was noted on the basis of ultrasound standard explorations. No patient received antidiabetic or hypocholesterolemic treatment or any other cardiovascular drug during the study. Written consent was obtained from each subject after a detailed description of the procedure was given by the general practitioner. This protocol was approved by the Ethics Committee of Saint Germain en Laye (France).

After a 1-month placebo period, the 69 patients were randomized in a double-blind study comparing 3 parallel groups: the verapamil group (V group; n=23; 15 men and 8 women) treated with the calcium entry blocker verapamil (240 mg/d)[11,12]; the trandolapril group (T group; n=23; 10 men and 13 women) treated with the converting enzyme inhibitor trandolapril (2 mg/d)[8–10]; and the combination group (V+T group; n=23; 13 men and 10 women) treated with a fixed combination of verapamil (180 mg/d) and trandolapril (2 mg/d).[8,9] The trandolapril dose was chosen on the basis of a preliminary double-blind study in 42 patients with essential hypertension (distinct from those included in the present investigation) who had been randomized between placebo and 0.5, 1, 2, 4, and 8 mg trandolapril for 8 days. The antihypertensive effect, determined 24 hours after administration of the last tablet, was completely achieved with 2 mg, at which dose the systolic blood pressure reduction plateau was clearly observed. Because of the long duration of the trandolapril dosage (≥24 hours), the verapamil dosage was limited to 180 mg/d.[8–10] In the present investigation, each drug was given orally at 8 AM in a single morning dose. The duration of the active treatment period was 6 months between day 0, the end of the preinclusion placebo period, and day 180. Ten patients did not complete the study for reasons independent of drug treatment: 2 in group V, 5 in group T, and 3 in group V+T. Plasma potassium, creatinine, uric acid, glucose, total cholesterol, and hepatic enzymes were measured on days 0 and 180 and did not change significantly.

Hemodynamic investigations were performed 24 hours after administration of the last tablet, at the end of the preinclusion placebo period (day 0), and at day 180. Each subject was investigated at 10 AM in a controlled environment of 22±2°C. After 20 minutes of rest in a supine position, systolic and diastolic blood pressures and heart rate were determined every 3 minutes with an oscillometric recorder (model 845, Dinamap, Critikon) placed on the left arm. Then, arterial measurements were made on the right common carotid artery, the brachial artery, and finally the abdominal aorta. Arterial parameters were studied exactly at the same points: 2 cm proximal to the carotid bifurcation, 3 cm proximal to the aorto-iliac bifurcation, and 3 cm proximal to the brachial artery bifurcation. Echocardiography was then performed. All measurements were analyzed by 2 physicians blinded to treatment, clinical data, and physical examination.

Systolic-diastolic variations in carotid, brachial, and aortic diameters were measured with an original pulsed ultrasound echotracking system based on the Doppler shift. The details of this method have been described elsewhere.[3,14] Briefly, the system allows transcutaneous assessment of the displacement of the arterial wall during the cardiac cycle and hence the time-dependent change in arterial diameter to its initial diameter at the start of the cardiac cycle, knowing that the availability of the ECG trigger facilitates the detection of the peak distension of the artery relative to its initial diameter. Displacement of the arterial wall is obtained by processing the Doppler signals originating from 2 selected sample volumes, thereby allowing evaluation of the systolic (Ds) and diastolic (Dd) diameters, stroke change of diameter (or distension) during systole (Ds−Dd), and relative stroke change of diameter ([Ds−Dd]/Dd). To estimate arterial stiffness, distensibility was expressed as (dV/dP)/V, where dV is the systolic-diastolic changes in the volume of the arterial segment, dP is the local pulse pressure (systolic minus diastolic blood pressure; see below), and V is the diastolic arterial volume. Assuming that the increase in volume (dV) is caused only by arterial distension (and not by elongation), the cross-sectional distensibility can be expressed as DC=(dA/dP)/A, where A is the diastolic arterial cross-sectional area, and dA is the systolic-diastolic change in cross-sectional area determined with a cylindrical model of the artery. Cross-sectional distensibility was calculated from 8 to 10 successive measurements of pulsatile diameter and pressure on the same arterial segment. Reproducibility of the carotid artery measurements was based primarily on the determination of the coefficient of variation (SD expressed as a percentage of the mean of several successive measurements).[15] First, reproducibility was assessed during the recording of 3 to 8 successive cardiac cycles. The mean coefficients of variation determined under these conditions were 1% and 6% for Dd and Ds−Dd, respectively. Second, reproducibility was assessed during 12 measurements made by each of 2 observers over a 90-minute period in 5 subjects. Each of the 12 measurements was the mean of 3 to 8 values corresponding to 3 to 8 cardiac cycles. Under similar conditions, the mean intraobserver coefficients of variation were 3% and 8% for Dd and Ds−Dd, respectively. After 6 months, the coefficients of variation measured under the same conditions were 7.8% and 13.9%, and the repeatability coefficients (SD of the estimated difference between 2 repeated measurements) were 0.36 and 60 μm, respectively.[15] For the abdominal aorta, the coefficient of variation was studied in 7 normotensive subjects by use of the same procedure. Interobserver coefficients of variation were 1.5% and 7.8% for Dd and Ds−Dd, respectively. Intraobserver coefficients of variation were 4.6% and 10.5%, respectively.[16] Similar values have been reported by us and others for brachial artery diameter measurements.[17,18] Coefficients of variation for distensibility have been given in detail elsewhere.[15–19]

For local pulse pressure determinations, brachial and radial artery systolic, diastolic, and mean pressures were considered equivalent, taking into account the small degree of pressure wave amplification between these sites.[6,19,20] The carotid pressure wave was measured by applanation tonometry and calibrated from the brachial pressure wave, assuming that the mean pressure (determined from Dinamap) was the same at both sites and that pulse pressure at the 2 sites can be reliably determined by use of generalized transfer functions.[5,6,19,20] Therefore, the carotid pressure wave was calibrated with the assumption that brachial and carotid diastolic and mean blood pressures were equal.[19] The mean blood pressure on the carotid pressure wave was computed from the area of the carotid pressure wave in the corresponding heart period and set equal to brachial mean blood pressure. Carotid pressure amplitude was then computed

from the diastolic blood pressure and the position of mean blood pressure on the carotid pressure wave.[19] Thoracic aortic pressure waves were derived from the radial artery pressure wave with the SphygmoCor system (PWV Medical).[5] This device applies a generalized transfer function to determine the aortic curve from the radial pressure wave and has been validated in detail elsewhere.[5,6] Separately, and with the appropriate transfer function, ascending aortic pressure waves were synthesized from the carotid waves determined by tonometry. There was close agreement between the contour of the aortic pressure waves and the values of augmentation for the thoracic aortic pressure wave synthesized from the 2 sites.[20] At each site, pulse pressure was averaged for a series of waves over a 10-second period. The repeatability coefficients after 1- and 3-month intervals were 6.8 and 7.2 mm Hg, respectively.[19,21] Finally, brachial pulse pressure was used to determine the abdominal aorta pulse pressure. In fact, it has been clearly shown that brachial pulse pressure evaluated with an auscultatory method and abdominal aorta pulse pressure measured with invasive techniques differ by <10%, with slightly lower values for the brachial artery.[22,23] Furthermore, there are indications that these differences are reduced and even disappear after 50 years of age.[6]

Aortic pulse wave velocity (PWV) was determined by use of an automatic device, the Complior (Colson), which allowed online pulse wave recording and automatic calculation of PWV.[24] Briefly, common carotid artery and femoral artery pressure waveforms were recorded noninvasively with a TY-306-Fukuda pressure-sensitive transducer (Fukuda). The pressure waveforms were digitized at the sample acquisition frequency of 500 Hz. The 2 pressure waveforms were then stored in a memory bank. A preprocessing system automatically analyzed the gain in each waveform and adjusted it to equalize the 2 signals. Details of this procedure have been published previously.[24] When the operator observed a pulse waveform of sufficient quality on the computer screen, digitization was suspended, and calculation of the time delay between the 2 pressure upstrokes was initiated. Measurement was repeated over 10 different cardiac cycles, and the mean was used for the final analysis. The distance traveled by the pulse wave was measured over the body surface as the distance between the two recording sites (D), whereas pulse transit time (t) was automatically determined by the Complior; PWV was automatically calculated as PWV=D/t. Validation of this automatic method and its reproducibility have been reported previously, with an intraobserver and interobserver repeatability coefficients of >0.90.[24]

To determinate carotid intima-media thickness (IMT), ultrasound examinations of the cervical arteries were performed with the patient in the recumbent position by use of a Sigma 44 KONTRON (Kontron Instruments) with a transducer frequency of 7.5 MHz.[19] This system provides an axial resolution of 0.30 mm. Acquisition, processing, and storage of B-mode images were computer assisted with software specifically designed for longitudinal studies (EUREQUA, TSA).[25,26] Measurements involved a primary scanning of the common carotid arteries, carotid bifurcations, and origin (first 2 cm) of the internal carotid arteries. Then, the IMT, measured on the far wall of the middle and distal common carotid artery as the distance between the lumen-intima interface and the media-adventitia interface, was calculated with an automated edge detection algorithm. One transversal and 2 longitudinal measurements of IMT were completed on both the right and left common carotid arteries. Optimal images showing the far wall were stored on a special disk. Both near and far walls of all arterial segments were scanned longitudinally and transversally to assess the presence of plaques, defined as localized echo structures protruding into the vessel lumen for which the IMT was ≥2 mm.[19,25] Subjects with plaques were excluded from the present study. For quality assessment, IMT readings and measurements were analyzed at the end of the study. In previous studies,[25,26] it has been shown that both the interobserver and intraobserver variations in IMT associated with the scanning procedure were substantially reduced after the repositioning functions of the EUREQUA software had been used. The aforementioned variabilities (expressed as absolute differences and correlation coefficients) were 0.10 mm (r=0.58) and 0.10 mm (r=0.62), respectively, with standard procedures, whereas corresponding values obtained with repositioning procedures were 0.07 mm (r=0.71) and 0.06 mm (r=0.77), respectively. For IMT measurement, the long-term (6-month) coefficient of variation was 5.2% and the repeatability coefficient was 91.6 μm (personal data).

Finally, for cardiac mass, 2-dimensionally directed M-mode echocardiography was performed with a Sigma 44 KONTRON (see above) by use of 2.5- and 3.5-MHz transducers. Echocardiograms were performed by a highly experienced sonographer. Measurements of left ventricular dimensions were made at end diastole according to the recommendations of the American Society of Echocardiography. Measurement readings were performed blindly on 5 cycles by 2 experienced physician readers using a digitizing tablet and were averaged. Left ventricular mass (LVM) (in grams) was calculated according to the Penn convention and converted in LVM index (LVMI) by dividing by body height[2.7].[27] Intrareader correlation for LVM was r=0.96 for the 2 readers. Interreader correlation for LVM was r=0.93 (mean difference, 7 g; SD, 10.1 g).[28] The long-term reproducibility of LVM measurements made in a previous blinded study showed that the correlation between the baseline LVM and LVM after 16 weeks of placebo treatment was r=0.98 (mean difference, 12 g; SD, 11.2 g).[29]

Statistical analyses were performed with SPSS for Macintosh 4.0 (SPSS Inc). Baseline values were compared with 1-way ANOVA and did not show any difference. For analysis of the principal objectives (blood pressure and PWV measurements), 2 types of tests were used. First, ANOVA with repeated measures with time comparison and time-by-group comparison of 3 therapeutic groups (groups V, T, and V+T) and 2 therapeutic groups (grouping V and T against V+T) was performed. In case of significant comparison group, a contrast analysis was needed to determine which groups differed. In a second test, ANOVA with 1 factor (therapeutic groups) was done on relative differences that were computed as final value minus basal value divided by basal value. In this case, the 3- and 2-group comparisons were also performed as done with ANOVA with repeated measures. For the parameters not included as principal objectives, only the 3-therapeutic-group comparison and the 2 types of analysis (ANOVA with repeated measures and ANOVA with relative difference) were made. Finally, a MANOVA adjusted to the percent change in mean blood pressure was performed, thereby allowing detection of a site effect (cardiac versus carotid structure, carotid artery versus brachial artery versus abdominal aorta) independent of drug effect. A value of $P \leq 0.05$ was considered significant.

Results

Changes in Blood Pressure and Aortic PWV

Table 1 indicates the mean values before and after treatment and percent changes. Time effects and inter–3-group and inter–2-group comparisons are also indicated. After drug treatment, systolic, diastolic and mean pressures and aortic PWV decreased significantly (P<0.01) in all groups (Table 1). For inter–3-group comparison, mean blood pressure was reduced to a significantly higher extent in the V+T group. Bitherapy (inter–2-group comparison) reduced diastolic and mean pressures significantly more than monotherapy.

As shown in Table 2, before and after treatment, radial (or brachial) artery pulse pressure was significantly higher than carotid and thoracic aorta pulse pressure (P<0.01). Radial (considered equal to brachial), carotid, and thoracic aorta pulse pressures decreased significantly (P<0.01) in the 3 treatment groups without any difference between them.

TABLE 1. Brachial Blood Pressure Changes in the Treatment Groups

	V Group	T Group	V+T Group	*P*, Before vs After (Time Effect)	*P*, Inter–3-Group Comparison	*P*, Inter–2-Group Comparison
Systolic BP, mm Hg						
Before	156±12	160±15	163±16	<0.01	NS	0.06
After	137±17	141±15	137±19			
(Before−after)/Before, %	−12±9	−12±8	−16±9		NS	0.07
Diastolic BP, mm Hg						
Before	96±7	101±7	100±6	<0.01	0.09	0.03
After	86±10	90±11	84±9			
(Before−after)/before, %	−10±10	−11±8	−15±10		NS	0.04
Mean BP, mm Hg						
Before	113±8	118±8	118±7	<0.01	0.04	0.01
After	101±11	104±12	99±11			
(Before−after)/before, %	−10±9	−11±7	−16±9		0.05	0.02
Heart rate, bpm						
Before	78±10	77±9	79±11	NS	NS	NS
After	78±11	74±10	77±14			
(Before−after)/before, %	−1±13	−5±12	−2±14		NS	NS
Pulse wave velocity, m/s						
Before	13±4	13±2	13±2	<0.01	NS	NS
After	11±3	11±3	11±2			
(Before−after)/before, %	−13±6	−12±12	−14±10		NS	NS

BP indicates blood pressure. Values are mean±SD. For mean BP, contrast analysis is V/V+T=0.02; T/V+T=0.06; V/T=NS. Note that the time effect takes into account the 6 measurements noted "before" and "after."

Changes in Arterial Function and Diameter

For the carotid artery (Table 3), there was a significant decrease in diameter ($P<0.01$) and increase in absolute and relative stroke change in diameter and distensibility ($P<0.01$). For the brachial artery, there was no change in diameter but a significant increase in stroke change in diameter and distensibility ($P<0.01$). For the abdominal aorta, there was a significant decrease in diameter ($P<0.01$) and increase in stroke change in diameter and distensibility ($P<0.01$; Figure). For the 3 arteries, no group effect was observed (the Figure).

Table 4 indicates the statistical analysis performed according to the site of arterial measurements. A significant site effect, independent of group effect, was observed for absolute and relative stroke changes of diameter ($P=0.002$), distensibility ($P=0.05$; Figure), and diastolic diameter ($P=0.05$). Under the V+T combination, mean diameter decreased less ($P=0.04$) and stroke changes of diameter ($P=0.004$) and distensibility ($P=0.06$) increased more than under monotherapy. The increase in distensibility was constantly more pronounced at the brachial artery site (Figure).

Changes in Cardiac and Carotid Structures

Diastolic diameter and septal and posterior wall thicknesses decreased significantly after all treatments, resulting in a significantly decreased cardiac mass ($P<0.01$). In absolute value (g), the mean LVM decrease for the entire population was 19 g. According to multiple regression analysis, it

TABLE 2. Pulse Pressure Changes in the Treatment Groups

	V Group	T Group	V+T Group	*P*, Before vs After (Time Effect)	*P*, Inter–3-Group Comparison
Radial PP, mm Hg					
Before	53±12	55±12	58±14	<0.01	NS
After	51±10	48±10	49±13		
Carotid PP, mm Hg					
Before	44±12	45±12	48±15	<0.01	NS
After	39±9	41±11	40±14		
Aortic PP, mm Hg					
Before	41±11	44±11	45±14	<0.01	NS
After	37±9	38±10	37±13		

PP indicates pulse pressure. Values are mean±SD. For time effect, see Table 1.

TABLE 3. Changes in Carotid Artery, Brachial Artery, and Abdominal Aorta Parameters in the Treatment Groups

	V Group	T Group	V+T Group	*P*, Before vs After (Time Effect)	*P*, Inter–3-Group Comparison
Carotid artery					
Diastolic diameter, mm					
Before	7.1±0.7	7.1±0.8	7.2±0.9	<0.01	NS
After	6.9±0.7	6.8±0.6	7.0±0.9		
Absolute stroke change in diameter, μm					
Before	307±70	300±99	310±82	<0.01	NS
After	332±77	340±93	351±84		
Relative stroke change in diameter, %					
Before	4.4±1.0	4.2±1.1	4.3±1.0	<0.01	NS
After	5.0±1.2	5.0±1.3	5.1±1.0		
Distensibility, kPa^{-1}					
Before	1.7±0.7	1.5±0.5	1.6±0.7	<0.01	NS
After	2.1±0.9	2.1±0.9	2.2±0.8		
Brachial artery					
Diastolic diameter, mm					
Before	4.4±0.8	4.2±0.7	4.4±0.7	NS	NS
After	4.2±0.8	4.1±0.7	4.4±0.8		
Absolute stroke change in diameter, μm					
Before	117±40	109±27	117±37	<0.01	NS
After	157±46	132±41	158±61		
Relative stroke change in diameter, %					
Before	2.7±1.0	2.6±0.5	2.7±0.9	<0.01	NS
After	3.8±1.0	3.2±0.9	3.5±1.1		
Distensibility, kPa^{-1}					
Before	0.8±0.3	0.8±0.2	0.7±0.3	<0.01	NS
After	1.2±0.3	1.1±0.4	1.3±0.6		
Abdominal aorta					
Diastolic diameter, mm					
Before	19.1±2.8	19.5±2.4	18.0±2.1	<0.01	NS
After	17.8±2.0	18.5±2.4	17.5±2.3		
Absolute stroke change in diameter, μm					
Before	605±191	638±202	504±169	<0.01	NS
After	745±201	744±196	652±216		
Relative stroke change in diameter, %					
Before	3.2±0.9	3.3±0.9	3.0±0.8	<0.01	NS
After	4.2±1.2	4.0±1.0	3.8±1.3		
Distensibility, kPa^{-1}					
Before	1.0±0.4	0.9±0.4	0.9±0.3	<0.01	NS
After	1.4±0.6	1.4±0.5	1.3±0.3		

Values are mean±SD. Time effect takes into account all together the 6 parameters noted "before" and "after."

appeared that the decreased cardiac mass was significantly correlated with 3 parameters: the LVMI baseline value, percent decrease in mean arterial pressure, and thoracic aorta pulse pressure (r^2=0.33).

After drug treatment, carotid wall thickness decreased similarly in the treatment groups (P<0.01) (Table 5). In the entire population, the mean absolute decrease was 30 μm (range, −220 and 150 μm). The absolute or percent decrease did not correlate with the decrease in mean arterial pressure or carotid pulse pressure but was exclusively correlated with the IMT baseline value (r^2=0.07). The percent decrease in carotid IMT was significantly less pronounced than that of cardiac mass (site effect, P=0.02).

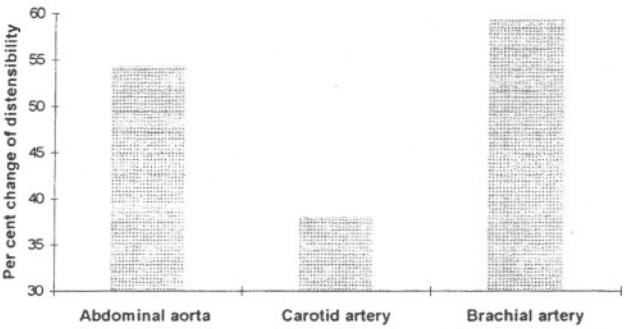
Discussion

In the present study, the functional and structural changes in the heart and conduit arterial vessels under long-term antihypertensive therapy were compared by use of the converting

TABLE 4. Analysis of Site Effects (Abdominal Aorta, Carotid Artery, and Brachial Artery) for Pulse Pressure and Arterial Measurements

	Mean, %	SD, %
Pulse pressure (P=NS)		
Abdominal aorta	−10.4	22.2
Carotid artery	−9.6	21.7
Brachial artery	−9.6	16.0
Diastolic diameter (P=0.05)		
Abdominal aorta	−4.9	5.9
Carotid artery	−3.0	4.7
Brachial artery	−2.0	7.9
Absolute stroke change in diameter (P=0.002)		
Abdominal aorta	28.3	36.1
Carotid artery	13.3	18.6
Brachial artery	31.4	34.2
Relative stroke change in diameter (P=0.002)		
Abdominal aorta	31.2	34.7
Carotid artery	17.9	17.6
Brachial artery	37.0	37.8
Distensibility (P=0.05)		
Abdominal aorta	54.4	51.1
Carotid artery	38.1	39.5
Brachial artery	59.5	58.8

Note that except for pulse pressure, there was a significant site effect for the 4 studied arterial parameters despite the large SD.



Percent change in distensibility in 3 studied arterial territories: abdominal aorta, carotid artery, and brachial artery. Note that differences were significant (P<0.05).

enzyme inhibitor trandolapril), the calcium entry blocker verapamil, or their combination in a population of 69 subjects with essential hypertension. We found (1) that blood pressure was significantly lowered, affecting mean arterial pressure and pulse pressure measured independently, with a more significant decrease for the V+T combination, and (2) that cardiovascular structure and function were also significantly modified, involving increased arterial distensibility and regression of cardiac and, to a much lesser extent, carotid hypertrophies. Whereas the latter findings were quite similar for each drug and their combination, arterial changes differed largely according to the site of arterial measurements, suggesting that the pressure-independent properties of each arterial segment were an important determinant of the vascular changes obtained with long-term treatment of hypertension with converting enzyme inhibition, calcium blockade, or their combination.

Study Limitations

For obvious ethical reasons, the present study was a double-blind but not a placebo-controlled study. Thus, it remains to be determined whether antihypertensive treatment truly modifies blood pressure and cardiovascular structure and function. However, in this population of hypertensive subjects, significant data suggest that a regression toward the mean is an unlikely explanation for the blood pressure and arterial function changes observed. Regarding blood pressure, a

TABLE 5. Changes in Cardiac and Carotid Structure in the Treatment Groups

	V Group	T Group	V+T Group	P, Before vs After (Time Effect)	P, Inter–3-Group Comparison
Septal thickness, mm					
Before	9.4±1.9	8.9±1.6	9.1±2.0	<0.01	NS
After	9.0±1.8	8.4±1.7	8.6±2.0		
Posterior wall thickness, mm					
Before	8.6±1.5	8.3±1.2	8.1±2.1	<0.01	NS
After	8.1±1.2	7.9±1.3	7.8±1.4		
Diastolic diameter, mm					
Before	50.0±3.1	53.8±3.8	54.3±5.7	<0.02	NS
After	53.4±3.1	53.2±3.6	53.7±4.1		
LVMI, g/cm					
Before	51.7±11.3	51.9±11.2	51.4±17.6	<0.01	NS
After	47.0±10.7	47.0±10.1	47.5±17.1		
Common carotid wall thickness, mm					
Before	0.72±0.16	0.68±0.13	0.72±0.20	<0.01	NS
After	0.70±0.18	0.64±0.11	0.69±0.16		

Values are mean±SD. For time effect, see Table 1.

major argument was that the 2-drug combination produced a significantly greater decrease in mean arterial pressure than each compound alone. Concerning arterial changes, we showed in the Methods section that in the absence of treatment, the different hemodynamic parameters remained largely unchanged over time. Furthermore, the repeatability coefficients were low compared with their respective baseline values. In addition, tracings were always analyzed by 2 physicians blinded to treatment, clinical data, and physical examination. Thus, a sequence bias is highly unlikely. Finally, the changes in arterial geometry and function exhibited distinct site effects, particularly for pulsatile changes in diameter and distensibility.

For cardiac and carotid structures, the situation is more complex. An important finding was that carotid artery IMT was poorly modified under treatment, whereas cardiac mass decreased significantly in all 3 treatment groups (site effect, $P=0.02$). A simple calculation indicates that we had a substantial likelihood of detecting at 6 months differences in IMT between groups that were >91.6 μm, a value that approximates a 13% reduction in baseline IMT. Furthermore, our coefficient value fits with those reported in the literature.[30–32] Any difference smaller than these values (ie, ≈ 30 μm in the present investigation) may be considered of little relevance in view of the intersubject variation observed in this and previous studies.[25,31,32] Therefore, it is safe to conclude that we observed few modifications in carotid IMT whereas the decrease in cardiac mass was clearly significant.

Comments on Findings

In a preliminary study, we determined during an 8-day period that the optimal trandolapril dose to ensure 24-hour efficacy was 2 mg. In this report, we showed that trandolapril combined with verapamil at a dosage (180 mg/d) effective for <24 hours produced a significantly greater antihypertensive effect than trandolapril (2 mg/d) or verapamil (240 mg/d) alone.[8–10,33] Because we independently measured mean and pulse pressures and because pulse pressure was reduced more substantially with the drug combination, the results point to drug effects acting on both small arteries (decrease in mean arterial pressure and hence vascular resistance) and large arteries (decrease in pulse pressure, mainly in the thoracic aorta).

In the presence of a significant blood pressure reduction, a decrease in the diameter of conduit arteries is expected as a passive consequence of the decreased distension pressure. In this study, this hemodynamic pattern was observed for elastic and musculoelastic arteries, like the common carotid artery and the abdominal aorta, but not for the muscular radial or brachial artery. A possible explanation is that the latter was the site of drug-induced vascular smooth muscle relaxation, which can be observed even when blood pressure is lower.[6,16,18] Clinical pharmacological studies in normal volunteers[34,35] have previously shown that although little change in brachial artery diameter is obtained under verapamil, more substantial dilating properties may be observed with converting enzyme inhibitors, even in the absence of significant blood pressure variations. Converting enzyme inhibitors are known to cause a significant relaxation of large arteries through several possible mechanisms, including blockade of angiotensin II and/or changes in endothelial function through bradykinin, nitric oxide, or their combination.[36] After converting enzyme inhibition, endothelial vascular changes in the brachial artery independent of blood pressure lowering have been previously reported in hypertensive humans.[37]

Until recently, most reports in the literature invariably studied compliance and distensibility from in vitro arterial segments subjected to a steady pressure to determine the static pressure-diameter curve.[6] Subsequently, when several arteries were simultaneously studied and compared in vitro, it was easy to differentiate between pressure and drug effects on the arterial wall. That methodology differs totally from the dynamic distensibility measurements that we made in the present clinical study. In a given subject, when arteries of different sites are compared, the comparison is obviously made at the same mean arterial pressure (which is constant along the arterial tree) but at different pulse pressures because of the pulse pressure amplification in humans.[6] To the best of our knowledge, the present study is the first to calculate distensibility from the local pulse pressures of 3 different arterial segments in vivo. Because there was a parallelism between blood pressure reduction and increased distensibility, there is no doubt that mechanical factors had a major role to explain the increase of distensibility. Nevertheless, such changes in distensibility were observed even after adjustment for the percent decrease in mean arterial pressure and predominated on the brachial artery. This finding suggests a significant contributive role of nonpressure mechanisms, principally at the level of muscular arteries.

Although a number of studies have shown that drug treatment of hypertension undoubtedly decreases cardiac mass, discrepancies have been reported regarding the effect of each particular antihypertensive drug.[38–42] Whereas some meta-analyses indicated that converting enzyme inhibitors decreased cardiac mass more than calcium entry blockers, several prospective studies showed the same decrease in cardiac mass for a similar lowering of blood pressure.[41,42] In the present investigation, the observed decrease in cardiac mass was above the reproducibility limits (>50 g) of the method reported by us and others.[38–42] We noted similar diminutions of cardiac hypertrophy in the 3 treatment groups. Furthermore, the reduction in cardiac hypertrophy clearly paralleled the lowering of blood pressure evaluated in terms of either mean arterial or pulse pressure. These findings are in clear contrast to the changes in carotid wall thickness, which were significantly less pronounced than those of cardiac mass and did not parallel the blood pressure reduction. Moreover, when the IMT change was compared with the repeatability coefficient of the measurement, the change in carotid wall thickness could be considered clinically negligible. It is noteworthy that regression of carotid hypertrophy has been observed mainly in groups of hypercholesterolemic patients treated with statin or fibrate[43] compounds, which are known to be devoid of hemodynamic effects. In hypertensive subjects like those included in the MIDAS study,[44] little change in the degree of carotid hypertrophy has been reported after antihypertensive therapy with diuretics or calcium entry

blockers. Duration of treatment may be a major factor to consider in the interpretation of such trials.

In conclusion, we showed that administration of a combination of trandolapril and verapamil to hypertensive subjects decreased mean arterial and pulse pressures more than each compound alone. The blood pressure reduction was associated with significant increases in carotid, brachial, and abdominal aorta distensibility, the extent of which depended on the site of cardiovascular measurements. The changes in cardiovascular structure were dissociated under drug treatment, involving regression of cardiac hypertrophy but little change in carotid arterial structure.

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References

1. Darné B, Girerd X, Safar M, Cambien F, Guize L. Pulsatile versus steady component of blood pressure: a cross-sectional analysis and a prospective analysis on cardiovascular mortality. *Hypertension*. 1989;13:392–400.
2. Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension*. 1994;23:395–401.
3. Hoeks APG, Brands PJ, Smeets GAM, Reneman RS. Assessment of the distensibility of superficial arteries. *Ultrasound Med Biol*. 1990;16: 121–128.
4. Tardy YJ, Meister JJ, Perret F, Brunner HR, Arditi M. Noninvasive estimate of the mechanical properties of peripheral arteries from ultrasonic and photoplethysmographic measurements. *Clin Phys Physiol Meas*. 1991;3:360–367.
5. Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J*. 1993;14:160–167.
6. Nichols WW, O'Rourke MF, eds. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*. 4th ed. London, UK: Edward Arnold Publishers; 1998:54–113, 201–222, 284–292, 347–401.
7. Lafléche A, Gautier S, Topouchian J, Wilmet CS, Girerd X, Safar ME, Benetos A. Differential responses of the heart and vasculature to chronic blood pressure reduction in essential hypertension. *Clin Pharmacol Ther*. 1998;64:96–105.
8. Kirchengast M. Preclinical considerations and results with the combination of verapamil and trandolapril: blood pressure reduction and beyond. *J Hypertens*. 1997;15(suppl 2):S27–S33.
9. Messerli FH. Complementary actions and risk reduction: the rationale for combination of an angiotensin converting enzyme inhibitor with a non-dihydropyridine calcium antagonist. *J Hypertens*. 1997;15(suppl 2):S35–S38.
10. Pauly NC, Safar ME. Comparison of the efficacy and safety of trandolapril and captopril to 16 weeks on mild-to-moderate essential hypertension. *J Cardiovasc Pharmacol*. 1994;23(suppl 4):S73–S75.
11. Van Zwieten PA. Calcium entry blockers (calcium antagonists). In: *Handbook of Hypertension*. Amsterdam, Netherlands: Elsevier Science; 1984:331–342.
12. Epstein M. Calcium antagonists in the management of hypertension. In: *Calcium Antagonists in Clinical Medicine*. Philadelphia, Pa: Hanley & Belfus; 1998:155–176.
13. Asmar RG, Benetos A, Darné BM, Pauly NC, Safar ME. Converting enzyme inhibition: dissociation between antihypertensive and arterial effects. *J Hum Hypertens*. 1992;6:381–385.
14. Benetos A, Laurent S, Hoeks AP, Boutouyrie P, Safar ME. Arterial alterations with aging and high blood pressure: a noninvasive study of carotid and femoral artery. *Arterioscler Thromb*. 1993;13:90–97.
15. Girerd X, Giannattasio C, Moulin C, Safar M, Mancia G, Laurent S. Regression of radial artery wall hypertrophy and improvement of carotid artery compliance after long term antihypertensive treatment in elderly patients. *J Am Coll Cardiol*. 1998;31:1064–1073.
16. Benetos A, Asmar R, Gautier S, Salvi P, Safar ME. Heterogeneity of the arterial tree in essential hypertension: a noninvasive study of the terminal aorta and the common carotid artery. *J Hum Hypertens*. 1994;8:501–507.
17. Boutouyrie P, Lacolley P, Laurent S, London GM, Safar ME. Intrinsic modifications of the brachial and radial arteries in hypertensive humans. *J Clin Invest*. 1994;17:97–106.
18. Kool MJ, Lusterman FA, Breed JG, Struyker Boudier HA, Hoeks AP, Reneman RS, Van Bortel LM. The influence of perindopril and the diuretic combination amiloride+hydrochlorothiazide on the vessel wall properties of large arteries in hypertensive patients. *J Hypertens*. 1995; 13:839–848.
19. London GM, Guerin AP, Marchais SJ, Pannier B, Safar ME, Day M, Metivier F. Cardiac and arterial interactions in end-stage renal disease. *Kidney Int*. 1996;50:600–608.
20. Chen-Huan C, Nevo E, Fetics B, Pak PH, Yin FCP. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure: validation of generalized transfer function. *Circulation*. 1997;95:1827–1836.
21. Laurent S, Caviezel B, Beck L, Girerd X, Billaud E, Boutouyrie P, Hoeks A, Safar M. Carotid artery distensibility and distending pressure in hypertensive humans. *Hypertension*. 1994;23(pt II):878–883.
22. Imura T, Yamamoto K, Kanamori K, Mikami T, Yasuda H. Noninvasive ultrasonic measurement of the elastic properties of the human abdominal aorta. *Cardiovasc Res*. 1986;20:208–214.
23. Länne T, Stale H, Bengtsson H, Gustafsson D, Bergqvist D, Sonesson B, Lecerof H, Dahl P, Noninvasive measurement of diameter changes in the distal abdominal aorta in man. *Ultrasound Med Biol*. 1992;18:451–457.
24. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac A-M, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement: validation and clinical application studies. *Hypertension*. 1995;26:485–490.
25. Bonithon-Kopp C, Ducimetiere P, Touboul P-J, Feve J-M, Billaud E, Courbon D, Heraud V. Plasma angiotensin-converting enzyme activity and carotid wall thickening. *Circulation*. 1994;89:952–954.
26. Touboul PJ, Prati P, Scarabin PY, Adrai V, Thibout E, Ducimetiere P. Use of monitoring software to improve the measurements of carotid wall thickness by B-mode imaging. *J Hypertens*. 1992;10(suppl 5):S37–S41.
27. De Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, De Divitis O, Alderman MH, Left ventricular size and body size in normotensive children and adults: assessment of allometric relations and of the impact of overweight. *J Am Coll Cardiol*. 1992;20:1056–1062.
28. London GM, Pannier B, Guerin AP, Marchais SJ, Safar ME, Cuche JJ. Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease: comparative effects of ACE inhibition and calcium channel blockade. *Circulation*. 1994;90: 2786–2796.
29. London GM, Marchais SJ, Guerin AP, Metivier F, Safar ME, Fabiani F, Froment L, Salt and water retention and calcium blockade in uremia. *Circulation*. 1990;82:105–113.
30. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam study. *Circulation*. 1997;96:1432–1437.
31. Bond MG, Wilmoth SK, Enevold GL, Stricland HL. Detection and monitoring of asymptomatic atherosclerosis in clinical trials. *Am J Med*. 1989;86(suppl 4A):33–36.
32. Stensland-Bugge E, Bonaa KH, Joakimsen O. Reproducibility of ultrasonographically determined intima-media thickness is dependent on arterial wall thickness: the TROMSO study. *Stroke*. 1997;28:1972–1980.
33. Lücher TF, Wenzel RR, Moreau P, Takase H. Vascular protective effects of ACE inhibitors and calcium antagonists: theoretical basis for a combination therapy in hypertension and other cardiovascular diseases. *Cardiovasc Drugs Ther*. 1995;9:509–523.
34. Richer C, Thuilliez C, Giudicelli JP. Perindopril, converting enzyme blockade, and peripheral arterial hemodynamics in the healthy volunteer. *J Cardiovasc Pharmacol*. 1987;9:94–102.

35. Thuilliez C, Duhaze P, Fournier C, Lapierre V, Giudicelli JF. Arterial and venous effects of verapamil in normal volunteers. *Fundam Clin Pharmacol*, 1987;1:35–44.
36. Safar M, Van Bortel L, Struijker-Boudier H. Resistance and conduit arteries following converting enzyme inhibition in hypertension. *J Vasc Res*. 1997;81:34–67.
37. Asmar RG, Pannier B, Santoni JPH, Laurent S, London GM, Levy BI, Safar ME. Reversion of cardiac hypertrophy and reduced arterial compliance after converting enzyme inhibition in essential hypertension. *Circulation*. 1988:78:941–950.
38. Kaplan NM, Lieberman E. *Clinical Hypertension*. 4th ed. Baltimore, Md: Williams and Wilkins; 1986:180–272.
39. Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hypertrophy in essential hypertension: a meta-analysis of randomized double-blind studies. *JAMA*. 1996;275:1507–1513.
40. Devereux RB, De Simone G, Ganau A, Roman MJ. Left ventricular hypertrophy and geometric remodeling in hypertension: stimuli, functional consequences and prognostic implications. *J Hypertens*. 1994; 12(suppl 10):S117–S127.
41. Dahlof B, Pennert K, Hansson L. Regression of left ventricular hypertrophy: a meta-analysis. *Clin Exp Hypertens*. 1992;14:173–180.
42. Gottdiener JS, Reda DJ, Massie BM, Materson BJ, Williams DW, Anderson RJ, for the VA Cooperative Study Group on Antihypertensive Agents. Effect of single-drug therapy on reduction of left ventricular mass in mild to moderate hypertension: comparison of six antihypertensive agents. *Circulation*. 1997;95:2007–2014.
43. Byington RP, Furberg CD, Crouse JR III, Espeland MA, Bond AG. Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *Am J Cardiol*. 1995;76:54C–59C.
44. Borhani NO, Mercuri M, Borhani PA, Buckalew VM, Canossa-Terris M, Carr AA, Kappagoda T, Rocco MV, Schnaper HW, Sowers JR, Bond MG. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS): a randomized controlled trial. JAMA. 1996; 276:785–791.