Reversion of Cardiac Hypertrophy and Reduced Arterial Compliance After Converting Enzyme Inhibition in Essential Hypertension

R.G. Asmar, B. Pannier, J.Ph. Santoni, St. Laurent, G.M. London, B.I. Levy, and M.E. Safar

Blood pressure, forearm arterial hemodynamics (with a pulsed Doppler flowmeter), and echocardiographic parameters were studied in 16 patients with sustained essential hypertension before and 3 months after administration of the converting enzyme inhibitor perindopril. In a single-blind study versus placebo, it was shown that perindopril significantly reduced blood pressure ($p<0.01$), whereas there was an increase in brachial blood flow ($p<0.01$) because of a simultaneous increase in blood flow velocity ($p<0.01$) and arterial diameter ($p<0.01$). During a 5-minute period of wrist occlusion, blood flow velocity was reduced to a greater extent with perindopril than with placebo ($p<0.001$), whereas corresponding reductions in arterial diameter were equivalent, indicating that the increase in diameter after perindopril could not be explained simply on the basis of flow-dependent dilatation. During active treatment, brachial artery compliance increased ($p<0.01$) and pulse wave velocity decreased ($p<0.01$), whereas there was no change in the tangential tension of the arterial wall, defined as the product of mean arterial pressure and arterial diameter. Four weeks after treatment was stopped, blood pressure and forearm arterial hemodynamics returned toward baseline values. Cardiac mass was significantly decreased after perindopril ($p<0.01$) and remained decreased 4 weeks after cessation of treatment. The study showed that the arterial modifications caused by perindopril, (i.e., an increase in arterial diameter and compliance) were largely unrelated to blood pressure reduction and involved a drug-related relaxation of arterial smooth muscle and that a differential response in cardiac and arterial changes occurred after the treatment was stopped. (*Circulation* 1988;78:941–950)

Epidemiological studies have shown that damage of large arteries is a major contributory factor in the high cardiovascular morbidity and mortality observed in untreated hypertension.[1] Contrasting with this finding, therapeutic trials have indicated that antihypertensive drug treatment may reduce blood pressure without lowering the incidence of coronary ischemic accidents.[2] These results were the first to demonstrate a clear dissociation between the level of blood pressure and the status of the cardiovascular system in patients treated for hypertension. Subsequently, it was shown on the basis of animal experiments and clinical studies[3] that drug-induced reduction in blood pressure is not consistently associated with reversal of cardiac hypertrophy and that such reversal depends on the etiology of the hypertension and the type of antihypertensive compound. More recently, similar findings have been observed for peripheral large arteries.[4] Depending on the drug used, arterial compliance may be increased or remain low despite adequate blood pressure reduction. Because ischemic lesions continue to occur as a consequence of injury to large arteries in treated hypertensive patients, such observations are important for a better understanding of the effects of antihypertensive therapy.

Converting enzyme inhibitors are antihypertensive compounds that simultaneously cause a decrease in blood pressure through arterioladilatation,[5] a reversion of cardiac hypertrophy,[5] and an increase in

From the Diagnostic Center and the Hypertension Research Center, Broussais Hospital, Paris.

Supported by a grant from the Institut National de la Santé et de la Recherche Médicale (INSERM), the Association pour l'Utilisation du Rein Artificiel (AURA), the Association Claude Bernard, and the Ministère de la Recherche, Paris.

Address for correspondence: Professeur Michel Safar, Centre de Diagnostic, Hôpital Broussais, 96 rue Didot, 75614 Paris Cedex 14.

Received April 28, 1987; revision accepted May 5, 1988.

brachial artery diameter and compliance.[4,6] However, several questions remain to be answered concerning the role of large arteries. First, the increase in arterial diameter contrasts with the decrease in blood pressure and suggests a relaxation of arterial smooth muscle, the mechanism of which remains unexplained in hypertensive patients.[4] Second, the increase in arterial compliance has principally been described on the basis of a first-order Windkessel model of the circulation.[7] This assumes that pressure oscillations are simultaneous in all parts of the arterial tree and, hence, that pulse wave velocity is quasi-infinite.[8] Because the converting enzyme inhibitor captopril has been shown to decrease pulse wave velocity,[9] it is important that the increase in arterial compliance caused by converting enzyme inhibitors could be described on the basis of models derived from the Moens-Korteweg equation, which assumes a finite value of wave velocity. Finally, animal experiments[10] have shown that there may be complete dissociation between cardiac and arterial changes after antihypertensive drug therapy. Indeed, cardiac hypertrophy is easily reversed, whereas arterial changes remain unmodified, a finding that has been poorly investigated in humans.

In this trial, the converting enzyme inhibitor perindopril[11] was studied in patients with sustained essential hypertension to investigate the changes in forearm arterial hemodynamics and echocardiographic parameters produced by long-term treatment. Noninvasive methods were used, involving echocardiography and pulsed Doppler flowmetry.

Patients and Methods

Patients

Sixteen patients with sustained hypertension (12 men and four women) were included in the study. Age range was between 24 and 61 years (mean, 49 years). Mean body weight and body surface area were respectively 71 ± 2 kg and 1.83 ± 0.03 m^2 ($\pm$SEM). In all patients, previous treatments, including diuretics or β-blocking agents or both, were discontinued at least 4 weeks before the study. In all 16 subjects, diastolic pressure remained above 100 mm Hg throughout this ambulatory washout period. Patients had no signs, symptoms, or history of cardiac or renal failure, coronary insufficiency, or major diseases other than hypertension. The cardiothoracic ratio on chest x-ray was within the normal range. On the basis of previously described[7,9] thorough investigations, all patients were considered to have essential hypertension. Informed consent was obtained from each patient after a detailed description of the procedure. The protocol was approved by INSERM (Institut National de la Santé et de la Recherche Médicale).

Study Design

Of the 18 patients recruited during the washout period, two were found to be placebo-responders after 4 weeks of follow-up. The 16 remaining hypertensive patients had a diastolic blood pressure equal to or more than 100 mg Hg just before beginning (T0) the active treatment period. Perindopril was then given as an oral once-daily dosage of 2 mg, this dosage having been determined in previous pharmacodynamic studies.[12] After 4 weeks, the dosage was increased to 4 mg once a day if the diastolic pressure was equal to or more than 95 mm Hg. After another 4-week treatment, the dosage was increased to 8 mg/day in resistant patients. Active treatment was stopped after a total of 12 weeks. At this time (T1), the active dose was 4 mg in eight patients, 8 mg in seven patients, and 2 mg in one patient. Thereafter, a second placebo period was instituted (4 weeks), and the study was stopped at this time (T2). Hemodynamic investigations were performed at T0, T1, and T2; T0 and T2 correspond to the two placebo periods and T1 corresponds to the end of active treatment.

The hemodynamic study began at 9 AM during the day of hospitalization. It was carried out at a controlled room temperature of 20 ± 0.5° C, the patients having rested for 30 minutes in the recumbent position. Arterial blood pressure and heart rate were measured automatically every 2 minutes at the left arm with an oscillometric blood pressure recorder, the DINAMAP TYPE 845 apparatus.[13] The same values of blood pressure were recorded at the left and right arms. Mean arterial pressure (MAP) was calculated as the sum of the diastolic pressure and one third of the pulse pressure. Blood samples for plasma renin activity and converting enzyme activity were taken from an indwelling catheter and assessed with standard techniques.[14] In the 16 hypertensive patients, hemodyanmic measurements were carried out first on the right brachial artery, with determination of forearm arterial hemodynamics, pulse wave velocity, and brachial artery compliance. Thereafter, echocardiography was performed. Because two patients did not attend the scheduled clinic at T3, data were obtained from only 14 patients.

Forearm Arterial Hemodynamics

Forearm hemodynamic values were obtained with a bidimensional pulsed Doppler system, the probe being fixed with a stereotactic device over the course of the brachial artery, as previously described and validated.[15] This apparatus enabled the diameter and the blood velocity of the artery to be measured by two fundamental characteristics: a bidimensional recording of the Doppler signals and a range-gated time system of reception. The former involved the use of a probe containing two transducers, forming between them an angle of 120° so that when Doppler signals recorded by each transducer were equal in absolute value, the ultrasonic incidence with the vessel axis was 60°. With the latter, it was possible to select the delay from the emission and the duration of the reception and to convert this time echographically into the depth and width of the Doppler measurement volume. A pedal

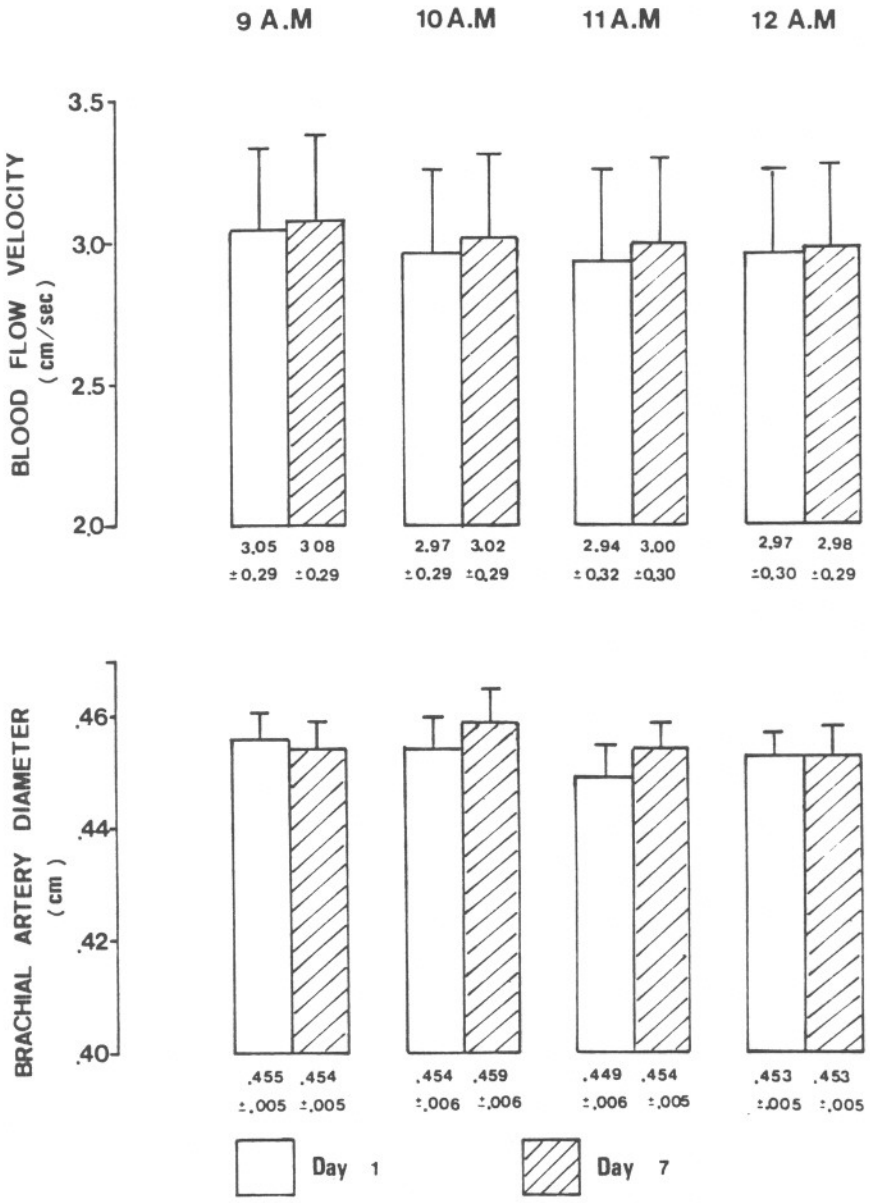

FIGURE 1. *Bar charts of short-term and long-term spontaneous variability of Doppler measurements.*

incorporated with the apparatus enabled the investigator to vary automatically the depth and width of the measurement volume by 0.4-mm increments. To determine the arterial diameter, the width of the measurement volume was reduced to the smallest convenient value with a sufficient reflected energy (about 0.4 mm), and its depth from the transducer was progressively increased. This was continued across the lumen of the artery, with a small measurement volume, and permitted the recording of velocities of the different stream lines involved in the arterial flow. Thus, the first and last Doppler signals recorded when crossing the vessel corresponded to the vessel walls, and the difference in depth between these two signals corresponded to the internal arterial diameter. To take into account the ultrasonic incidence angle, a correction was made by multiplying this difference by sine 60°, this being the angle used in the measurement. Once the arterial diameter was determined, the velocity of the whole arterial blood column was measured. For this, the width of the measurement volume was increased to the value of the arterial diameter. Its depth from the transducer was then adjusted so as to superimpose the measurement volume and the arterial lumen. The arterial blood velocity was expressed in centimeters per second, and mean arterial blood velocity was electronically integrated. Brachial artery blood flow was calculated as the product of blood velocity and cross-sectional area, the latter deduced from the arterial diameter (D) by a cylindrical representation of the artery ($S = 3.14\ D^2/4$). Arterial blood flow was expressed in milliliters per minute. Local vascular resistance (mm Hg/ml · sec) was calculated as the ratio between simultaneous MAP and mean blood flow. The tangential tension (T) of the

brachial artery was defined, according to LaPlace's law, as $T = MAP \times D/2$ and was expressed in millimeters of mercury per centimeter. Immediately after the baseline determinations, the wrist was occluded for 5 minutes with a pneumatic cuff inflated to a suprasystolic pressure (250 mm Hg). Arterial diameter and blood flow velocity were rapidly measured again up to 5 minutes. No significant change in systemic blood pressure or heart rate was observed during the period of occlusion.

The variability of the Doppler measurements was studied in six subjects (independently of the 16 patients in the present study). After 30 minutes of rest, repeat measurements of brachial artery diameter and blood flow velocity were performed throughout at 9, 10, 11, and 12 AM (two or three determinations at each hour) to evaluate short-term variability. The measurements were repeated 7 days later, under the same conditions and in the same patients, to evaluate long-term variability. All measurements were made by the same researcher. The results are summarized in Figure 1. Three-way analysis of variance[16] did not demonstrate any interaction between day and hour nor were there any hour or day effects. Short-term and long-term variability was approximately 2.2% for the arterial diameter and 18.7% for blood flow velocity.

Determination of Brachio-Radial Pulse Wave Velocity and Brachial Artery Compliance

For the determination of brachio-radial pulse wave velocity (PWV), two pulse transducer heads (Electronics for Medicine) were fixed to the skin over the most prominent parts of the right brachial and radial arteries. The time delay was measured between the feet of simultaneously recorded pulse waves, with a paper speed of 150 mm/sec. The foot, which contains the high-frequency information,[8] was defined as the point obtained by extrapolating the wave front downward and measured from the intersection of this line with a straight line extrapolation of the last part of the diastolic curve.[17] Measurement of the distance between the two transducers was then used to calculate pulse wave velocity. This was averaged over at least one respiration cycle of about 10 beats.

In primates, changes in pulse wave velocity have been shown to be very good indicators of arterial stiffness both under baseline conditions and after administration of vasoactive substances.[8,17–24] In the present study, the variability of the method was studied by measuring pulse wave velocity before and after placebo in both short-term and long-term situations. In the former, measurements were performed at 9 and 12 AM, the placebo being administered at 9:15 AM in 11 healthy volunteers.[25] MAP and pulse wave velocity did not change significantly, their respective preplacebo and postplacebo values being 83 ± 2 and 85 ± 2 mm Hg and 9.7 ± 0.5 and 9.1 ± 0.5 m/sec, respectively. A similar study was performed in seven hypertensive patients before and after 4 weeks of administration of placebo (personal data). MAP before and after placebo was 123 ± 4 and 121 ± 4 mm Hg (NS), and pulse wave velocity was 12.6 ± 1.2 and 12.2 ± 1.4 m/sec (NS).

For the determination of brachial artery compliance, the equation of Bramwell and Hill[18] was used according to the following formula:

$$PWV = \sqrt{VdP/\rho dV}$$

where V is arterial volume, dV is the change in volume, dP is the change in pressure, and ρ is the blood density. From this equation, it is easy to calculate brachial arterial compliance (BAC) as

$$BAC = dV/dP = V/\rho PWV^2$$

because V can be expressed in terms of radius per unit length:

$$dV/dP = 3.14R^2/\rho PWV^2$$

where R is the inner radius of the artery (D/2). In this equation, dV/dP is expressed in centimeters to the fourth power per dyne times 10^{-7}, D in centimeters, PWV in meters per second, and ρ equals 1.06.[5]

Echocardiography

M-mode echocardiography was performed with an echocardiograph V3280 (Electronics for Medicine) with a 2.25-mHz transducer and a recorder at a paper speed of 50 mm/sec. Each patient was studied in the left lateral position (30° rotation approximately) to obtain a good visualization of the left ventricular internal diameter, the left interventricular septal thickness, and the left ventricular posterior wall thickness. The transducer was placed in the third or fourth intercostal space near the left sternal edge. Care was taken to record distinct echoes from both the anterior and posterior walls of the aortic root and the aortic leaflets to obtain accurate measurement of the aortic diameter.[26] Left ventricular systolic (LVSD) and diastolic (LVDD) diameter, interventricular septal thickness (IVST), and left ventricular posterior wall thickness (PWT) at both end diastole and end systole were measured at the level of the chordae tendinae, just below the mitral valve. These measurements were made in each trace with the leading-edge technique and according to the usual recommendations of the American Society of Echocardiography,[26] except for the measurement of the interventricular septal thickness where we did not include the endocardium of the right ventricle. Up to five beats were measured routinely and averaged. Left ventricular ejection time (LVET) was measured from a simultaneously recorded carotid pulse tracing. An electrocardiogram was also recorded simultaneously. Echocardiograhic left ventricular mass (LVM) was estimated according to the formula[26,27] of $LVM = 1.04[(IVST + LVDD + PWT)^3 - (LVDD)^3] - 13.6$ g. The value was converted into the LVM index (LVMi) by dividing by the body surface area and was expressed in grams per meter squared. Mass:volume ratio was

TABLE 1. **Changes in Blood Pressure, Heart Rate, and Brachial Artery Hemodynamics**

	T0 (placebo)	T1 (active treatment)	T2 (placebo)
Systolic blood pressure (mm Hg)	173.4 ± 4.6	149.1 ± 4.1*	168.2 ± 3.3
Diastolic blood pressure (mm Hg)	106.9 ± 1.7	94.1 ± 3.5*	107.4 ± 2.4
Mean blood pressure (mm Hg)	128.9 ± 2.5	112.4 ± 3.6*	127.6 ± 2.4
Heart rate (beats/min)	71.0 ± 1.8	70.5 ± 2.4	70.3 ± 2.7
Brachial artery diameter (cm)	0.448 ± 0.015	0.489 ± 0.011*	0.463 ± 0.013
Blood flow velocity (cm/sec)	6.58 ± 0.89	8.91 ± 1.59*	6.26 ± 0.77
Blood flow (ml/min)	63.7 ± 9.2	104.1 ± 19.8*	66.6 ± 10.2
Pulse wave velocity (m/sec)	10.09 ± 0.53	8.75 ± 0.24*	9.99 ± 0.43
Arterial compliance (dynes/cm^4/10^{-7})	1.29 ± 0.21	1.84 ± 0.15†	1.37 ± 0.18
Vascular resistance (mm Hg · sec/ml)	165.07 ± 30.46	97.64 ± 17.63*	153.79 ± 26.45
Tangential tension (mm Hg · cm)	27.1 ± 1.3	27.2 ± 1.0	27.3 ± 1.0

Values are mean ± SEM.
*$p<0.01$ in comparison with T0 and T2; †$p<0.05$.

also evaluated. The mean velocity of circumferential fiber shortening (VCF) was calculated as the percent change in left ventricular diameter divided by the left ventricular ejection time and expressed as circumferences per second. The ejection fraction was calculated with standard methods.[26,27]

Echocardiographic dimensions (diameter and thickness) were measured by two observers in a double-blind fashion. Agreement between the two, and reproducibility of readings by the same observer, were within 1 mm.[28] A second echocardiographic study was done on a separate group of eight normotensive and 12 hypertensive patients after 3 months, as previously described.[29] End-diastolic volume (ml) was 121 ± 6 and 126 ± 4 in normotensive (NS) and 132 ± 8 and 141 ± 10 in hypertensive patients (NS). Cardiac mass (g) was 160 ± 5 and 167 ± 6 in normotensive (NS) and 262 ± 8 and 251 ± 8 in hypertensive patients (NS), respectively. No treatment was given, and no significant change in blood pressure occurred. For the evaluation of cardiac mass, it should be noted that the calculation was based on the assumption that the longitudinal axis of the left ventricle is always twice the anteroposterior diameter, a valid assumption in relatively young hypertensive patients who have no history, symptoms, or signs of myocardial damage and who, therefore, can be assumed to have symmetrically contracting ventricles.[30]

Statistical Analysis[16]

Data are expressed as mean ± SEM. Two-way analysis of variance was used for statistical evaluation, followed by Newman-Keuls tests. $p<0.05$ was considered as significant.

Results

Perindopril significantly reduced blood pressure ($p<0.01$) but had no significant effect on heart rate (Table 1). Plasma converting enzyme activity after active treatment (T1) was significantly inhibited (51.4 ± 19.7%) compared with T0 (100%) and T2 (158.2 ± 21.1%) ($p<0.01$). Plasma renin activity (ng/ml/hr) was significantly higher at T1 (5.34 ± 2.14) than at T0 (2.66 ± 1.02) and T2 (2.01 ± 1.06) ($p<0.05$).

Table 1 and Figure 2 indicate that with active treatment, there was a significant increase in arterial diameter ($p<0.01$), blood flow velocity ($p<0.01$), blood flow ($p<0.01$), and arterial compliance ($p<0.05$) and a significant decrease in pulse wave velocity ($p<0.01$) and vascular resistance ($p<0.01$). No significant change in tangential tension occurred (Table 1). During wrist occlusion, arterial diameter and blood flow velocity were significantly reduced ($p<0.001$) at T0, T1, and T2 as well. Mean arterial diameter during wrist occlusion was 0.414 ± 0.02 cm at T0, 0.446 ± 0.01 cm at T1, and 0.434 ± 0.02 cm at T2 (NS). Mean arterial velocity at T0, T1, and T2 was 3.02 ± 0.28, 3.37 ± 0.33, and 2.78 ± 0.27 cm/sec, respectively. Figure 3 summarizes the changes in arterial diameter and blood flow velocity produced by wrist occlusion. Although the decrease in blood flow velocity was significantly higher at T1 than at T0 or T2 ($p<0.001$), the reduction in arterial diameter was similar for all three periods.

Table 2 and Figure 4 show that active treatment caused a significant decrease in cardiac mass at T1 ($p<0.01$), secondary to a significant reduction in

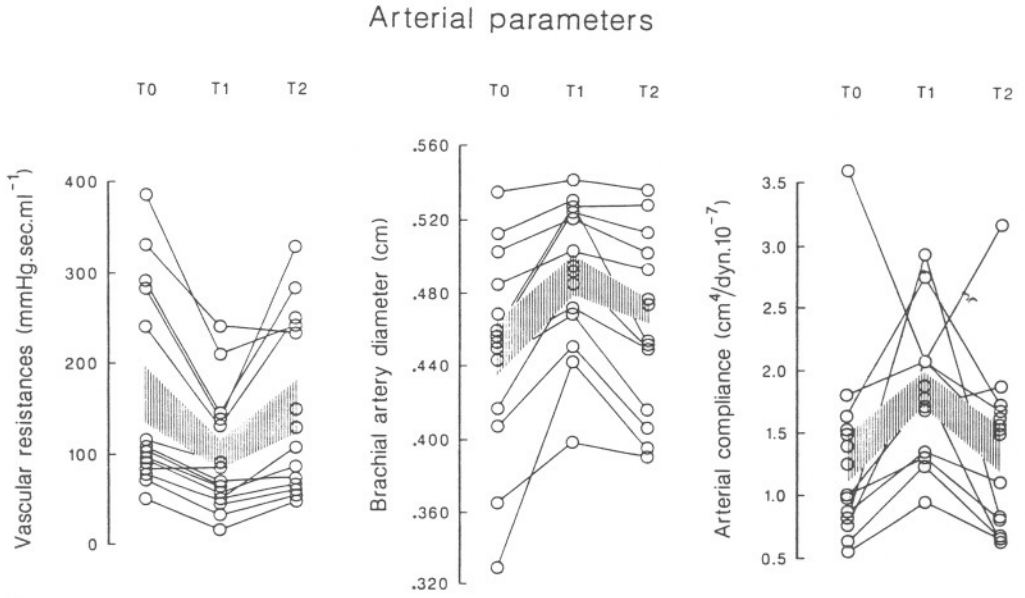

FIGURE 2. *Plots of individual values of brachial vascular resistance, arterial diameter, and compliance during follow-up. Hatched lines represent mean value±SEM. Significance of variations are indicated in Table 1.*

septal thickness ($p<0.01$), posterior wall thickness ($p<0.01$), and end-diastolic volume ($p<0.05$). After treatment was stopped (T2), septal thickness, posterior wall thickness, and cardiac mass (Figure 4) remained significantly reduced ($p<0.05$; $p<0.01$), whereas end-diastolic volume returned toward basal values. Ejection fraction, VCF, and left ventricular fractional shortening did not change during the study.

Discussion

The most important findings of the present study were the increase in brachial artery diameter and compliance produced by perindopril and the differential responses in cardiac and arterial changes observed after the cessation of active treatment. It is clear that the validity of such results are dependent on the relative sensitivity and reliability of the techniques used for the long-term study of arterial hemodynamics and cardiac mass. An ideal approach would be to have a placebo-time control group at T0, T1, and T2, enabling the reliability of the techniques used and the influence of time to be assessed. However, because of the ethical difficulties in maintaining a placebo group of sustained hypertensive patients over 16 weeks, a single-blind design versus placebo was used to evaluate the changes in arterial and cardiac parameters. For this reason, the limitations of the noninvasive techniques used in the study will be discussed before attempting to interpret the principal results.

Limitations of Noninvasive Cardiac and Arterial Techniques

As far as arterial hemodynamics are concerned, the discussion will be limited to the Doppler flowmetry, as the validity of pulse wave velocity as an index of arterial stiffness has been widely accepted for many years.[8,17,24] As shown elsewhere,[15-31] the measurement of arterial diameter by Doppler ultrasound involves a certain degree of error. For the echo received from the arterial (particularly distal) wall to be interpretable, the gate width must be small enough to avoid dispersion and the power large enough to get an interpretable echo. The maximal error for brachial artery diameter determinations has been shown to be 0.035 ± 0.015 cm.[15] On the other hand, our study of short-term and long-term variability has shown a 2.2% approximation of measurements, a finding that agrees with the significant changes in arterial diameter produced by antihypertensive agents in long-term double-blind studies.[6,7,32] In contrast with arterial diameter, the variability of blood flow velocity was greater, although its measurement is easier and more accurate. This peculiarity is attributable to the well-known rapidity of changes in cutaneous blood flow and to the rich innervation of the hand,[31] favoring instantaneous modifications in blood flow velocity. Finally, comparisons of the variability of arterial diameter and flow velocity strongly suggest that compliance determinations are even more reproducible than blood flow determinations in the forearm.[6,7,32]

As far as echocardiographic parameters are concerned, numerous studies have documented sources of error derived from intraobserver and interobserver variability and interstudy reproducibility.[30] The absolute reductions in left ventricular wall thickness from which calculated cardiac mass changes are derived are usually 1–2 mm. This is close to the limit of variability attributable to measurement errors.[30,33] These considerations are of obvious importance in serial studies involving long-term changes. However, Devereux et al[27] have demonstrated close correlations between cardiac mass in paired echocar-

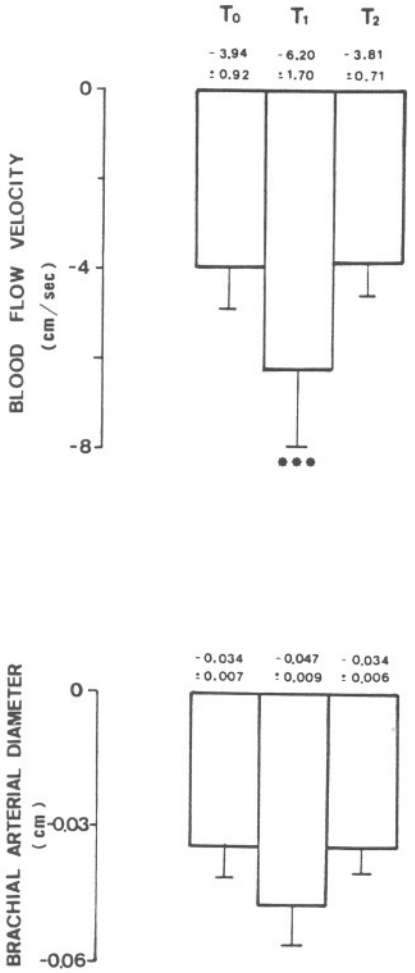

FIGURE 3. *Bar charts of brachial artery hemodynamics: changes observed after rapid wrist occlusion. At each period, the decrease in blood flow velocity and arterial diameter was highly significant* ($p<0.001$). *Statistical comparison for differences between periods showed that the decrease in blood flow velocity was significantly greater at T1 only* (***$p<0.001$) *in comparison with T0 and T2.*

diograms in eight subjects ($r=0.98$; SD = 28 g) and readings of 24 echocardiograms by two experienced investigators ($r=0.94$; SD = 41 g). These results were found to be strikingly similar to the mean difference of 26 g observed between measurements on echocardiograms performed more than a year apart in 53 normal subjects.[34] They are also smaller than the standard deviation of 43 g obtained in a comparison of echocardiographic and necropsy measurements.[27] In the present study, the long-term follow-up that we have performed without any treatment (see "Patients and Methods") agrees with these findings. On the other hand, the changes observed with perindopril (T0) and after the treatment was stopped (T2) accord with the results of studies in which serial changes in a control group receiving a placebo were compared with changes in the treatment group.[35]

Finally, the differential responses in cardiac and arterial parameters are influenced not only by the sensitivity and reliability of each technique but also by the relative sensitivity of the two techniques when used together in long-term follow-up. The main problem with both techniques is the positioning of the transducer. For echocardiographic measurements, the wall thicknesses and chamber dimensions used should reflect the true minor axis as closely as possible to prevent tangential displays of the wall and the left ventricular chamber.[30] For Doppler measurements, the problem is to determine exactly the angle between the ultrasound beam and the vessel axis. In this regard, it is clear that the Doppler technique enables a very precise mathematical evaluation of the angle, as previously reported.[15] Indeed, with the double transducer probe used in this study, the reproducibility of the measurement angle is less than 2%.[15]

Increase in Brachial Artery Diameter

With single-blind design versus placebo, the study clearly showed that the converting enzyme inhibitor perindopril causes an increase in brachial artery diam-

TABLE 2. Changes in Echocardiographic Parameters

	T0 (placebo)	T1 (active treatment)	T2 (placebo)
End-diastolic diameter (cm)	5.27 ± 0.12	5.15 ± 0.14	5.17 ± 0.14
End-systolic diameter (cm)	3.30 ± 0.15	3.13 ± 0.16	3.14 ± 0.15
End-diastolic volume (ml)	135.0 ± 6.9	128.0 ± 8.1*	129.6 ± 8.1
End-systolic volume (ml)	39.0 ± 5.1	33.8 ± 5.2	34.0 ± 4.8
Ejection fraction (%)	0.72 ± 0.03	0.75 ± 0.02	0.75 ± 0.02
Velocity of circumferential fiber shortening (circ/sec)	1.32 ± 0.07	1.39 ± 0.07	1.40 ± 0.06
Left ventricular fractional shortening (%)	0.37 ± 0.02	0.39 ± 0.02	0.39 ± 0.02
Septal thickness (cm)	1.13 ± 0.02	1.03 ± 0.02†	1.07 ± 0.02‡
Posterior wall thickness (cm)	1.08 ± 0.03	0.99 ± 0.02†	1.04 ± 0.02§
Mass index (g/m^2)	147.2 ± 6.4	124.5 ± 7.2†	134.3 ± 6.4†
Mass/volume (g/ml)	2.04 ± 0.08	1.81 ± 0.07†	1.95 ± 0.05§

Values are mean ± SEM.
*$p<0.05$ and †$p<0.01$, T1 versus T0 and T2.
‡$p<0.01$ and §$p<0.05$, T1 versus T0.

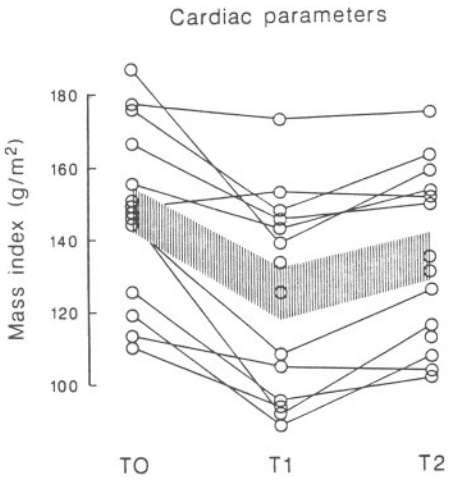

FIGURE 4. *Individual values of cardiac mass during follow-up. Hatched lines represent mean value±SEM. Significance of variations are indicated in Table 2.*

eter. Because there was also a simultaneous reduction in blood pressure, the findings indicate that active changes of the arterial wall are involved.[4,8] Theoretically, vasodilator drugs may increase arterial diameter through two possible mechanisms[36,37]: indirect flow-dependent dilatation and direct smooth muscle relaxation. Because brachial blood flow increased significantly with perindopril, the former mechanism will be considered first.

Studies in dogs have shown that epicardial coronary and femoral arteries dilate in response to increases in blood flow.[38,39] Any maneuver that increases flow, such as release of a transient arterial occlusion, causes dilatation of large arteries.[38] If the same stimulus is used, but flow is prevented from increasing by a flow-limiting stenosis, no dilatation of the large vessels occurs.[38] Evidence is accumulating that this dilatation is dependent on the endothelium.[39] Removal of the endothelium in isolated perfused canine coronary or femoral arteries in situ is able to abolish the flow-dependent dilatation.[36,39] In the case of the converting enzyme inhibitor perindopril, the possible role of the endothelium must be carefully considered because endothelial cells contain large amounts of converting enzyme and may be a privileged site of action of converting enzyme inhibitors.[40] On the other hand, the brachial artery dilatation attributable to converting enyzme inhibition may be influenced by bradykinin release, the mechanism of which is endothelium dependent.[41,42]

In the present study, the role of flow-dependent dilatation was evaluated from the hemodynamic effects of wrist occlusion at suprasystolic blood pressure level. The manoeuver consistently resulted in significant reduction in diameter, blood flow velocity, and volumic blood flow at each period of the study (T0, T1, and T2). These changes may have been attributed to a direct or reflexly mediated rise in local vascular resistance. After perindopril (T1), the significant increase in blood flow velocity, observed under basal conditions, was no longer observed during wrist occlusion. This finding suggests either that the vasodilator effect of perindopril was predominantly attributable to relaxation of hand arteries or that a reflex vasoconstriction of small forearm arteries in response to wrist occlusion might have compensated for the vasodilator effect of perindopril. The increase in brachial artery diameter in response to perindopril was significant at T1. However, the increase did not occur during wrist occlusion (Figure 3). Several explanations may be suggested. First, the mechanism of the relaxation of large arteries after perindopril may have been flow-dependent because it no longer occurred when the increase in blood flow velocity was suppressed.[43] However, this is probably not the only mechanism, as the converting enzyme inhibitor captopril has been shown to increase the caliber of the common carotid artery without any significant increase in blood flow velocity in hypertensive subjects.[44] Second, the lack of any significant increase in brachial artery diameter during wrist occlusion could have been attributable to the small number of patients or, third, to the counteracting effect of a reflexly mediated vasoconstriction in response to venous dilatation[45] or an arousal stimulus[46] on inflation of the wrist cuff.

An alternative explanation to flow-dependent dilatation for the increased brachial artery diameter is smooth muscle relaxation.[9] Studies in healthy volunteers have shown that increasing doses of perindopril (causing a 90% decrease in plasma converting enzyme) produced changes in brachial and carotid arterial diameters only at the highest doses.[47] This suggests that the drug affects large arteries by mechanisms other than the simple inhibition of circulating converting enzyme. Local modifications of the vascular tissue may be related not only to converting enzyme inhibition but also to the role of prostaglandin release and/or kinin accumulation and, finally, inhibition of the sympathetic nervous system.[48]

Increase in Brachial Artery Compliance

After perindopril administration, not only the caliber of the brachial artery was expected to be modified but also the viscoelastic properties of its wall and, hence, its distensibility. According to the Moens-Korteweg and Bramwell and Hill equations,[8,18] pulse wave velocity reflects the distensibility characteristics of large arteries, which, in turn, determine vascular impedance (or total opposition to pulsatile flow). The distensibility of arteries depends on several factors, such as the elastic modulus of the arterial wall, the geometry of the vessel (i.e., its diameter and thickness), and the extent to which the arterial wall is stretched (i.e., transmural pressure).[49] All of these factors should be evaluated when the distensibility changes of arteries are being investigated. The brachioradial pulse wave velocity decreased significantly after perindopril, whereas brachial artery diameter

increased and the distending pressure decreased. As the arterial wall thickness (assumed to be relatively thin) is supposed to vary inversely with radius (i.e., to become thinner when arterial diameter increases[8,49]), the geometric and mechanical modifications of the brachial artery need to be taken into account in explaining the compliance enhancement after perindopril. Table 1 shows that whereas blood pressure and arterial diameter were significantly modified, tangential tension did not change at the different periods of the study. This finding does not support the hypothesis that geometrical (arterial diameter) and mechanical (transmural pressure) modifications underlie the increase in compliance but strongly suggests that drug-related intrinsic modifications of the arterial wall are involved in the changes in compliance and distensibility.

It is well accepted[8,49] that the compliance of the brachial artery wall is a function of two viscoelastic elements: one is passive and related to the fibrous connective tissue of the wall (elastin and collagen), and the second is active and related to the activity of smooth muscle. In essential hypertension, thickening of the arterial wall results from smooth muscle hyperplasia, hypertrophy, and hyperreactivity, together with an increased synthesis of collagen and acid mucopolysaccharides.[49,50] These changes are responsible for an increase in the stiffness of both the passive and active viscoelastic elements.[49,50] In the present study, the role of the passive element after perindopril did not seem to be of major importance in determining the changes in the viscoelastic properties of the arterial wall because tangential tension did not vary significantly. Concerning the effect of vascular smooth muscle activity on vessel distensibility, experimental studies reported in the literature present conflicting results.[5,49] Whereas some investigators have reported that activation of vascular muscle increases vessel stiffness, others believe the opposite, that is, that activation of vascular muscle reduces vessel stiffness.[49] These differences are probably related to the method of evaluation used (i.e., plotting the stiffness indexes as a function of different factors such as radius, strain, pressure, or stress).[49] Most investigators who have studied the distensibility changes as a function of diameter or volume changes in the arteries have reported that activation of vascular muscle reduces vessel distensibility, whereas a decrease in muscle activity increases distensibility.[8,49] Our results are in general agreement with the latter interpretation.

Differential Responses in Cardiac and Arterial Changes After Cessation of Active Treatment

As previously reported with other converting enzyme inhibitors,[3,5,33] perindopril caused a significant decrease in left ventricular mass, principally because of a decrease in septal thickness and posterior wall thickness. However, 4 weeks after the treatment was stopped, cardiac mass remained low, whereas blood pressure and arterial compliance had returned toward baseline values.

As mentioned above, the present findings may be influenced by the relative sensitivity of the two techniques used to study the cardiac and arterial changes. Because the accuracy of our noninvasive hemodynamic measurements largely agrees with well-established long-term studies, hypotheses other than technical problems may be advanced. The finding that cardiac mass remained low 4 weeks after cessation of active treatment does not mean that it will not return toward baseline values later. In this regard, our findings suggest only that the time constant for reversal of cardiac and arterial changes may be different in hypertensive patients after cessation of active treatment. Because reversal of structural changes was indeed observed in the heart after perindopril, one possibility is that structural changes may be different in the heart and vessels. Studies in hypertensive animals have shown that captopril causes minimal changes in aortic structure, whereas cardiac hypertrophy is reduced.[10] The finding is consistent with the observation that in several animal models of hypertension, significant increases in collagen biosynthesis and total collagen content are observed in the larger arteries.[50,51] In contrast, the collagen concentration often remains essentially unchanged, especially in treated animals.[50,51]

In conclusion, the present study has shown that in patients with sustained essential hypertension, the converting enzyme inhibitor perindopril increases brachial artery diameter and compliance through drug-mediated modifications of the arterial wall, these being largely unrelated to the blood pressure modifications. The arterial changes seemed mainly to affect smooth muscle activity and were dissociated from cardiac effects after the treatment was stopped.

Acknowledgment

We thank Mrs. Daniéle Hobart for her excellent assistance.

References

1. Kannel WB, Stokes J: Hypertension as a cardiovascular risk factor, in Bulpitt CJ (ed): *Handbook of Hypertension, vol 6*. Elsevier Science Publishers BV, 1985, pp 14–34
2. Thompson SG: An appraisal of the large scale trials of antihypertensive treatment, in Bulpitt CJ (ed): *Handbook of Hypertension, vol 6*. Elsevier Science Publishers BV, 1985, pp 331–343
3. Tarazi RC: The role of the heart of hypertension. *Clin Sci* 1982;63:347s–358s
4. Safar ME, Bouthier JA, Levenson JA, Simon ACh: Peripheral large arteries and the response to antihypertensive treatment. *Hypertension* 1983;5(suppl III):III-63–III-68
5. Fouad FM, Tarazi RC: Restoration of cardiac function and structure by converting enzyme inhibition: Possibilities and limitations of long-term treatment in hypertension and heart failure. *J Cardiovasc Pharmacol* 1986;8(suppl 1):S53–S57
6. Simon AC, Levenson JA, Bouthier JD, Benetos A, Achimastos A, Fouchard M, Maarek B, Safar ME: Comparison of oral MK-421 and propranolol in mild to moderate essential hypertension and their effects on arterial and venous vessels of the forearm. *Am J Cardiol* 1984;53:781–785

7. Simon ACh, Levenson J, Bouthier JD, Safar ME: Effects on chronic administration of Enalapril and Propranolol on the large arteries in essential hypertension. *J Cardiovasc Pharmacol* 1985;7:856–861
8. O'Rourke MF: *Arterial Function in Health and Disease*. Edinburgh/London/New York, Churchill Livingstone, 1982, pp 312–386
9. Safar ME, Laurent S, Bouthier JA, London GM: Comparative effects of captopril and isosorbide dinitrate on the arterial wall of hypertensive human brachial arteries. *J Cardiovasc Pharmacol* 1986;8:1257–1261
10. Rorive GL, Carlier PG, Foidart JM: The structural responses of the vascular wall in experimental hypertension, in Zanchetti A, Tarazi RC: *Handbook of Hypertension, vol 7: Pathophysiology of Hypertension—Cardiovascular Aspects*. Elsevier Science Publishers, BV, 1986, pp 427–453
11. Vincent M, Remond G, Portevin B, Serkiz B, Laubie M: Stereo selective synthesis of a new perhydroindole derivative of chiral iminodiacid, a potent inhibitor of angiotensin converting enzyme. *Tetrahedron Lett* 1982;23:1677–1680
12. Laubie M, Schiavi P, Vincent M, Schmitt H: Inhibition of angiotensin I converting enzyme with S 9490: Biochemical effects, interspecies differences, and role of sodium diet in hemodynamic effects. *J Cardiovasc Pharmacol* 1984; 6:1076–1082
13. Silas JH, Barker AT, Ramsay LE: Clinical evaluation of Dinamap 845 automated blood pressure recorder. *Br Heart J* 1980;42:202–207
14. Ryan JW, Chung A, Ammons C, Carlton ML: A simple radio essay for angiotensin converting enzyme. *Biochemistry* 1977; 167:501–504
15. Safar ME, Peronneau PA, Levenson JA, Totomoukouo JA, Simon AC: Pulsed Doppler: Diameter, blood flow velocity and volumic flow of the brachial artery in sustained essential hypertension. *Circulation* 1981;63:393–400
16. Sokal RR, Rohlf FJ: *Biometry, the Principles of Statistics in Biological Research*. New York, Freeman and Co, 1981, pp 321–400
17. Gribbin B, Pickering TG, Sleight P: Arterial distensibility in normal and hypertensive man. *Clin Sci* 1979;56:413–417
18. Bramwell JC, Hill AV: The velocity of the pulse wave in man. *Proc Soc Lond (Biol)* 1922;93:298–306
19. McDonald DA: *Blood Flow in Arteries*. Baltimore, Williams and Wilkins, 1974, pp 238–282
20. Smulyan H, Csermely TJ, Mookherjee S, Warner RA: Effect of age on arterial distensibility in asymptomatic humans. *Arteriosclerosis* 1983;3:199–205
21. Smulyan H, Vardan S, Griffiths A, Gribbin B: Forearm arterial distensibility in systolic hypertension. *J Am Coll Cardiol* 1982;3:387–393
22. Farrar DJ, Bond MG, Sawyer JK, Green HD: Pulse wave velocity and morphological changes associated with early atherosclerosis progression in the aortas of cynomolgus monkeys. *Cardiovasc Res* 1984;18:107–118
23. Farrar DJ, Green HD, Bond MG, Wagner WD, Gobbee RA: Aortic pulse wave velocity, elasticity, and composition in a nonhuman primate model of atherosclerosis. *Circ Res* 1978; 43:52–62
24. Farrar DJ, Green HD, Wagner WD, Bond MG: Reduction in pulse wave velocity and improvement of aortic distensibility accompanying regression of atherosclerosis in the rhesus monkey. *Circ Res* 1980;47:425–432
25. Safar ME, Laurent SL, Bouthier JD, London GM, Mimran AR: Effect of converting inhibitors on hypertensive large arteries in humans. *J Hypertens* 1986;4(suppl 5):S285–S289
26. Sahn DJ, Demaria A, Kisslo J, Weyman A: The Committee on M-mode Standardization of the American Society of Echocardiography. Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072–1083
27. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N: Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J Cardiol* 1986;57:450–458
28. Bouthier JD, De Luca N, Safar ME, Simon ACh: Cardiac hypertrophy and arterial distensibility in essential hypertension. *Am Heart J* 1985;109:1345–1352
29. London GM, Fabiani F, Marchais SJ, De Vernejoul MC, Guerin AP, Safar ME, Metivier Llach F: Uremic cardiomyopathy: An inadequate left ventricular hypertrophy. *Kidney Int* 1987;31:973–980
30. Liebson PHR, Savage DD: Echocardiography in hypertension: A review. *Echocardiography* 1986;3:181–218
31. Levy BI, Oliva Y, Martineaud JP: Hand arterial blood flow responses to local venous congestion. *Am J Physiol* 1981; 240(*Heart Circ Physiol* 9):H980–H983
32. Levenson J, Simon AC, Benetos A, Achimastos A, Iannascoli F, Safar ME: Vasodilator effect of a new adrenergic receptor drug, medroxalol, on hypertensive forearm vessels. *Hypertension* 1986;8(suppl I):I-174–I-179
33. Fouad-Tarazi FM, Liebson PR: Echocardiographic studies of regression of left ventricular hypertrophy in hypertension. *Hypertension* 1987;9(suppl II):II-65–II-68
34. Devereux RB, Hammond IW, Lutas EM, Spitzer MC, Alderman MH, Laragh JH: Year-to-year variability of echocardiographic measurements in normal subjects (abstract). *J Am Coll Cardiol* 1984;3:516
35. Rowlands DB, Glover DR, Ireland MA, McLeay AB, Stallard TJ, Littler WA: Assessment of left ventricular mass and its response to hypertensive treatment. *Lancet* 1982;1:467–470
36. Jaffe MD: High flow dilatation. *Lancet* 1981;1:1237–1238
37. Dobrin PB, Rovick AA: Influence of vascular smooth muscle on contractile mechanics and elasticity of arteries. *Am J Physiol* 1969;217:1644–1652
38. Hantze TH, Vatner SF: Reactive dilation of large coronary arteries in conscious dogs. *Circ Res* 1984;54:50–57
39. Pohl U, Holtz J, Busse R, Bassenge E: Crucial role of endothelium in the vasodilator response to increased flow in vivo. *Hypertension* 1986;8:37–44
40. Dzau VJ: Vascular wall renin-angiotensin pathway in control of the circulation: A hypothesis. *Am J Med* 1984;77:31–36
41. Mimran A, Targhetta R, Laroche B: The antihypertensive effect of Captopril. Evidence for an influence of Kinins. *Hypertension* 1980;2:732–737
42. Vanhoutte PM, Houston DS: Platelets, endothelium and vasospasm. *Circulation* 1985;27:728–734
43. Jaffe MD, Rowe PW: Mechanism of arterial dilatation following occlusion of femoral artery in dogs. *Am J Physiol* 1970;218:1156–1160
44. Bouthier JD, Safar ME, Benetos A, Simon ACh, Levenson JA, Hugue ChM: Haemodynamic effects of vasodilating drugs on the common carotid and brachial circulations of patients with essential hypertension. *Br J Clin Pharmacol* 1986;21:137–142
45. Gaskell P, Burton AC: Local postural vasomotor reflexes arising from the limb veins. *Circ Res* 1953;1:27–39
46. Henrisken O, Sejrsen P: Local reflex in micro circulation in human skeletal muscle. *Acta Physiol Scand* 1977;99:19–26
47. Richer C, Thuillez C, Giudicelli JF: Perindopril, converting enzyme blockade, and peripheral arterial hemodynamics in the healthy volunteer. *J Cardiovasc Pharmacol* 1987;9:94–102
48. Vidt DG, Bravo EL, Fouad FM: Captopril. *N Engl J Med* 1982;306:214–219
49. Dobrin PB: Vascular mechanics, in Shepherd JT, Abboud FM (eds): *Handbook of Physiology, sect 2. The Cardiovascular System, vol III, Peripheral Circulation and Organ Blood Flow, pt 1*. Bethesda, Md, American Physiological Society, 1983, pp 65–102
50. Wolinsky H: Response of the rat aortic media to hypertension. *Circ Res* 1970;26:507–522
51. Ooshima A, Fuller GC, Cardinate GJ, Spector S, Udenfriend S: Increased collagen synthesis in blood vessels of hypertensive rats and its reversal by antihypertensive agents. *Proc Natl Acad Sci USA* 1974;71:3019–3023

KEY WORDS • forearm arterial hemodynamics • converting enzyme inhibitor • essential hypertension • cardiac hypertrophy