Treatment for one year with perindopril: effect on cardiac mass and arterial compliance in essential hypertension

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Blood pressure, forearm arterial haemodynamics and echocardiographic parameters were studied in patients with sustained essential hypertension before and after administration of the angiotensin converting enzyme (ACE) inhibitor perindopril for 1 year. Perindopril significantly reduced blood pressure and at the same time increased brachial artery blood flow, diameter and compliance. As part of the haemodynamic investigation, a 5-min period of wrist occlusion was performed. Blood flow velocity decreased significantly to the same extent with perindopril and with placebo, but the corresponding reductions in arterial diameter were smaller with perindopril than with placebo, indicating that the increase in diameter following perindopril could not be explained solely on the basis of a flow-dependent dilation. After 3 months, treatment was stopped for 4 weeks. Blood pressure and forearm arterial haemodynamics returned towards baseline values. However, cardiac mass, which was significantly decreased after perindopril administration, remained decreased 4 weeks after cessation of treatment. In seven responder patients, perindopril was continued as sole therapy for 8 months. Arterial compliance remained elevated and cardiac mass diminished. The study showed that the arterial changes caused by perindopril involved a drug-related relaxation of arterial smooth muscle and that there was a differential response in cardiac and arterial changes following long-term treatment.

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Introduction

Therapeutic studies have shown that antihypertensive drug treatment, while lowering blood pressure, does not necessarily reduce the incidence of coronary ischaemic accidents [1]. These studies were the first to describe a dissociation between the level of blood pressure and the status of the cardiovascular system in patients treated for hypertension. More recently, similar findings have been observed for peripheral large arteries [2]. Depending on the drug used, arterial compliance may be increased or remain low despite adequate blood pressure reduction.

Angiotensin converting enzyme inhibitors are antihypertensive compounds which simultaneously cause a decrease in blood pressure through a mechanism of arteriolo-dilation [3], reversion of cardiac hypertrophy [3] and an increase in brachial artery diameter and compliance [4,5]. The increase in arterial diameter is in contrast with the reduction in blood pressure, suggesting that a relaxation in arterial smooth muscle overrides the decrease in blood pressure through mechanisms which remain largely unexplained. However, animal experiments [6] have shown that there may be a complete dissociation between cardiac and arterial changes following antihypertensive drug therapy. Cardiac hypertrophy can be easily reversed [7] whereas arterial changes remain unmodified, a finding which has as yet been poorly investigated in man [2].

In the present study, the ACE inhibitor perindopril [8] was administered for 1 year in patients with sustained essential hypertension. The changes in forearm arterial

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haemodynamics and echocardiographic parameters following long-term treatment were studied at repeated intervals using non-invasive techniques. Some of the results have been reported in detail elsewhere [2].

Materials and methods

Patients

Sixteen patients with sustained essential hypertension (12 males, 4 females) were included in the study [2]. Their ages ranged between 24 and 61 years (mean 49 years). The 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. After extensive screening as previously described [2,4,5], all the patients were diagnosed as having essential hypertension [2,4,5]. Informed consent was obtained from each patient after a detailed description of the procedure. The study protocol was approved by INSERM (Institut National de la Santé et de la Recherche Médicale).

Previous treatments, including diuretics or β-blocking agents or both, were discontinued at least a month before the study in all patients. Placebo was administered during this ambulatory wash-out period. All 16 subjects had a diastolic blood pressure above or equal to 100 mmHg at the end of this placebo period (T0). Perindopril was then given once a day in an oral dose of 2 mg, which was doubled to 8 mg in resistant patients at each monthly visit [8,9].

Active treatment was stopped after 3 months. At this time (T3), eight patients, classified as resistant, had a diastolic blood pressure above or equal to 90 mmHg. A diuretic was then added to perindopril and the subjects were excluded from the protocol. Eight patients, classified as responders, had a diastolic blood pressure below or equal to 90 mmHg. In order to assess the responsiveness to perindopril treatment more accurately in seven of these patients, a second placebo period was instituted for 1 month. At the end of the second placebo period (T4), perindopril was again given and continued for 9 months. The study was then stopped (T12).

Data for analysis were obtained from seven responder patients (six males and one female). Their ages ranged from 24 to 55 years (mean 45 years). Mean body weight and body surface area (± s.e.m.) were, respectively, 73± 4 kg and 1.87 ± 0.06 m^2. At T12 the effective dose of perindopril was 4 mg in six patients and 8 mg in one patient.

Haemodynamic investigations were performed at T0, T3, T4 and T12 in the seven responder patients, T0 and T4 corresponding to the end of placebo periods, T3 and T12 to the end of the active treatment periods. Haemodynamic studies were carried out during hospitalization for 1 day, at a controlled room temperature of 20 ± 0.5°C, the patients having rested for 30 min in the recumbent position, beginning at 9 a.m. Arterial blood pressure and heart rate were measured automatically every 2 min in the left arm with an oscillometric blood pressure recorder, the Dinamap Type 845 apparatus [10]. Similar blood pressure values were recorded in both arms. Mean arterial pressure was calculated as the sum of the diastolic pressure and one-third pulse pressure. In all hypertensive patients, haemodynamic measurements were carried out first, on the right brachial artery, followed by determination of forearm arterial haemodynamics, pulse wave velocity and brachial artery compliance. After these measurements, echocardiograms were taken.

Forearm arterial haemodynamic measurements

Forearm haemodynamic measurements were obtained using 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 [11]. This apparatus allowed the diameter and the blood velocity of the artery to be measured using two fundamental characteristics, a bidimensional recording of the Doppler signals, and a range-gated time system of reception. For the former, a probe containing two transducers was used, forming between them an angle of 120°, so that when the Doppler signals recorded by each transducer were equally in absolute value, the ultrasonic incidence with the vessel axis was 60°. With the latter value, 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. 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 allowed 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 position of 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, as previously described [11]. The arterial blood velocity was expressed in centimetres 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 value being derived from the arterial diameter (D), using a cylindrical representation of the artery ($S = 3.14D^2/4$). Arterial blood flow was expressed in millilitres per minute. Vascular resistance (mmHg/ml per s) was calculated as the ratio between simultaneous mean blood pressure and mean blood flow.

Immediately following the baseline determinations, forearm and systemic haemodynamic parameters were reassessed during a 5-min period of distal circulatory occlusion. Distal circulatory occlusion of the right forearm territory was accomplished by inflating a pneumatic wrist cuff to a suprasystolic pressure of 250 mmHg. The brachial artery diameter and blood flow velocity were measured from the second to the fifth minute of the distal

circulatory occlusion period. Values of blood flow velocity and brachial artery diameter were significantly reduced following distal circulatory occlusion without any other change during the 3-min period of measurement. Systolic, diastolic, mean arterial pressure and heart rate were measured in the left arm, using the Dinamap Type 845 apparatus, during the same period. No significant change occurred in these parameters during the distal circulatory occlusion period.

The variability of the Doppler measurements was studied in six other subjects (independently of the 16 patients in the present study) as detailed elsewhere [2,12]. Short and long-term variations were approximately 2.2% for the arterial diameter and 18.7% for blood flow velocity.

Determination of brachioradial pulse wave velocity and brachial artery compliance [13–15]

For the determination of brachioradial pulse wave velocity, 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/s. The foot, which contains the high-frequency information, 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. 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.

The variability of the method was studied by measuring pulse wave velocity before and after placebo after both acute and long-term administration. In the acute study, measurements were performed at 9 a.m. and 12 a.m., the placebo being administered at 9.15 a.m. in 11 healthy volunteers. Mean arterial pressure and pulse wave velocity did not change significantly, their respective pre- and post-placebo values being 83 ± 2 and 85 ± 2 mmHg and 9.7 ± 0.5 and 9.1 ± 0.5 m/s. A similar study was performed in seven hypertensive patients before and after 4 weeks' administration of placebo. Mean arterial pressure pre- and post-placebo was 123 ± 4 and 121 ± 4 mmHg (NS) and pulse wave velocity was 12.6 ± 1.2 and 12.2 ± 1.4 m/s (NS) [2].

For the determination of brachial artery compliance, the equation of Bramwell and Hill [16] was used:

$$PWV^2 = VdP/pdV$$

where PWV is pulse wave velocity, V is arterial volume, dV is the change in volume, dP is the change in pressure and p is the blood density. From this equation, it is possible to calculate brachial arterial compliance (BAC) as:

$$BAC = dV/dP = V/pPWV^2$$

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

$$dV/dP = 3.14R^2/pPWV^2$$

where R is the inner radius of the artery (D/2). In this equation dV/dP is expressed in cm^4 dyn 10^{-7}, with D in cm, PWV in m/s and p as 1.06.

Echocardiography

M-mode echocardiography was performed using an echocardiograph V3280 (Electronics for Medicine) amplified with a 2.25-mHz transducer. Each subject was studied in the left lateral position (approximately 30° rotation) in order to obtain 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, in order to obtain accurate measurement of the aortic diameter. Left ventricular systolic and diastolic diameter, interventricular septal thickness and left ventricular posterior wall thickness 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 using the leading-edge technique, following the usual recommendations of the American Society of Echocardiography [17]. Three beats were measured routinely, or up to five if the recording was difficult to obtain. The mean of these measurements was used for calculations. Left ventricular ejection time was measured from a simultaneously recorded carotid pulse tracing. An ECG was also recorded simultaneously. Echocardiographic left ventricular mass (LVM) was estimated [17,18] from the classical formula:

$$LVM = 1.04\,[(IVST + LVDD + PWT)3 - (LVDD)3] - 13.9\ g$$

where IVST is interventricular septal thickness, LVDD is left ventricular diastolic diameter and PWT is left ventricular posterior wall thickness. The value was converted into the LVM index (LVMi) by dividing by the body surface area and was expressed in g/m^2. The reproducibility of this method has been described in detail elsewhere [2,19].

Statistical analysis [12]

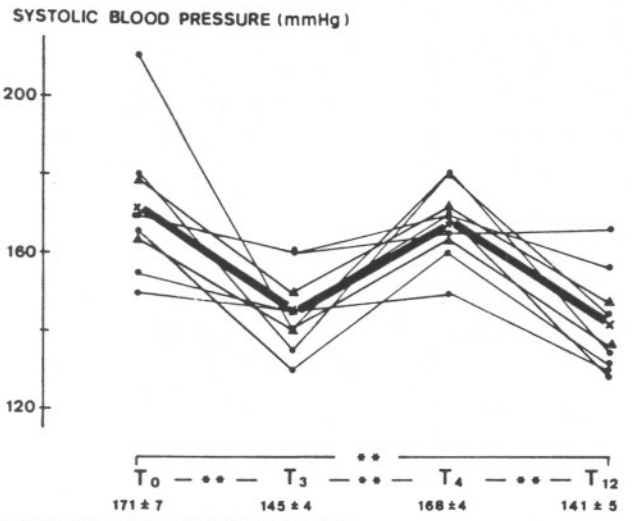
For the seven patients who were included in the long-term follow-up, data were expressed as means ± s.e.m. Two-way analysis of variance was used for statistical evaluation followed by Newman–Keuls tests. $P < 0.05$ was considered significant.

Results

Perindopril significantly reduced systolic blood pressure (Fig. 1; 171 ± 5 mmHg at T0 and 141 ± 5 mmHg at T12; $P < 0.01$), diastolic blood pressure (107 ± 2.8 mmHg at T0 and 88 ± 3.3 mmHg at T12; $P < 0.01$) and mean arterial pressure (128.0 ± 4.3 at T0 and 106.0 ± 3.9 mmHg at T12; $P < 0.01$). No significant effect on the heart rate (71.0 ± 3.1 beats/min at T0 and 73.2 ± 6.7 beats/min at T12) was observed.

With active treatment there was a significant increase in brachial artery diameter (Fig. 2; $P < 0.01$ at T3 and $P < 0.05$ at T12) and brachial blood flow (Fig. 2; $P < 0.05$ for both T3 and T4). Brachial artery compliance increased (Fig. 3; $P < 0.01$ for both T3 and T12) and brachial vascular resistance decreased (Fig. 3; $P < 0.05$ for both T3 and T12).

No significant change in brachial blood flow velocity occurred (Table 1; 7 ± 0.7 cm/s at T0 and 7.5 ± 0.9 cm/s



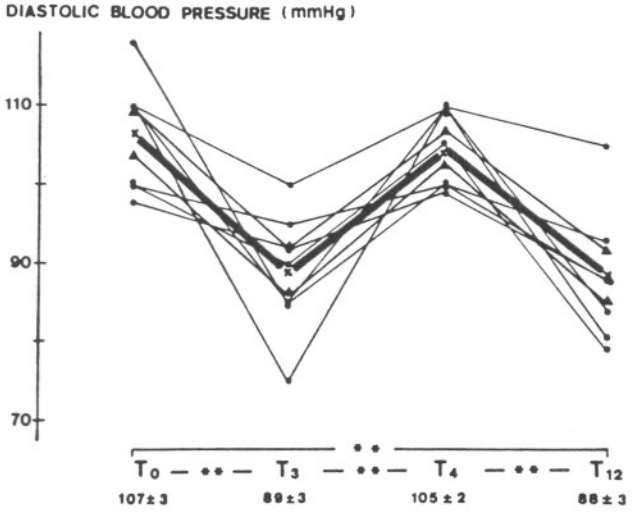
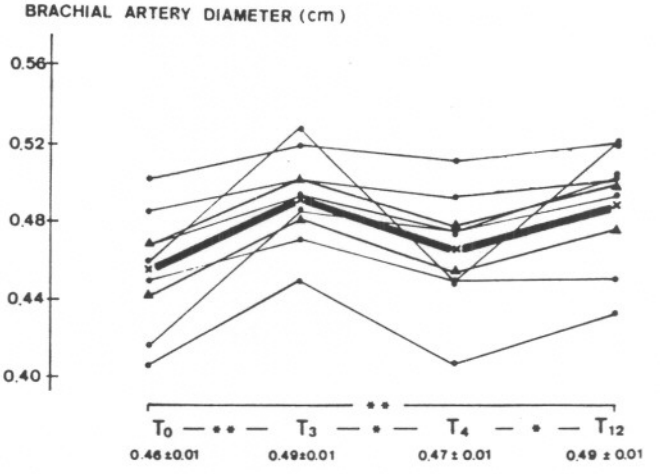


Fig. 1. Blood pressure changes. O——O, Individual values; ×——×, mean values. *$P < 0.05$, **$P < 0.01$. T_0, end of placebo period; T_3, end of 3-month active treatment; T_4, end of second placebo period; T_{12}, end of 9-month active treatment period.



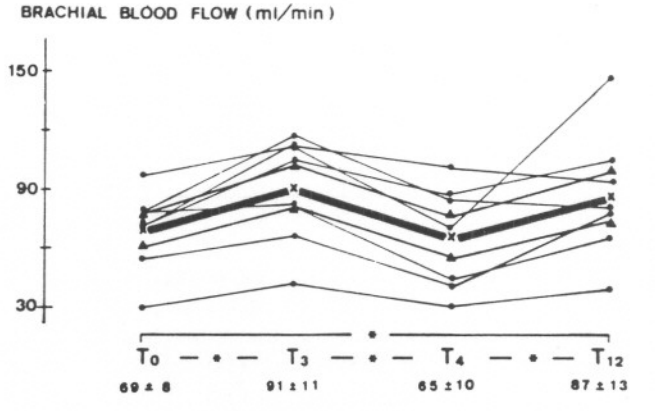


Fig. 2. Brachial artery diameter and blood flow changes. O——O, Individual values; ×——×, mean values. *$P < 0.05$, **$P < 0.01$. T_0, end of placebo period; T_3, end of 3-month active treatment; T_4, end of second placebo period; T_{12}, end of 9-month active treatment period.

at T12). During wrist occlusion brachial artery blood flow velocity and arterial diameter were significantly reduced. Table 1 summarizes the changes in flow velocity and arterial diameter before and after wrist occlusion. The reduction in brachial blood flow velocity following wrist occlusion was similar for all four periods (T0, T3, T4 and T12) The brachial artery diameter was also significantly reduced after wrist occlusion. However, analysis of variance showed that the brachial artery diameter was significantly increased at T12 compared with T0. The result was observed before ($P < 0.01$) and after ($P < 0.05$) wrist occlusion.

Table 2 shows that active treatment caused a significant decrease in cardiac mass due to a significant reduction in septal wall thickness and left ventricular posterior wall thickness. The left ventricular mass index and septal wall thickness (Fig. 4) were, respectively, 156 ± 9 g/m^2 and 1.15 ± 0.04 cm at T0 and 116 ± 6 g/m^2 and 0.96 ± 0.04 cm at T12 ($P < 0.01$). After the second placebo period (T4), both values were significantly increased but remained significantly lower than T0 values (Fig. 4 and Table 2).

Discussion

The most important findings of the present study were the increase in brachial artery diameter and compliance produced by perindopril following treatment for 1 year, and the differential responses in cardiac and arterial changes observed after active treatment ceased. It is clear that the validity of these results depends on the relative sensitivity and reliability of the techniques used for the long-term study of arterial haemodynamics and cardiac mass. As shown elsewhere [11,20], 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 obtain an interpretable echo. The maximal error for brachial artery diameter determinations has been shown to be 0.035 ± 0.015 cm [11]. Our study of short- and long-term variability has shown a 2.2% approximation of measurements, a finding

Table 1. Effect of wrist occlusion.

		T0	T3	T4	T12
Brachial blood flow velocity (cm/s)	B	7.0 ± 0.7	7.8 ± 0.7	6.2 ± 0.7	7.5 ± 0.9
	A	3.5 ± 0.4**	3.6 ± 0.6**	3.0 ± 0.4**	2.8 ± 0.2**
Brachial artery diameter (cm)	B	0.46 ± 0.01‡‡	0.49 ± 0.01‡	0.47 ± 0.01‡	0.49 ± 0.0††
	A	0.43 ± 0.02**NS	0.46 ± 0.01*NS	0.43 ± 0.02*‡	0.47 ± 0.02**†

*$P < 0.01$, **$P < 0.05$, A versus B; †$P < 0.01$, ††$P < 0.05$, T12 versus T0; ‡$P < 0.01$, T3 versus T4 and T4 versus T12; ‡‡$P<0.05$, T0 versus T3; NS, not significant T0 versus T3 and T3 versus T4.

Table 2. Echocardiographic changes.

	T0	T3	T4	T12
End-diastolic diameter (cm)	5.39 ± 0.11	5.26 ± 0.16	5.34 ± 0.12	5.28 ± 0.14
End-systolic diameter (cm)	3.50 ± 0.12	3.27 ± 0.16	3.35 ± 0.09	3.32 ± 0.13
Ejection fraction (%)	0.69 ± 0.03	0.74 ± 0.02	0.72 ± 0.02	0.72 ± 0.02
Velocity of circumferential fibre-shortening (circ/s)	1.21 ± 0.05	1.34 ± 0.10	1.32 ± 0.08	1.31 ± 0.09
Septal wall thickness (cm)	1.15 ± 0.04	1.02 ± 0.04**	1.09 ± 0.04**	0.96 ± 0.04**
Left ventricular posterior wall thickness (cm)	1.09 ± 0.05	1.00 ± 0.04*	1.04 ± 0.04	0.93 ± 0.02**
Left ventricular mass index (g/m)	156 ± 9	128 ± 9**	141 ± 8*	116 ± 6**

*$P < 0.05$ versus T0; **$P < 0.01$ versus T0. All values are ± s.e.m.

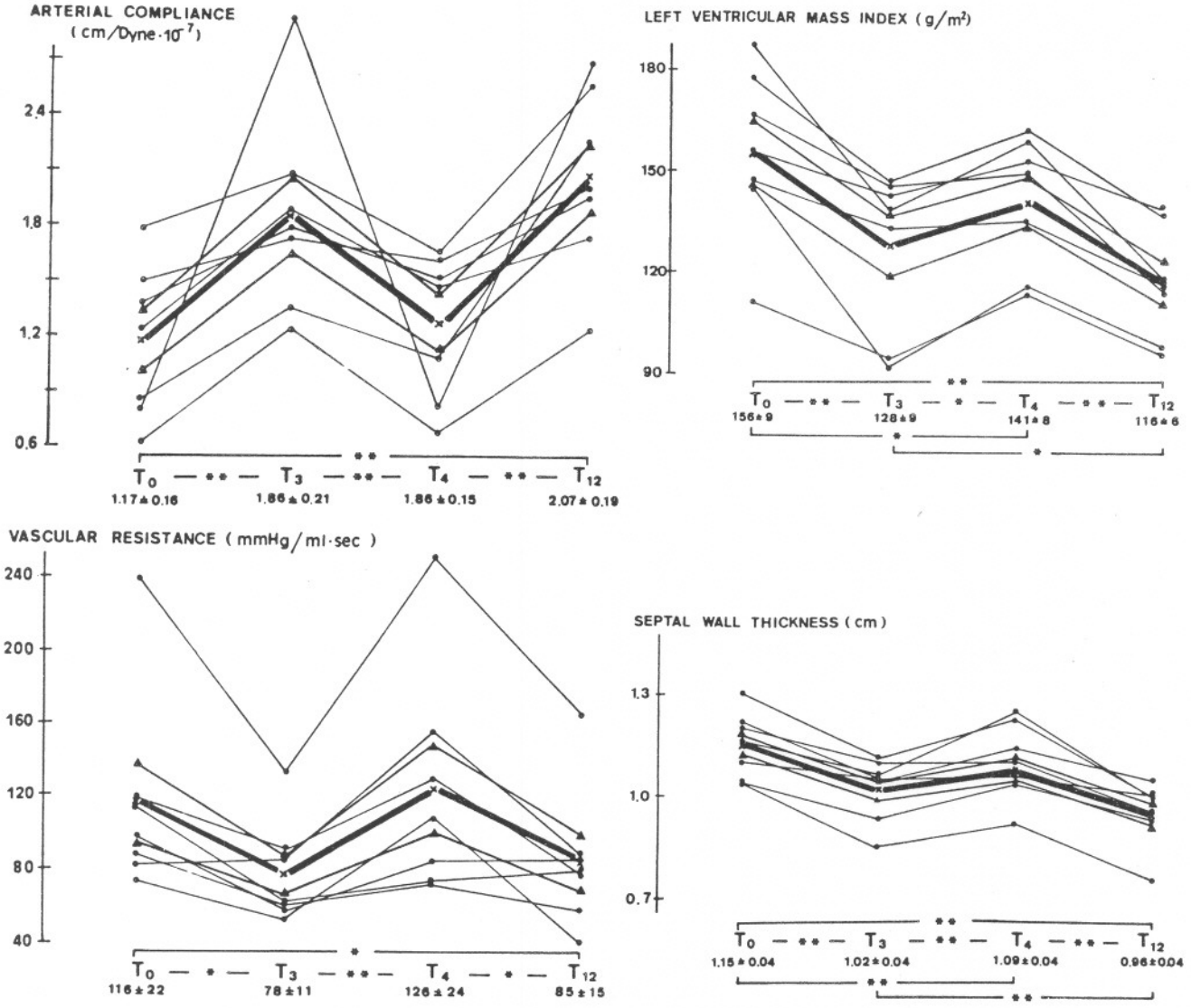


Fig. 3. Forearm changes: vascular resistance and arterial compliance. O——O, Individual values; ×——×, mean values. *$P < 0.05$, **$P < 0.01$. T_0, end of placebo period, T_3, end of 3-month active treatment; T_4, end of second placebo period; T_{12}, end of 9-month active treatment period.

Fig. 4. Echocardiographc changes. O——O, Individual values; ×——×, mean values. *$P < 0.05$, **$P < 0.01$. T_0, end of placebo period, T_3, end of 3-month active treatment; T_4, end of second placebo period; T_{12}, end of 9-month active treatment period.

which agrees with the significant changes in arterial diameter produced by antihypertensive agents observed in long-term double-blind studies [4,5]. In contrast to the arterial diameter findings, there was a greater variability of blood flow velocity, although this measurement is easier and more accurate. This peculiarity is due to the well-known rapidity of change in cutaneous blood flow and to the rich innervation of the hand [20], which produces instantaneous changes in blood flow velocity.

Using a single-blind design versus placebo, our study clearly showed that the ACE inhibitor perindopril caused an increase in brachial artery diameter and compliance. Since there was also a simultaneous reduction in blood pressure, this finding indicates that active changes occurred in the arterial wall. Vasodilator drugs can increase arterial diameter via two possible mechanisms, indirect flow-dependent dilation and direct smooth muscle relaxation [21,22]. Since brachial blood flow increased significantly with perindopril, the former mechanism is considered first.

Animal studies have shown that epicardial coronary and femoral arteries dilate in response to increases in blood flow [21,23]. Any factor that increases flow, such as release of a transient arterial occlusion, causes dilation of the large arteries [21,23]. Evidence is accumulating that this dilation is dependent on the endothelium [24]. Removal of the endothelium in isolated perfused canine coronary or femoral arteries *in situ* abolishes the flow-dependent dilation [21,24]. In the case of the ACE inhibitor perindopril, the possible role of the endothelium must be taken into account as endothelial cells contain large amounts of ACE and may be a favoured site of action of ACE inhibitors [25–27]. In the present study, the role of flow-dependent dilation was evaluated from the haemodynamic effects of wrist occlusion at a supra-systolic blood pressure level. This manoeuvre consistently caused a significant reduction in diameter and blood flow velocity. However, with both placebo and perindopril a similar reduction in blood flow velocity was observed, whereas arterial diameter remained increased with perindopril (Table 1). This finding does not support the hypothesis that high-flow dilation alone can explain the increased brachial artery diameter observed after perindopril administration, and that direct smooth muscle relaxation occurred. 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 [28]. This suggests that the drug affects large arteries by mechanisms other than the simple inhibition of circulating ACE. Local modifications of the vascular tissue may be related to ACE inhibition alone but prostaglandin release and/or kinin accumulation, and finally, inhibition of the sympathetic nervous system [29] might also contribute to the smooth muscle relaxation.

As previously reported with other ACE inhibitors [3], perindopril caused a significant decrease in left ventricular mass, principally due to 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. After the treatment was restarted cardiac mass decreased further, while arterial compliance increased but not more so than at the beginning of the treatment. These findings strongly suggest that the time constant for reversal of cardiac and arterial changes may be different in hypertensives following treatment. Since reversal of structural changes has been observed in the heart after the administration of perindopril it is possible that these structural changes may differ in the heart and the vessels during long-term treatment. Studies in hypertensive animals have shown that captopril causes minimal changes in aortic structure, whereas cardiac hypertrophy is reduced [7,30,31].

In conclusion, the present study has shown that in patients with sustained essential hypertension, the ACE inhibitor perindopril increased brachial artery diameter and compliance during long-term treatment via drug-mediated modifications of the arterial wall, these changes 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.

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