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Haemodynamic effects of perindopril in essential hypertension

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Summary: Blood pressure, forearm arterial haemodynamics and echocardiographic parameters were studied in patients with sustained essential hypertension before and after administration of the ACE inhibitor, perindopril. In a single blind study versus placebo, perindopril significantly reduced BP and at the same time increased brachial artery diameter, blood flow and compliance. As part of the haemodynamic investigation, a 5 minute wrist occlusion was performed. During this period, blood flow velocity and arterial diameter decreased but the reduction in diameter was smaller with perindopril after one year's treamtnet showing an increase in brachial artery diameter. This result indicates that the increase in brachial arterial diameter following perindopril could not be explained solely on the basis of a flow dependent dilation. When perindopril was withdrawn after three months of treatment and replaced by placebo for four weeks, BP and forearm arterial haemodynamics returned towards baseline values. However, cardiac mass which was significantly decreased after perindopril remained decreased four weeks after cessation of treatment. In the seven normalised patients, perindopril was continued for one year; arterial compliance remained increased 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.

Introduction

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] On the other hand, therapeutic studies have shown that anti-hypertensive drug treatment, while reducing BP, does not necessarily reduce the incidence of coronary ischaemic accidents.[2] These results demonstrate a clear dissociation between the level of BP and the status of the cardiovascular system in patients treated for hypertension. More recently, animal experiments and clinical studies[3] showed that drug-induced reduction in BP is not always associated with reversal of cardiac hypertrophy and improvement in arterial compliance.[4–6] In fact, cardiac hypertrophy can be reversed whereas arterial changes remain unmodified. Such observations are important to consider for a better understanding of the effects of anti-hypertensive therapy.

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In the present study, the ACE inhibitor, perindopril,[7,8] was administered to patients with sustained, essential and uncomplicated hypertension in chronic treatment for up to one year. The changes in forearm arterial haemodynamics and the echocardiographic parameters were studied at repeated intervals using non-invasive methods.

Materials 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 anti-hypertensive treatment was discontinued at least four weeks before the study. In all 16 subjects, diastolic pressure (DBP) remained above 100 mmHg Patients had no signs, symptons, or history of

cardiac or renal failure, coronary insufficiency, or major diseases other than hypertension. On the basis of previously described investigations,[9,10] 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 Sante et de la Recherche Medicale).

Study design

Of the 18 patients recruited during the washout period, two were found to be placebo-responders after four weeks to follow-up. The 16 remaining hypertensive patients had a DBP $\geqslant$ 100 mgHg just before beginning (M0) the active treatment period. Perindopril was then given as an oral once daily dosage of 2 mg.[8] After four weeks, the dosage was increased to 4 mg once a day if DBP $\geqslant$ 95 mmHg. After another four weeks treatment, the dosage was increased to 8 mg if necessary. Thereafter, a second placebo period was instituted for four more weeks (M4).

At the end of the fourth month (M4) eight patients, classified as resistant, had a DBP > 90 mmHg. A diuretic was then added to perindopril and the subjects were excluded from the protocol. Eight patients classified as normalised, had a DBP $\leqslant$ 90 mmHg. At the end of the second placebo period (M4) perindopril was again given and continued in these normalised patients for nine months. The study was then stopped (M12).

Haemodynamic investigations were performed at M0, M3 and M4 in all patients and at M12 only in the normalised patients. M0 and M4 corresponded to the end of the placebo periods, M3 and M12 to the end of the active treatment periods. Haemodynamic studies were carried out during hospitalisation for one day, at a controlled room temperature of 20 ± 0.5°C, the patients having rested for 30 minutes in the recumbent position, beginning at 9 a.m. Arterial BP and heart rate were measured automatically every 2 min in the left arm with an oscillometric BP recorder[11] (Dinamap Type 845). The same values of BP were recorded with 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.[12] In the 16 hypertensive patients, haemodynamic measurements were carried out first on the right brachial artery, with determination of forearm arterial haemodynamics, pulse wave velocity, and brachial artery compliance. Thereafter, echocardiography was performed. Because two patients did not attend the scheduled clinic at M4 data was obtained from only 14 patients at M4.

In the one year follow-up study, data for analysis was obtained from seven normalised patients (six males and one female). Their ages ranged from 24 to 55 years (mean 45 years). Mean body weight and body surface area ($\pm$SEM) were, respectively, 73 ± 4 kg and $1.87 \pm 0.06 m^2$. At M12 the effective dose of perindopril was 4 mg in six patients and 8 mg in one patient.

Method

Forearm arterial haemodynamic measurement

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.[13] 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 equal in 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.[13] The arterial blood velocity was expressed in cms/sec and mean arterial blood velocity was electronically integrated. Brachial artery blood flow was calculated

as the product of blood velocity and cross-sectional area (S), 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 ml/min.

Immediately following the baseline determinations, forearm and systemic haemodynamic parameters were re-assessed during a 5 minute 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. 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 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 a.m. (two or three determinations at each hour) to evaluate short-term variablity. 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. Three way analysis of variance[14] 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 probes (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 paper speed of 150 mm/sec. The foot, which contains the high-frequency information,[15,16] 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.[16,17] 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 administraion of vasoactive substances.[15-23] 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 a.m. the placebo being administered at 9.15 a.m. in 11 healthy volunteers.[24] MAP and pulse wave velocity did not change significantly, their respective pre-placebo and post-placebo values being 83 ± 2 and 85 ± 2 mmHg 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 mmHg (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[17] 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 dynes/$cm^4 \times 10^{-7}$, D in centimetres. PWV in metres per second, and ρ equals 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 dia-

stolic 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.[25] 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[26,27] from the classical formula:

$$LVM = 1.04[(IVST + LVDD + PWT)^3 - LVDD)^3] - 13.9 \text{ g}$$

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.[25-29]

Statistical analysis[14] Data were 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.

Data were analysed for the 14 patients who reached the second placebo period (M4): and then for the 7 normalised patients treated by perindopril for one year (M12).

Results

Patients achieving the second placebo-period, M4 (n = 14)

Perindopril significantly reduced BP ($P < 0.01$) but had no significant effect on heart rate (Table I). Plasma ACE activity after active treatment M3 was significantly inhibited (51.4 ± 19.7%) compared with M0 (100%) and M4 (158.2 ± 21.1%) ($P < 0.01$). Plasma renin activity (ng/ml/hr) was significantly higher at M3 (5.34 ± 2.14) than at M0 (2.66 ± 1.02) and M4 (2.01 ± 1.06) ($P < 0.05$).

Table I indicates 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 ($P < 0.01$). During wrist occlusion, arterial diameter and blood flow velocity were significantly reduced ($P < 0.001$) at M0, M3, and M4. Mean arterial diameter during wrist occlusion was 0.414 ± 0.02 cm at M0, 0.446 ± 0.01 cm at M3 and 0.434 ± 0.02 cm at M4 (NS). Mean arterial velocity at M0, M3 and M4 was 3.02 ± 0.28, 3.37 ± 0.33, and 2.78 ± 0.27 cm/sec, respectively. Although the decrease in blood flow velocity was significantly higher at M3 than at M0 or M4 ($P < 0.001$), the reduction in arterial diameter was similar for all three periods.

Table II shows that active treatment caused a significant decrease in cardiac mass at M3 ($P < 0.01$), secondary to a significant reduction in septal thickness ($P < 0.01$), posterior wall thickness ($P < 0.01$), and end-diastolic volume ($P < 0.05$). After treatment was stopped (M4), septal thickness, posterior wall thickness, and cardiac mass remained significantly reduced ($P < 0.05$; $P < 0.01$), whereas end-diastolic volume returned toward basal values. Ejection fraction, velocity of circumferential fibre shortening (VCF), and left ventricular fractional shortening did not change during the study.

Normalised patients continuing perindopril to M12

Perindopril significantly reduced SBP (171 ±

Table I Changes in BP, heart rate and brachial arterial haemodynamics in the 14 patients who achieved the second placebo period (M4). Values are mean ± SEM

	M0 (placebo)	*M3 (active treatment)*	*M4 (placebo)*
Systolic BP (mmHg)	173.4 ± 4.6	149.1 ± 4.1*	168.2 ± 3.3
Diastolic BP (mmHg)	106.9 ± 1.7	94.1 ± 3.5	107.4 ± 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

*$P < 0.01$ in comparison with M0 and M4; †$P < 0.05$

Table II Changes in the echocardiographic parameters in the 14 patients who achieved the second placebo period (M4). Values are mean ± SEM

	M0 (placebo)	*M3 (active treatment)*	*M4 (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 (%)	0.723 ± 0.003	0.75 ± 0.02	0.75 ± 0.02
Velocity of circumferential fibre 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/m²)	147.2 ± 6.4	124.5 ± 7.2†	134.5 ± 6.4†
Mass/Volume (g/ml)	2.04 ± 0.08	1.81 ± 0.07†	1.95 ± 0.05§

*$P<0.05$ and †$P<0.01$, M3 versus M0 and M4.
‡$P<0.01$ and §$P<0.05$, M3 versus M0.

5 mmHg at M0 and 141 ± 5 mmHg at M12; $P<0.01$), DBP (107 ± 2.8 mmHg at M0 and 88 ± 3.3 mmHg at M12; $P<0.01$) and MAP (128.0 ± 4.3 at M0 and 106.0 ± 3.9 mmHg at M12; $P<0.01$). No significant effect on the heart rate (71.0 ± 3.1 beats/min at M0 and 73.2 ± 6.7 beats/min at M12) was observed.

With active treatment there was a significant increase in brachial artery diameter (Table III) ($P<0.01$ at M3 and $P<0.05$ at M12) and brachial blood flow ($P<0.05$ for both M3 and M12). Brachial artery compliance increased (Figure 1 ($P<0.01$ for both M3 and M12).

No significant change in brachial blood flow velocity occurred (Table III; 7 ± 0.7 cm/s at M0 and 7.5 ± 0.9 cm/s at M12). During wrist occlusion brachial artery blood flow velocity and arterial diameter were significantly reduced. Table III summarises the changes in flow velocity and arter-

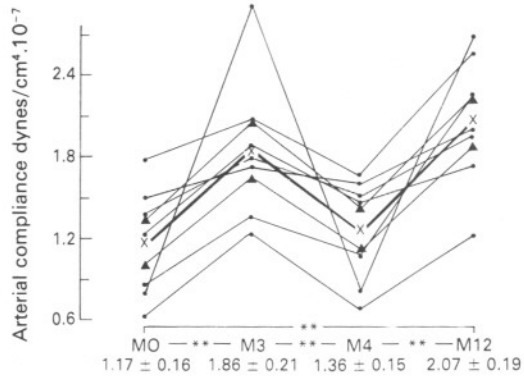

Figure 1 Changes in arterial compliance (●–●, individual values, ▲–▲, SEM; and ×–×, mean values. *$P<0.05$;** = $P<0.01$; M0 end of placebo period, M3 end of 3 month active treatment; M4 end of second placebo period; M12 end of 12 month active treatment period).

Table III Effect of wrist occlusion in 7 normalised patients treated by perindopril for one year (M12)

		M0	*M3*	*M4*	*M12*
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**1

*$P<0.01$, **$P<0.05$, A versus B; †$P<0.01$, ††$P<0.05$, M12 versus M0; ‡$P<0.01$, M3 versus M4 and M4 versus M12; ‡‡$P<0.05$, M0 versus M3; NS, not significant, M0 versus M3 and M3 versus M4.
B = Baseline
A = Wrist occlusion

ial diameter before and after wrist occlusion. The reduction in brachial blood flow velocity following wrist occlusion was similar for all four periods (M0, M3, M4 and M12). 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 M12 compared with M0. The result was observed before ($P < 0.01$) and after ($P < 0.05$) wrist occlusion.

Table IV shows that the 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 were, respectively, 156 ± 9 g/m^2 and 1.15 ± 0.04 cm at M0 and 116 ± 6 g/m^2 and 0.96 ± 0.04 cm at M12 ($P < 0.01$). After the second placebo period (M4), both values were significantly increased but remained significantly lower than M0 values (Table IV).

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 haemodynamics and cardiac mass. An ideal approach would be to have a placebo-time control group at M0, M3, M4 and M12, 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 one year, 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 haemodynamics 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.[15,16,18] As shown elsewhere,[13,30] the measurement of arterial diameter by Doppler ultra-sound 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.[13] 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 anti-hypertensives in long-term double-blind studies.[6,9,31] 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,[30] favouring 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.[6,9,31]

As far as echocardiographic parameters are concerned, numerous studies have documented

Table IV Echocardiographic changes in 7 normalised patients treated by perindopril for one year (M12)

	M0	*M3*	*M4*	*M12*
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 M0; **$P < 0.01$ versus M0. All values are ± SEM

sources of error derived from intraobserver and interobserver variability and interstudy reproducibility.[29] 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.[29,32] These considerations are of obvious importance in serial studies involving long-term changes. However, Devereux *et al.*[26] have demonstrated close correlations between cardiac mass in paired echocardiograms 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.[33] They are also smaller than the standard deviation of 43 g obtained in a comparison of echocardiographic and necropsy measurements.[26] 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 (M3-M12) and after the treatment was stopped (M4) accord with the results of the studies in which serial changes in a control group receiving a placebo were compared with changes in the treatment group.[34]

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 thickness 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.[29] For Doppler measurements, the problem is to determine exactly the angle between the ultra-sound 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.[13] Indeed, with the double transducer probe used in this study, the reproducibility of the measurement angle is less than 2%.[13]

Increase in brachial artery diameter and compliance

With single-blind design versus placebo, the study clearly showed that the ACE inhibitor perindopril causes an increase in brachial artery diameter and compliance.

Since there was also a simultaneous reduction in BP, 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 muslce relaxation.[35,36] 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.[37,38] Any factor that increases flow, such as release of a transient arterial occlusion, causes dilation of the large arteries.[37,38] Evidence is accumulating that this dilation is dependent on the endothelium.[38] Removal of the endothelium in isolated perfused canine coronary or femoral arteries *in situ* abolishes the flow dependent dilation. In the case of 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.[39,40] In the present study, the role of flow-dependent dilation was evaluated from the haemodynamic effects of wrist occlusion at a supra-systolic BP 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 III). 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 ACE) produced changes in brachial and carotid arterial diameters only at the highest dose.[41] 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,[42] and finally, inhibition of the sympathetic nervous system[42,43] might also contribute to the smooth muscle relaxation.[44,45]

Differential responses in cardiac and arterial changes after cessation of active treatment

As previously reported with other ACE inhibitors,[5,32] perindopril caused a significant decrease in left ventricular mass, principally because of a decrease in septal thickness and posterior wall thickness. However, four weeks after the treatment was stopped, cardiac mass remained low,

whereas BP and arterial compliance had returned towards 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 non-invasive haemodynamic measurements largely agrees with well established long term studies, hypotheses other than technical problems may be advanced. The finding that cardiac mass remained low four weeks after cessation of active treatment does not mean that it will not return towards 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.[46] 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.[47] In contrast, the collagen concentration often remains essentially unchanged, especially in treated animals.[47,48]

In conclusion, the present study has shown that in patients with sustained essential hypertension, the ACE inhibitor perindopril increases brachial artery diameter and compliance through drug-mediated modifications of the arterial wall, these being largely unrelated to BP 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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Discussion

P. Sever: Have you studied any of your subjects one year after treatment with perindopril and then stopped the drug for one month to see whether there is a slower time course of return of the BP? What surprised me was how rapidly all your parameters returned to the pretreatment stage after treatment for three months, because we know that in some of the longer term trials, not so much with ACE inhibitors but with beta-blockers and diuretics, the haemodynamic parameters actually take quite a long time to return to the pretreatment state.

R. Asmar: I agree with you. The study design was exactly as I showed; it was only for four months and we had 16 patients. The Ethics Committee of Broussais Hospital told us that we could continue the study only with the normalised subjects. We had only seven of them. I tried to convince the Committee to permit us to stop after one year, but they refused. I agree with you that the most important point would be to see after one year what had happened to the arterial parameters.

C. Brown: Dr. Mulvany has shown effects in animals on arterial wall structure, but those were in small arterioles and your experiments were in large arteries. I wonder if you could make any comment on any relation between effects in large arteries and in arterioles?

R. Asmar: When I showed that perindopril decreases BP this includes both systolic and diastolic. When you look at the SBP, one of the determinants is arterial compliance, and when you look at the DBP, one of the determinants is the vascular resistance which is in the small arteries. I think that we must look at the differences between the small and the large arteries and the small arteries are more reflected in the DBP and the large arteries in the SBP.

As to the effect of perindopril on the small and large arteries in humans and in animals, Bernard Levy studied perindopril in SHR and Goldblatt rats and looked at the effect of perindopril on compliance. He showed that perindopril increased arterial compliances especially in Goldblatt and to a lesser extent in SHR rats, and he even found a structure modification. This was possible because they were animal experiments.

P. Sever: There was some data published a couple of years ago by Agabiti-Rosei and his colleagues from Italy looking at the resistance to flow at maximal dilatation in the forearm in a group of patients who were treated, I think, with either calcium antagonists or ACE inhibitors and they were able to show after a year's treatment that the resistance to flow at maximum dilatation was decreased, particularly in the group on ACE inhibitors. Would you think that that is primarily due to an increased compliance of large arteries or to structural change in small arteries?

R. Asmar: It's impossible to say. Experience in animals has shown clearly that this flow vasodilatation is endothelium dependent and you can see interaction between ACE and endothelium, but I can't give a clear answer. I think Moser in Germany used to study this in dogs, looking at flow vasodilatation in dogs with and without endothelium and he showed that without endothelium it didn't occur. He also showed that with artificial stenosis after the measurements for the same flow, he didn't have any vasodilatation.

P. Sever: Is that flow-dependent dilatation more important in large than in small arteries?

R. Asmar: It is difficult to say which one is more important.

L. Jespersen: I think that it should be said in answer to your question that the difference between small and large arteries is not that big in the rat, because in the rat even the aorta is a muscular organ, but in human beings there are large differences between resistance vessels and distributional arteries.