Journal of Human Hypertension (1996) 10, 77–82

Arterial stiffness, hydrochlorothiazide and converting enzyme inhibition in essential hypertension

A Bénétos, A Laflèche, R Asmar, S Gautier, A Safar and ME Safar
Department of Internal Médecine and INSERM U337, Broussais Hospital, Paris, France

In a randomized double blind study, the arterial changes produced either by hydrochlorothiazide plus amiloride (Group I), or by hydrochlorothiazide plus captopril (Group II) were investigated in two territories of the arterial tree, the common carotid artery and the terminal aorta. Arterial echo-tracking techniques of high resolution and applanation tonometry were used to evaluate non-invasively the indices of arterial stiffness and carotid wave reflections. In Groups I and II, there was a similar significant decrease in brachial blood pressure (BP) and carotid diastolic diameter and an increase in aortic compliance and distensibility. Groups I and II differed significantly in aortic diastolic diameter which decreased in Group I but not in Group II, and in carotid wave reflections which were modified in Group II but not in Group I. Thus, captopril associated with hydrochlorothiazide resulted in a shift in the carotid arterial reflection wave from systole to diastole with no reduction in the aortic diastolic dimension. For similar BP reduction, the combination of hydrochlorothiazide and amiloride had no significant effect on the carotid reflection wave, but caused a significant reduction in the aortic diastolic diameter. These intergroup differences were related to the presence or absence of converting enzyme inhibition.

Keywords: hypertension; arterial system; diuretic compounds; converting enzyme inhibition

Introduction

For the same blood pressure (BP) reduction, antihypertensive drugs do not cause the same arterial changes in hypertensive subjects.[1] Whereas converting enzyme inhibitors, calcium entry blockers and alpha (and some beta) blocking agents increase brachial and systemic arterial compliance, no substantial change is observed following propranolol, dihydralazine, and mostly, the diuretic compound hydrochlorothiazide.[2,3]

Cross-section epidemiological studies have shown that aortic pulse wave velocity, a classical marker of arterial stiffness, increases with age more markedly in urban populations with high sodium intake than in rural populations with low-sodium intake.[4] Longitudinal studies in hypertensive subjects indicate that low sodium intake is associated with a dilatation of the brachial, and not of the carotid, artery.[5] Studies in animals and humans suggest that increased salt sensitivity of genetic origin is associated with an increase in arterial stiffness.[6,7] From such findings, it should be logical to expect that chronic diuretic treatment in hypertension may be associated with a decrease in arterial stiffness.

The modest arterial changes following chroniz thiazide treatment might result from several possibilities. Firstly, the BP reduction following diuretic treatment is mild,[5] resulting in unsignificant changes in passive arterial stiffness. However animal studies showed that some diuretic compounds might decrease arterial stiffness independently of pressure changes.[8] Secondly, changes in salt and water depletion produced by diuretic treatment causes simultaneously a stimulation of the sympathetic and renin-angiotensin systems, which in turn may be responsible for arterial constriction. Indeed norepinephrine and angitotensin II may constrict the large and medium-sized muscular arteries in hypertensive subjects.[9,10]

The purpose of the present study was to evaluate whether, in the presence of diuretic treatment, the blockade of the renin-angiotensin system may reverse the arterial rigidity observed in subjects with essential hypertension. For this, we compared the arterial changes observed during long-term treatment by hydrochlorothiazide plus amiloride with those obtained from an association of hydrochlorothiazide with the converting enzyme inhibitor, captopril. Using new arterial echo-tracking techniques of high resolution,[11,12] two different arterial territories were investigated non-invasively: the common carotid artery, and the terminal aorta.

Subjects and methods

Twenty-four subjects, (17 men and 7 women) were selected from the Hypertension Center, Broussais Hospital, Paris. All these subjects had mild to moderate essential hypertension with a diastolic BP between 95 and 114 mm Hg. Criteria for selection of patients have been extensively published.[12] Age (± s.e.m.) was 48 ± 2 years (range 22–71). Weight and

Correspondence: ME Safar, Director, Service de Médecine I, Hôpital Broussais, 96 rue Didot, Paris CEDEX 75 674, France
Received 14 June 1995; revised 15 November 1995; accepted 21 November 1995

height were 70 ± 3 kg and 167 ± 2 cm, respectively. In all hypertensive subjects, treatments were discontinued 1 month before the study, and diastolic BP (by conventional spymomanometry) remained above 95 mm Hg throughout this placebo washout-period. Patients had no signs, symptoms or history of cardiac, renal or cerebrovascular accident or major diseases other than hypertension. On the basis of conventional echography, no stenosis >30% of the lumen area or atheromatous plaque of the common, internal carotid, or ilio-femoral arteries were noticed. The evaluation of velocities with a continuous Doppler device confirmed the absence of any significant lesions of the studied segments. Twelve patients presented mild hypercholesterolemia and six subjects smoked. No patient presented diabetes melitus or had antidiabetic treatment. Written consent was obtained from each subject after a detailed description of the procedure. The protocol was approved by the ethical committee of INSERM (Institute National de la Santé et de la Recherche Médicale, France).

After the 2 weeks placeo-period, a double blind randomized study was performed comparing two parallel groups: Group I ($n = 12$) (8 men and 4 women) with hydrochlorothiazide (50 mg/day) and amiloride (5 mg/day); Group II ($n = 12$) (9 men and 3 women) with hydrochlorothiazide (25 mg/day) plus captopril (50 mg/day). Each drug was given po at 08.00 as a single dose. Doses were chosen on the basis of already published pharmacokinetic and pharmacodynamic data on hydrochlorothiazide and captopril, indicating that: (i) 50 mg captopril produced an effective plasma angiotensin converting enzyme (ACE) blockade of the hydrochlorothiazide-induced activated renin-angiotensin system, and (ii) hydrochlorothiazide (50 mg/day) caused the same decrease in BP as hydrochlorothiazide (25 mg/day) plus captopril (50 mg/day).[13–15] Because changes in plasma potassium were shown to have no direct interference with changes in arterial stiffness,[1] amiloride was added to hydrochlorothiazide in order to control plasma potassium. On the other hand, previous studies in the literature[2,3] indicated that hydrochlorothiazide alone or associated to amiloride induced identical arterial changes. The duration of the active treatment period was 3 months between Day 0 (D0) and Day 90 (D90). Plasma potassium, creatinine, uric acid, glucose and total cholesterol were measured at D0 and D90. Baseline clinical and biological characteristics are indicated in Table 1.

Hemodynamic investigations were performed at the end of the placebo-period (D0) and of the trial (D90). Each subject was investigated in a controlled environment of 22 ± 3C. After 20 minutes of rest in the supine position, systolic and diastolic BP and heart rate were determined every 2 min by an oscillometric recorder (Model 845, Dinamap, Critikon, Tampa, FL, USA) positioned on the right arm. The same parameters were also measured with a mercury sphygmomanometer on the right arm. In this latter case, mean arterial pressure (MAP) was estimated by the formula MAP = DBP + (SBP–DBP)/3, where DBP and SBP are diastolic and systolic BP respectively. Then arterial measurements were performed at the sites of the right common carotid artery and the terminal aorta. Arterial parameters were studied exactly at the same points: 2 cm proximal to the carotid bifurcation and 3 cm proximal to the aorto-iliac bifurcation.

Table 1 Baseline clinical and biochemical characteristics

	Group I (n = 12)	*Group II* (n = 12)
Age (years)	47 ± 4	49 ± 3
Body weight (kg)	69 ± 4	71 ± 3
Body height (cm)	169 ± 3	166 ± 3
Plasma potassium (mmol/l)	4.23 ± 0.11	4.21 ± 0.08
Plasma total cholesterol (mol/l)	5.8 ± 0.4	6.0 ± 0.4
Plasma uric acid (μmol/l)	285 ± 20	299 ± 21
Plasma creatinine (μmol/l)	89 ± 2.8	90 ± 3.2

Systolic-diastolic variations of arterial diameter were measured by using an original pulsed ultrasound echo-tracking system based on Doppler shift.[11] The details of this method have been described elsewhere.[11,12] Briefly, the system enables the transcutaneous assessment of the displacement of the arterial wall during the cardiac cycle and hence, the time-dependent changes in arterial diameter relative to its initial diameter at the start of the cardiac cycle. The availability of the electrocardiogram (ECG) trigger facilitates the detection of the peak distention of the artery relative to its initial diameter. The displacement of the arterial wall is obtained by processing the Doppler signals originating from two selected sample volumes, enabling us to evaluate the stroke change in diameter during systole (Ds–Dd), the end-diastolic diameter (Dd), and the relative stroke change in diameter ([Ds–Dd]/Dd) (Ds: peak systolic diameter). The repeatability of the carotid artery measurement has been published in detail elsewhere.[16]

Carotid systolic-diastolic variations of BP were obtained using a pencil-type probe incorporating a high-fidelity strain-gauge transducer (Millar Instruments Inc, Houston, TX, USA). The instrument uses the principles of applanation tonometry as in ocular tonometry for registration of intraocular pressure. The use and accuracy of the tonometer were previously studied and validated on the exposed canine femoral artery, following catheterization in humans, and percutaneously on the human radial artery.[12,17,18] Intraobserver variability of the measurement was 4.7% and interobserver variability was 6.1%. Such levels of reproducibility can be achieved after 4–6 weeks use of the probes.

For the pulse pressure measurements at the site of the terminal aorta, brachial pulse pressure determinations by Dinamap were used. Due to the amplification of pressure waves from central to peripheral arteries,[18,19] it is possible that the values of aortic pulse pressure may be slightly underestimated by this procedure. However, we have previously shown[20] that brachial pulse pressure gives an acceptable approximation of intra-aortic pulse pressure because the square root of the brachial-aortic pulse wave velocity ratio does not differ greatly in hypertensive and in normotensive subjects

and is close to one. On the other hand, using invasive studies, Imura *et al*[21] have clearly shown that pulse pressure measured at the site of the brachial artery and of the terminal portion of the abdominal aorta are practically identical in terms of statistical significance.

For estimation of arterial stiffness,[11,12,16] compliance (C) was expressed as C = dV/dP, where dV the systolic-diastolic changes of the volume of the arterial segment, and dP the pulse pressure (systolic minus diastolic BP). Assuming that the increase in volume (dV) is caused only by the distention of the artery (and not by elongation), the cross-sectional compliance CC (compliance per unit of length) can be expressed as CC = dA/dP, where A is the arterial cross-sectional area and dA the systolic-diastolic change in cross-sectional area, using a cylindrical model of the artery. To consider the effect of the distention on the stretching of the arterial wall, we also used the distensibility coefficient DC (distensibility per unit of length), defined as DC = (dA/A)/dP. In the present study, CC and DC were calculated from non simultaneous measurements of pulsatile diameter and pressure on the same arterial segment and, therefore, are presented as estimations rather than as direct measurements.

Carotid wave reflections were obtained using applanation tonometry. The aortic or central artery pulse waveform in humans has been already described and generally shown to be quite similar to the carotid waveform, permitting us to evaluate central wave reflections from carotid tonometry.[17–19] The BP curve is known to manifest an inflection point (IP) that divides the pressure wave into an early (Pi) and mid-to-late systolic peak (Ppk) (Figure 1). The measured pressure waveform consists of both a forward or incident wave, and a backward, or reflected wave. The early systolic peak Pi belongs to the incident pressure wave and is quantified as the ratio (Pi/PP) of the total pulse pressure (PP). The mid to late systolic peak is interpreted as the result of the reflected wave returning from the peripheral site and responsible for an augmentation of the pulse and systolic BP. This augmentation is quantified as the height of the Ppk above Pi and expressed in percent (Ppk–Pi/PP).[16] Reproducibility is 8.1 ± 4.4%. Validation for the evaluation of carotid wave reflections, results from the study of the relationship between the aortic pressure waveform and aortic input impedance, which showed that a larger secondary rise of pulse pressure is associated with a greater oscillatory impedance spectrum due to differences in the magnitude of wave reflection.[19]

In this study all values are given as mean ± SEM. Comparison of arterial parameters and effect of treatment were done using an analysis of variance (ANOVA) followed by a paired Student's *t*-test.[22] The level of significance was $P < 0.05$.

Results

Tables 2 and 3 show that baseline values of BP and arterial parameters did not differ significantly in Groups I and II. Following drug treatment, brachial BP (systolic, diastolic, mean, pulse) decreased significantly ($P < 0.001$) and similarly in both groups.

In the carotid territory, the most predominant change was the significant drug-induced decrease in pulse pressure ($P < 0.01$) (Table 3). There was also a slight ($P < 0.05$) decrease in diastolic diameter, which was similar in Groups I and II.

In the aortic territory, together with the significant decrease in pulse pressure, there was a significant increase in compliance ($P < 0.01$) and distensibility ($P < 0.01$) with insignificant differences between Groups I and II (Table 3). Following drug treatment, diastolic diameter decreased in Group I but remained unchanged in Group II (Interaction $P < 0.01$). This finding was observed even after adjustment for age and baseline diameter.

Carotid wave reflections, evaluated from the (Ppk–Pi)/PP, decreased significantly in Group II and not in Group I (Figure 2) (Interaction: $P < 0.05$). Mean values at D0 and D90 were: for Group I, 0.29 ± 0.04 and 0.19 ± 0.04 (NS); for Group II, 0.34 ± 0.05 and 0.12 ± 0.04 ($P < 0.05$).

In both groups, no substantial change in plasma creatinine, glucose, cholesterol and uric acid occurred following drug treatment. Plasma potassium decreased similarly (–0.36 and –0.33 meq/l in Group I and II) ($P < 0.001$ before and after treatment).

Discussion

In this investigation, Group I (hydrochlorothiazide + amiloride) and Group II (hydrochlorothiazide + captopril) caused a similar decrease in BP. Thus it was possible to compare the drug-induced arterial changes for the same mean arterial pressure and pulse pressure at the carotid and aortic sites. Since no difference occurred between Group I and II for the decrease in carotid arterial diameter and the increase in aortic compliance and distensibility, such arterial changes may be considered as passive and secondary to the decrease in pressure distention. In contrast, two principal differences were observed in the behaviour of Groups I and II. Firstly, the diameter of the terminal aorta decreased in Group I but remained unchanged in Group II. Secondly, carotid wave reflections were markedly modified in Group II but not in Group I.

Whereas aortic diastolic diameter decreased substantially in Group I, no significant change occurred in Group II. Potassium loss does not seem to be responsible for the difference in behaviour since in both groups, the same decrease in serum potassium was observed. It seems more likely that the difference in behaviour between Group I and II may be due to the presence or absence of captopril. Indeed, captopril is known to dilate muscular arteries in hypertensive humans[1,10] and the degree of dilatation is inversely associated with the degree of BP reduction, which tends *per se* to produce a passive decrease in arterial diameter.[1,10] Therefore we suggest that the decrease in aortic diameter in Group I may be the result of a decrease in distension pressure (passive decrease) or of the stimulation of neurohormonal systems (active decrease) or a combi-

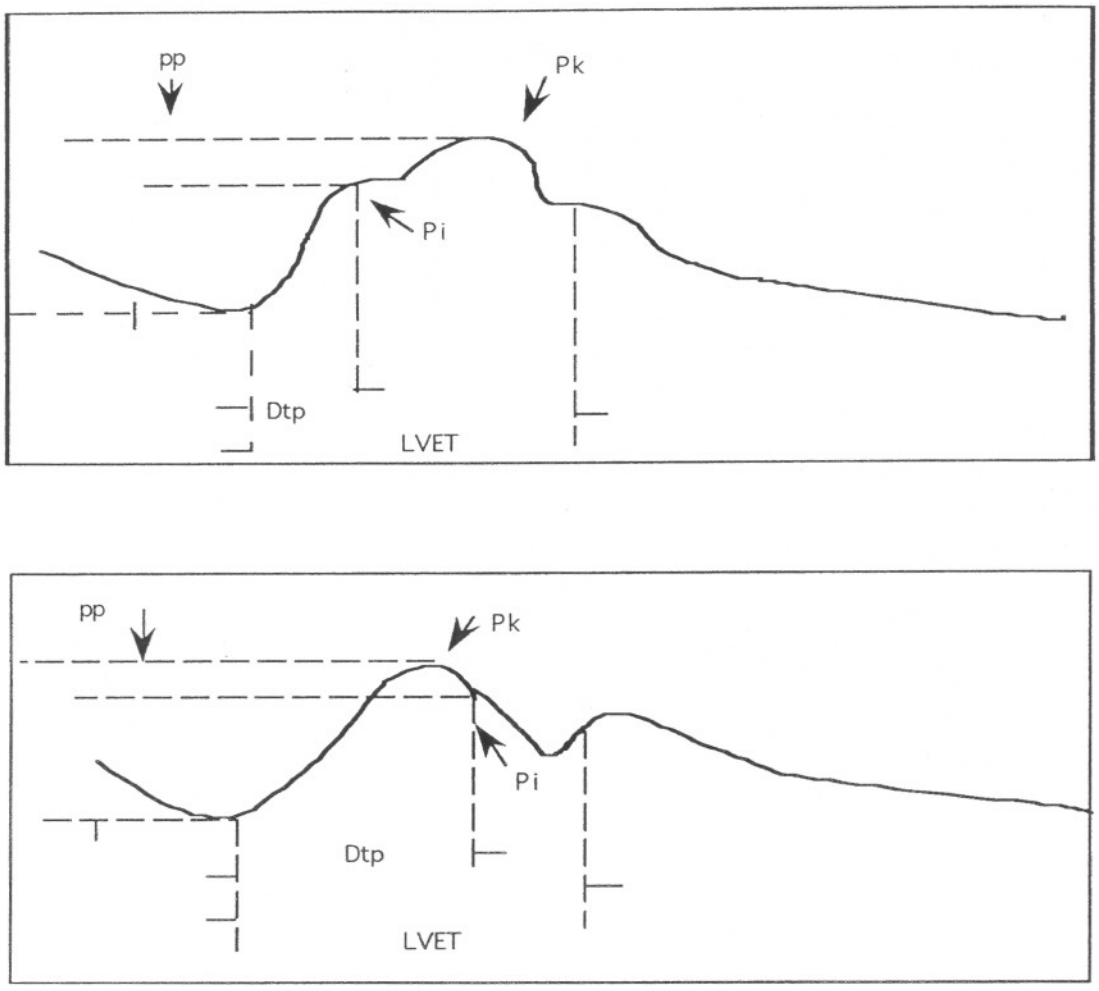

Figure 1 Tonometry changes in the carotid pressure waveform with definition of the calculated parameters for the study of wave reflexions. PP indicates pulse pressure; Pk, late systolic peak; Pi, height of shoulder; Δ P = (Pk–Pi); Δ P/PP, augmentation index; Dtp, time travel of reflected wave; and LVET, left ventricular ejection time. For details see text. Lower panel shows the effect of improved timing of wave reflection on carotid pressure waveform. Due to delayed return (increased Dtp), the reflected wave merges with incident wave in the very late systole and early diastole.

Table 2 Brachial BP and heart rate in Group I and II

		*D*0	*D*90
Systolic BP (mm Hg)	Group I	162 ± 4	136 ± 6***
	Group II	170 ± 5	140 ± 5***
Diastolic BP (mm Hg)	Group I	102 ± 2	86 ± 3***
	Group II	105 ± 2	91 ± 3***
Mean arterial pressure (mm Hg)	Group I	122 ± 2	105 ± 4***
	Group II	126 ± 3	108 ± 4***
Pulse pressure (mg Hg)	Group I	60 ± 3	50 ± 4***
	Group II	64 ± 5	49 ± 3***
Heart rate (b/mn)	Group I	75 ± 3	75 ± 2
	Group II	69 ± 2	72 ± 2

No difference in behaviour was observed between the 2 groups.
D: Day.
±1 s.e.m.
Group I: Hydrochlorothiazide + Amiloride (n = 12).
Group II: Hydrochlorothiazide + Captopril (n = 12).
***$P < 0.001$, D0 *vs* D90.

nation of both. On the other hand, whereas hydrochlorothiazide alone is associated with a decrease in aortic diameter, this decrease is offset in the subjects of Group II by the dilating properties of captopril. Interestingly, this finding is observed at the site of the terminal aorta and not of the carotid artery. Indeed, the amount of vascular smooth muscle is known to be higher in the vascular wall of the terminal aorta than in that of the thoracic aorta and the carotid artery.[19] Nevertheless, whether in Group II the captopril-induced arterial change is due to the angiotension II blockade, to the sympathetic inhibition or to other factors as bradykinin or prostaglandins cannot be documented from the present study.[10]

As well established,[17–19] the modifications of pulse pressure between central and peripheral arteries depend principally on non uniform arterial elasticity of arteries and on peripheral wave reflections. Several reports have previously shown that the (Ppk–Pi)/PP ratio is increased in hypertensive subjects and reflects in this population substantial changes in the amplitude and timing of wave reflections within the thoracic aorta.[17–19] Due to the

Table 3 Mean values of arterial parameters before and after 90 days of treatment

		Carotid artery		*Terminal aorta*	
		*D*0	*D*90	*D*0	*D*90
Diastolic diameter (Dd) (mm)	Group I	7.4 ± 0.4	7.0 ± 0.3*	16.2 ± 0.9	14.6 ± 0.8**[a]
	Group II	7.8 ± 0.2	7.4 ± 0.2*	16.4 ± 0.6	16.4 ± 0.5
Pulse pressure (mm Hg)	Group I	53 ± 3	40 ± 3**	60 ± 3	50 ± 3**
	Group II	51 ± 6	40 ± 4**	64 ± 5	49 ± 4**
Arterial compliance ($m^2.KPa^{-1}.10^{-7}$)	Group I	7.7 ± 0.6	7.7 ± 0.6	22.4 ± 3.1	22.9 ± 2.1
	Group II	6.6 ± 0.7	6.8 ± 0.8	18.7 ± 2.2	26.5 ± 4.2**
Arterial distensibility ($KPa^{-1}.10^{-3}$)	Group I	18.7 ± 1.4	20.2 ± 1.4	11.2 ± 1.5	14.8 ± 1.8**
	Group II	14.5 ± 1.5	15.8 ± 1.5	8.6 ± 0.8	12.7 ± 2.0**

±1 s.e.m.
Group I: Hydrochlorothiazide + Amiloride (n = 12).
Group II: Hydrochlorothiazide + Captopril (n = 12).
*$P < 0.05$; **$P < 0.01$ D90 *vs* D0 at D90.
[a]$P < 0.01$ significant difference between Group I and II at D90.

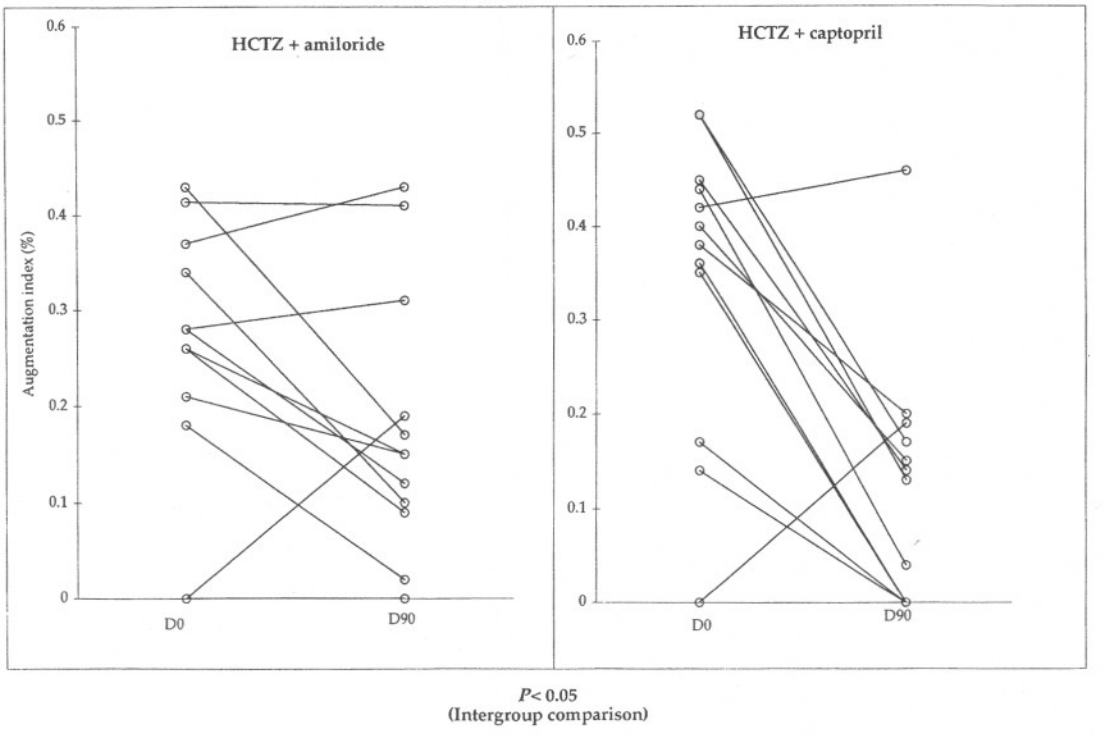

Figure 2 Changes in augmentation index [(Ppk–Pi)/PP ratio] in Groups I and II. For legends, see Tables 1–3.

increased stiffening of large arteries, earlier reflected wave return in hypertensive subjects are observed in the systolic (and not diastolic) component of the thoracic aorta BP curve, creating an elevation in the (Ppk–Pi)/PP ratio. One of the most important findings of the investigation was that the association of captopril to hydrochlorothiazide in Group II produced a significant change in the shape of carotid pulse pressure, with a significant reduction of the late systolic peak as evidenced from the decrease in the (Ppk–Pi)/PP ratio. Significant modifications in wave reflections have been largely documented following converting enzyme inhibition.[1,10,23,24] All of these studies clearly indicate that captopril and related drugs modify substantially the timing of wave reflections, causing the late systolic peak to return in diastole and not in systole. Since this change occurred in Group II but not in Group I, the weight of evidence suggests that this particular arterial change was related to the converting enzyme inhibition due to captopril.

A limit of caution should be added to the results of the present investigation. Because of the relatively small number of subjects, a loss of statistical power may be suspected, leading to an underestimation of the arterial changes produced by the association between hydrochlorothiazide and captopril. Whereas aortic (and not carotid) compliance and distensibility increased more substantially in Group II than in Group I, the expected intergroup difference was not significant (Table 3). On the other hand, in this investigation, the possible interaction

between diuretics and the renin-angiotensin system following drug treatment was simply deduced from the pharmacological intervention and did not involve other information on the status of the renin-angiotensin and of the sympathetic systems or on the degree of salt and water depletion. However, whether such information is more useful than a clear-cut pharmacological study remains the subject of debate and requires to be more extensively documented.[10]

In conclusion, the results of this study show that, for the same BP reduction the association of captopril to hydrochlorothiazide (but not hydrochlorothiazide plus amiloride), caused significant arterial changes, resulting in relative dilatation of muscular arteries and subsequent change in carotid wave reflections. It may be suspected that the modest arterial changes which are observed following diuretic treatment alone might be due to the concomitant stimulation of the renin-angiotensin and the sympathetic systems induced by salt and water depletion.

Acknowledgements

This study was performed with a grant from the Institut National de la Santé et de la Recherche Médicale (INSERM U 337), in the Association Claude Bernard and the Ministère de la Recherche et de la Santé Publique. We thank Mrs Sylvie Minne and Mrs Annette Seban for their excellent assistance.

References

1 Safar ME, Levy BI, Laurent ST, London GM. Hypertension and the arterial system: clinical and therapeutic aspects. *J Hypertens* 1990; **8** (Suppl 7): S113–S119.
2 Asmar RG *et al.* Comparison of effects of felodipine versus hydrochlorothiazide on arterial diameter and pulse-wave velocity in essential hypertension. *Am J Cardiol* 1993; **72**: 794–798.
3 Kool MJ *et al.* Effect of perindopril and amiloride/hydrochlorothiazide on haemodynamics and vessel wall properties of large arteries. *J of Hypertens* 1993; **11** (Suppl 5): S362–S363.
4 Avolio AP *et al.* Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension; comparison between urban and rural communities in China. *Circulation* 1985; **71**: 202–215.
5 Benetos A *et al.* Arterial effects of salt restriction in hypertensive patients. A 9-weeks, randomized double-blind, crossover study. *J of Hypertension* 1992; **10**: 335–360.
6 Benetos A *et al.* Carotid artery mechanical properties of Dahl salt-sensitive rats. *Hypertension* 1995; **25**: 272–277.
7 Draaijer P *et al.* Vascular distensibility and compliance in salt-hypertensive and salt-resistant borderline hypertension. *J Hypertens* 1993; **11**: 1199–1207.
8 Levy BI, Poitevin P, Safar ME. Effects of Indapmide on the mechanical properties of the arterial wall in deoxycorticosterone acetate-salt hypertensive rats. *Am J Cardiol* 1990; **65**: 28H–32H.
9 Laurent S *et al.* Increased response of brachial artery diameter to norepinephrine in hypertensive patients. *Am J Physiol* (Heart Circ Physiol 24), 1988; **255**: H36–H43.
10 Safar ME, Levy BL. Angiotensin converting enzyme inhibitors and large arterial structure and function. In: Robertson JL, Nicholls MG (eds). *The Renin Angiotensin System* (Vol II), Gower Medical: London, 1993, pp 951–959.
11 Hoeks APG, Brands PJ, Smeets GAM, Reneman RS. Assessment of the distensibility of superficial arterial arteries. *Ultrasound Med Biol* 1990; **16**: 121–128.
12 Benetos A *et al.* Arterial alterations with aging and high blood pressure. A noninvasive study of carotid and femoral artery. *Arteriosclr Thromb* 1993; **13**: 90–97.
13 Schoenberger JA, Wilson DJ. Once-daily treatment of essential hypertension with captopril. *J Clin Hypertens* 1986; **4**: 379–385.
14 Weber MA. Clinical experience with converting enzyme inhibitors in hypertension. *Am J Kidney Dis* 1987; **10** (Suppl 1): 45–56.
15 Ambrosini E, Borghi C, Costa FU. Captopril and hydrochlorothiazide: Rationale for their combination. *Br J Clin Pharmacol* 1987; **23**: 435–446.
16 Arcaro G *et al.* Stiffness of the common carotid artery in treated hypertensive patients. *J Hypertens* 1991; **9**: 947–954.
17 Kelly R *et al.* Non-invasive registration of the arterial pressure pulse waveform using high-fidelity applanation tonometry. *J Vasc Med Biol* 1989; **1**: 142–149.
18 London GM *et al.* Increased systolic pressure in chronic uremia: role of arterial wave reflections. *Hypertension* 1992; **20**: 10–19.
19 Nichols WV, O'Rourke MF. McDonald's blood flow in arteries; theoretic, experimental and clinical principles. In: Arnold E (eds). 3rd edn. London, 1990, pp. 77–124, 216–269, 398–411.
20 Isnard NP *et al.* Pulsatile diameter and elastic modulus of the aortic arch in essential hypertension: a noninvasive study. *J Am Coll Cardiol* 1989; **13**: 399–405.
21 Imura T *et al.* Non invasive ultrasonic measurement of the elastic properties of the human abdominal aorta. *Cardiovasc Res* 1986; **20**: 208–214.
22 Sokal RR, Rohlf FJ. Biometry, the Principles of Statistics in Biological Research Freeman and Co, NY, 1981; 321–400.
23 Ting CT *et al.* Arterial hemodynamics in human hypertension: Effects of angiotensin converting enzyme inhibition. *Hypertension* 1993; **22**: 839–846.
24 London GM *et al.* Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease. Comparative effects of ACE inhibition and calcium channel blockade. *Circulation* 1994; **90**: 2786–2796.