590

Journal of Human Hypertension (1991) **5**, 363–368

Long lasting arterial effects of the ACE inhibitor ramipril

Athanase Benetos, Roland Asmar, Daniel Vasmant, Philippe Thiéry and Michel Safar

INSERM (U 337), Broussais Hospital, Paris, France

Summary: **The aim of this study was to determine the acute and chronic arterial effects of the ACE inhibitor, ramipril. Fourteen patients (mean age 47 years) with mild to moderate essential hypertension completed the study. A first haemodynamic examination was performed at the end of a 15-day placebo period (D15) before and 3 hours after oral administration of ramipril, 5 mg. Then all the patients started a 4-week treatment with ramipril, 5 mg/day. At the end of this period (D42) the haemodynamic examination was repeated 24 hours after the last capsule intake, and then 3 hours after administration of ramipril 5 mg.**

Brachial and carotid artery haemodynamics were evaluated by a bidimensional pulsed Doppler system. Arterial distensibility was non-invasively studied in three different arterial segments (carotido-femoral, brachio-radial, femoro-tibial) by the evaluation of the pulse wave velocity.

Ramipril significantly decreased BP after acute or chronic administration. Chronic treatment with ramipril was followed by a long lasting increase in brachial artery diameter, a decrease in forearm vascular resistance, and an improvement in aortic distensibility. The other investigated arterial segments did not show any significant changes.

Our results suggest that long lasting arterial effects of the ACE inhibitor ramipril are partly pressure-independent and are related to an effect of this drug on arterial tone. These effects may be able to reduce the hypertensive cardiac and arterial abnormalities.

Introduction

Hypertension is associated with mechanical, functional and structural alterations of the arterial wall. Experimental, clinical and epidemiological studies have shown that these vascular abnormalities do contribute to the hypertension-induced cardiovascular complications. Moreover, a growing body of evidence suggests that various antihypertensive treatments may have different arterial effects, for the same degree of BP decrease.[1,2]

In other words, there is a dissociation between the BP reduction and the improvement of the arterial abnormalities. These data suggest that BP levels are not the sole factor responsible for the arterial and arteriolar alterations, and that the mechanisms which induce and maintain high BP may affect the arterial wall in different ways.[3]

Angiotensin converting enzyme (ACE) inhibitors are reported to be antihypertensive compounds which decrease BP, reverse cardiac hypertrophy,[4] and improve large artery compliance.[5] Previous studies have shown that the cardiac and arterial effects are not related to the degree of plasma ACE inhibition, nor to the degree of BP decrease.[6,7]

Moreover, there is growing evidence that locally produced angiotensin on the vascular wall exerts autocrine-paracrine effects, and can induce changes in the arterial tone and structure.[8,9] Therefore, it is possible that the arterial effects of ACE inhibitors may be related to a specific effect on the locally produced angiotensin and/or the activation of other vascular mechanisms which can induce a vasorelaxation.

The aim of this study was to determine the arterial effects of the ACE inhibitor ramipril, in

Correspondence: Dr. A. Benetos, Centre de Diagnostic, Hôpital Broussais, 96 rue Didot, 75014 Paris, France.

Accepted: 15 February 1991

relation to the acute and chronic hypotensive action of the drug.

Patients and methods

Fourteen patients (7 males and 7 females) aged 47 ± 3 (mean ± SEM) years with mild to moderate hypertension (diastolic BP = 95–115 mmHg) completed the study. Secondary hypertension was excluded according to appropriate clinical and laboratory criteria. Patients were considered to have established hypertension when they had a diastolic blood pressure (DBP) higher than 95 mmHg measured by sphygmomanometer (Korotkoff phase V) after 10 minutes of rest during two consecutive visits before inclusion.

All antihypertensive treatments were discontinued at least 3 weeks before the study. Sodium intake, estimated by urinary sodium output, was between 80–140 mEq/day. No patient had had cardiac, neurological or renal involvement. Informed consent for the study was obtained from the patients after a detailed description of the procedure.

At the inclusion day D0, the patients were given placebo capsules for a 2-week period. A first haemodynamic investigation was performed at the end of the placebo period (D15). The patients were advised not to take the placebo capsule on the morning of the investigation day. The study was carried out in a temperature-controlled room at 21–22.5°C after 20–30 min. of bed rest, the patients being in the supine position.

Systolic blood pressure (SBP), DBP and heart rate were measured automatically by a Dinamap 845 type device every 2 min. The baseline BP and heart rate were the mean of 8–10 measurements after 20–30 min. of bed rest. Mean blood pressure (MBP) was calculated from DBP plus one third pulse pressure. Peripheral haemodynamic parameters (diameter, mean velocity, and blood flow) were studied in the right common carotid and right brachial arteries, with a bi-dimensional pulse Doppler velocimeter (ALVAR) previously described and validated.[10] The long and short term reproductibility is approximately 3% for the arterial diameter and 14% for blood velocity.[11] Arterial distensibility was evaluated in three different vascular territories by measuring the pulse wave velocity (PWV).[12] The three arterial segments we have studied were the carotido-femoral, the brachio-radial and the femoro-tibial, the first reflecting aortic distensibility and the two others the upper and lower limb arterial distensibility. The inter-observer and intra-observer reproductibility of this method is approximately 6%.[13] After these parameters had been measured, blood was removed for plasma renin-aldosterone and converting enzyme activity. Supine plasma active renin and aldosterone were evaluated by radioimmunoassay.[14] Plasma ACE activity was evaluated by spectrophotometric assay.[15]

At the end of the procedure (≈1 hour), a capsule of the ACE inhibitor ramipril 5 mg was given. Previous studies have shown that 5 mg of ramipril significantly decreased BP, with a maximum effect 3 hours after drug administration.[16,17] Three hours later the procedure was repeated. Investigations were performed in the same order as for the baseline measurements.

All the patients then started a 4-week period of treatment with ramipril 5 mg, one capsule every morning. Patients were seen at the end of this period (D42), when the same procedure as in D15 was followed. Patients were advised not to take their capsule on the morning of the investigation day, so the last capsule was taken 24 h before the time of the investigation. At the end of the procedure, ramipril 5 mg was administered as in D15 and the haemodynamic measurements were repeated 3 hours later.

Statistical analysis

Data in the text and in the figures are given as mean ± SEM. The Wilcoxon test for matched pairs was used for statistical analysis. Correlations were determined by linear regression. The level of significance was 5%.

Results

Figure 1 shows the changes in BP and heart rate throughout the study. The first administration of ramipril dramatically decreased BP by 17 mmHg ± 2.8 for SBP and 11 mmHg ± 1.7 for DBP. Heart rate remained unchanged.

After a chronic 4-week administration, ramipril significantly decreased BP over 24 h. On D42 the residual effect of ramipril 24 h after the last ingestion, was statistically significant (Figure 1). The subsequent administration of ramipril induced a further drop in SBP and DBP by 15 ± 2.2 mmHg and 12 ± 2.0 mmHg respectively. We have found no relationship between the BP response to the first dose of ramipril and its chronic antihypertensive effect, i.e. the degree of BP drop 3 h after the first administration of ramipril could not predict the efficacy of this

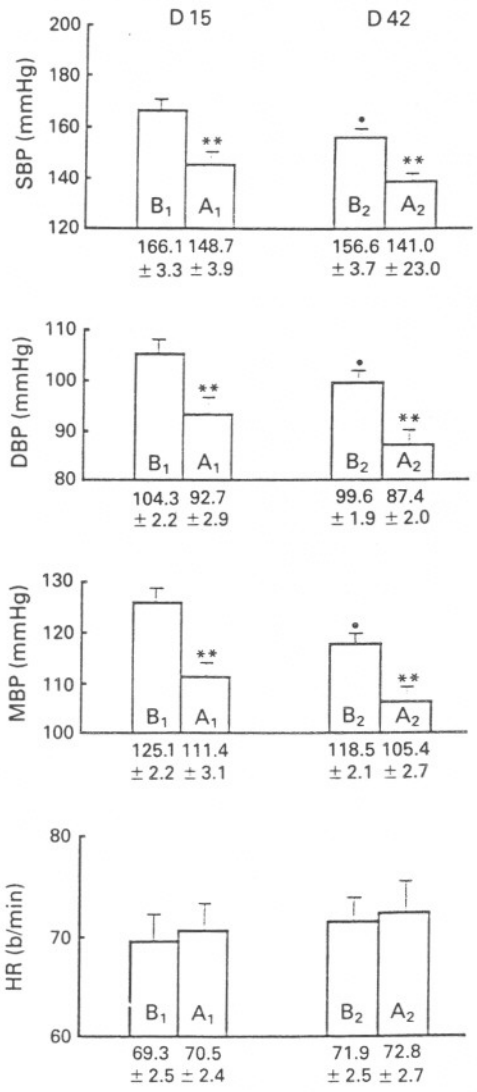

Figure 1 Blood pressure and heart rate changes during the different treatment periods (means ± SEM). B_1: baseline at day 15, A_1: 3 hrs after acute administration at day 15, B_2: baseline at day 42, A_2: 3 hrs after acute administration at day 42, SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, HR: heart rate. $^{*}P<0.01$ B_1 vs. B_2, $^{**}P<0.002$ B vs.A.

drug over 24 h after chronic administration. Angiotensin converting enzyme (ACE) was almost completely inhibited 3 h after the administration of ramipril on both D15 and D42 (Table I).

After chronic administration, ramipril inhibited ACE by more than 50% over 24 h. No correlation was found between the antihypertensive effect and the degree of plasma ACE inhibition after acute or chronic administration. Changes in ACE were followed, as expected, by a decrease in plasma aldosterone levels and an increase in plasma active renin (Table I).

Brachial and carotid artery haemodynamic parameters are shown in Table II. No change in brachial artery haemodynamics was observed after acute administration. However, chronic treatment with ramipril significantly increased brachial artery diameter and decreased forearm vascular resistance. Blood flow velocity and volumic flow remained unchanged. The chronic treatment with ramipril was not able to dilate the common carotid or to decrease local resistance in the carotid circulation. The only change observed in the common carotid artery was a slight but significant decrease in arterial diameter following the first administration of ramipril.

Among the three different arterial segments we have studied, only the carotido-femoral distensibility showed a significant improvement, indicating an important increase of the aortic compliance (Figure 2). Thus, carotido-femoral PWV significantly decreased after acute and chronic administration of ramipril.

A strong positive relationship was found between the changes in carotido-femoral PWV and SBP, but not DBP or MBP, after chronic treatment (B2-B1) (Figure 3). No such correlation was observed following acute administration of the drug.

Safety

Out of 15 patients included after a 2-week placebo period, one patient was excluded for a side-effect (persistent cough at D42). Two patients presented transient and mild side effects which allowed the continuation of the study (one cough, one fatigue).

Discussion

The effects of the ACE inhibitor ramipril on BP, heart rate and peripheral haemodynamic parameters were assessed in the present study. The results of this study are in agreement with previous reports showing that ramipril 5 mg/day was an efficacious antihypertensive drug which reduced BP after acute and chronic administration.[16,17]

Table I Plasma renin, aldosterone and converting enzyme mean values during the different treatment periods (means ± SEM)

		Day 14	*Day 42*
Plasma active renin (μg/ml)	B	24.2 ± 4.2	50.0 ± 8.0^{++}
	A	30.0 ± 5.6	69.5 ± 19.8
Plasma aldosterone (μg/ml)	B	112 ± 22	99 ± 13
	A	61 ± 7*	54 ± 5
Plasma converting enzyme (mU/ml)	B	17.0 ± 1.9	7.5 ± 1.3
	A	1.9 ± 0.5**	1.5 ± 0.4**

*$P<0.05$ B vs. A
**$P<0.001$ B vs. A
$^{++}P<0.001$ D_{42} vs. D_{14}
B: before ramipril administration, A: 3h after ramipril administration

Table II Brachial and carotid artery haemodynamic parameters

		Brachial artery		*Carotid artery*	
		D15	*D42*	*D15*	*D42*
Diameter (cm)	B	0.470 ± 0.023	0.510 ± 0.022**	0.633 ± 0.027	0.609 ± 0.031
	A	0.482 ± 0.026	0.501 ± 0.015	0.604 ± 0.024	0.613 ± 0.025
Mean blood velocity (cm/sec)	B	3.9 ± 0.3	4.0 ± 0.4	18.0 ± 1.1	19.3 ± 1.4
	A	3.8 ± 0.3	4.7 ± 0.4	17.9 ± 1.3	19.9 ± 1.6
Volume flow (ml/min)	B	42 ± 5	49 ± 5	346 ± 36	343 ± 38
	A	44 ± 6	55 ± 5	323 ± 44	358 ± 42
Local resistance (mmHg.sec/ml)	B	205 ± 22	163 ± 15**	24 ± 3	24 ± 3
	A	198 ± 32	140 ± 23	24 ± 3	20 ± 2

**$P<0.02$ baseline D15 vs. baseline D42. *$P<0.05$ before vs. after acute administration.

The residual BP effect (24 h after drug intake) following chronic treatment has shown that ramipril has a long lasting action. These effects observed with ramipril were comparable with those of other ACE inhibitors.[4]

The changes in BP after acute administration were followed by a slight decrease in carotid diameter, and no change in brachial artery parameters. At the same time, we have observed an improvement in aortic distensibility. The changes seemed to be mainly pressure-dependent. Actually, arterial diameter tended to decrease after acute BP reduction for purely mechanical reasons. The sharp decrease in BP after administration of a capsule of ramipril has reduced the arterial wall distension and therefore, increased distensibility. However, unlike acute arterial changes, chronic long lasting arterial haemodynamics could hardly be explained purely by mechanical pressure changes. This statement is based upon the following data.

— Aortic distensibility is improved after chronic treatment as much as after acute administration despite a much less hypotensive effect in the former case.
— Further decrease in BP on D42 after the last administration of ramipril did not induce any further change in aortic distensibility.
— The different arterial segments show heterogeneous responses to the drug.
— Changes in brachial artery haemodynamics occur only after chronic treatment.

These observations suggest that the chronic long lasting arterial effects of ramipril are partly pressure-independent and reflect an effect of this ACE inhibitor on the factors modulating the arterial tone. Actually, ACE inhibitors are shown to inhibit local tissue ACE and thus vascular-generated angiotensin II, and therefore to decrease the vascular tone.[8]

Another hypothesis to suggest is sympatho-inhibitory and/or vagal stimulatory effects of the ACE inhibitors.[18–20] Finally, it has also been suggested that since ACE also breaks down bradykinin, increased plasma or tissue levels of this peptide could participate in the vasodilatory effect of ACE inhibitors.[21,22]

The strong relationship we found between

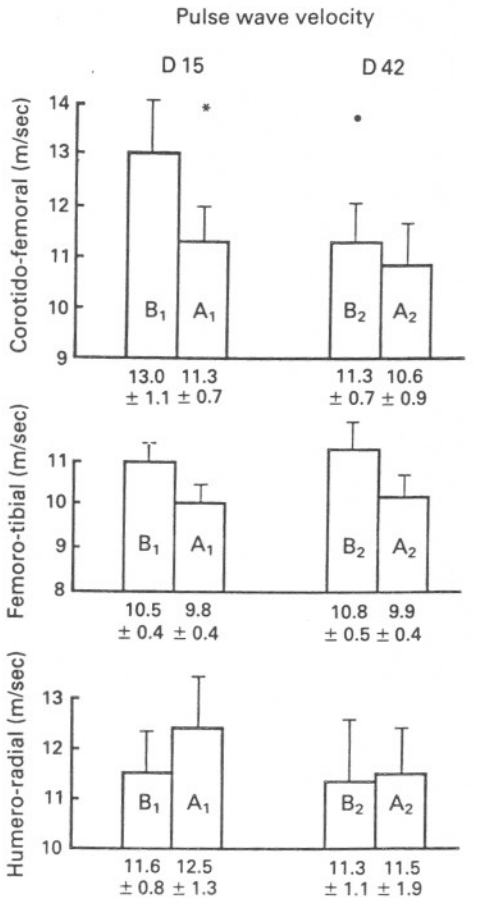

Figure 2 Pulse wave velocity changes during the different treatment periods (for abbreviations see Figure 1). •$P<0.02$ B_1 vs. B_2, *$P<0.01$ B vs. A

SBP decrease and PWV improvement after chronic administration is at variance with our conclusion that the chronic long lasting arterial effects of ramipril are partly pressure-independent, as stated above. Actually one could suggest that PWV changes follow the SBP drop. However no such relationship was found with

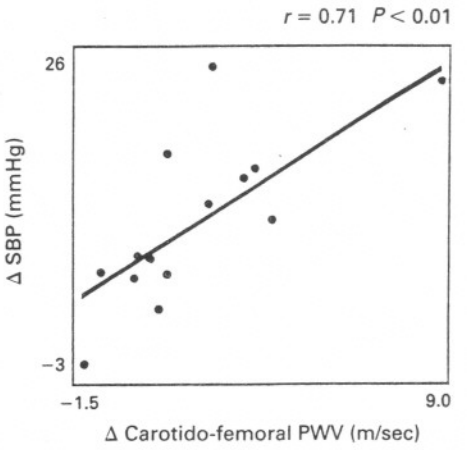

Figure 3 Changes in systolic blood pressure vs. modification in carotido-femoral PWV following chronic treatment, 24 hours after oral administration of ramipril 5 mg.

DBP or mean BP. Hence, we believe that the SBP decrease is the result and not the cause of improved compliance. Previous studies showed that SBP is mainly dependent on the aortic buffering function, i.e. the aortic compliance. Thus, decrease in compliance leads to an exaggerated elevation of SBP.[1] It is therefore possible that drugs improving arterial compliance and distensibility may be capable of decreasing SBP by this mechanism.

Conclusion

Chronic long lasting arterial effects of the ACE inhibitor ramipril seem to be partially pressure-independent: these effects may be able to reduce the hypertensive cardiac and arterial structural and functional abnormalities.

There is a heterogenicity of the different arterial segments in response to the treatment, reflecting anatomical and functional particularities.

Increased aortic distensibility may be partly responsible for chronic long lasting decrease in SBP.

References

1. Safar, M. Therapeutic trials and large arteries in hypertension. *Am Heart J* 1988, **115**: 702–710.
2. Safar, M., Toto Moukouo, J., Bouthier, J., Asmar, R., Levenson, J. & Simon, A. Arterial dynamics, cardiac hypertrophy and antihypertensive treatment. *Circulation* 1987, **75** (Suppl. I): 1156–1161.
3. Mulvany, M. The structure of the resistance vasculature in essential hypertension. *J Hypertens* 1987, **5**: 129–136.
4. Asmar, R., Heve, K., Lacolley, P., Santoni, J.P., Billaud, E. & Safar, M. Treatment for one year with perindopril: effect on cardiac mass and arterial complicance in essential hypertension. *J Hypertens* 1988, **6** (Suppl. 3): S33–S40.

5. Simon, A., Levenson, J., Bouthier, J., Benetos, A., Achimastos, A. & Safar, M. 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.
6. Benetos, A., Santoni, J. Ph., & Safar, M. Vascular effects of intravenous infusion of the ACE inhibitor perindoprilat. *J Hypertens* 1990, **8:** 819–826.
7. Levenson, J., Chau, N., Billaude, E. & Simon, A. Unrelated responses of brachial artery hemodynamics and renin-angiotensin system to acute converting enzyme inhibitors by enalaprilat in essential hypertension. *Am J Cardiol* 1988, **61:** 1056–1060.
8. Dzau, V.J. Circulating versus local renin-angiotensin system in cardiovascular homeostasis. *Circulation* 1988, **77** (Suppl. I): 14–113.
9. Re, R. & Rovigatti, U. New approaches of the study of the cellular biology of the cardiovascular system. *Circulation* 1988, **77** (Suppl. I): 114–117.
10. Levenson, J.A., Peronneau, P.A., Simon, A. & Safar M.E. Pulsed Doppler determination of diameter, blood flow velocity and volumic flow of brachial artery in man. *Cardiovasc Res* 1981, **15:** 164–170.
11. Laurent, S., Juilleart, L., London, G., Nussberger, J., Brunner H. & Safar, M. Increased response of brachial artery diameter to norepinephrine in hypertensive patients. *Am J Physiol* 1988, **255:** H36–H43.
12. Gribbin, B., Pickering, T. & Sleight, P. Arterial distensibility in normal hypertensive man. *Clin Sci* 1979, **56:** 413–417.
13. Asmar, R., Pannier, B., Santoni, J. *et al.* Reversion of cardiac hypertrophy and reduced arterial compliance after converting enzyme inhibitors in essential hypertension. *Circulation* 1988, **78:** 941–950.
14. Ménard, J., Guyenne, T., Corvol, P., Pau, B., Simon, D. & Roncucci, R. Direct immunometric assay of active renin in human plasma. *J Hypertens* 1985, **3** (Suppl. 3): S275–S278.
15. Le Treut, A., Coullious, H., Delbary, M., Larzul, J.J., De Labarthe, B. & Le Gall, J.Y. Le dosage de l'enzyme de conversion de l'angiotensine I par méthode spectrophotométrique. *Clin Chem Acta* 1979, **98:** 1–4.
16. Heber, M., Brigden, G., Caruana, P., Lahiri, A. & Raftery, E. First dose response and 24-hour antihypertensive efficacy of the new once-daily angiotensin converting enzyme inhibitor ramipril. *Am J Cardiol* 1988, **62:** 239–245.
17. Tochikubo, O., Asahina, S. & Kaneko, Y. Effect of ramipril on 24-hour variability of blood pressure and heart rate in essential hypertension. *Am J Cardiol* 1987, **59:** 83D–85D.
18. Morganti, A., Grassi, G., Giannattasio, C. *et al.* Effects of angiotensin converting enzyme inhibition on cardiovascular regulation during reflex sympathetic activation in sodium-replete patients with essential hypertension. *J Hypertens* 1989, **7:** 825–835.
19. Ajayi, A.A., Lees, K.R. & Reid, J.L. Effects of angiotensin converting enzyme inhibitor perindopril on autonomic reflexes. *Eur J Clin Pharmacol* 1986, **30:** 177–182.
20. West, J., Smith, S., Stallard, T. & Littler, W. Effects of perindopril on ambulatory intra-arterial blood pressure, cardiovascular reflexes and forearm blood flow in essential hypertension. *J Hypertens* 1989, **7:** 97–104.
21. Benetos, A., Gavras, H., Stewart, J., Vavrek, R., Hatinoglou, S. & Gavras, I. Vasodepressor role of endogenous bradykinin assessed by a bradykinin antagonist. *Hypertension* 1986, **8:** 971–974.
22. Carretero, O., Miyazaki, S. & Scicli, A. Role of kinins in the acute antihypertensive effect of the converting enzyme inhibitor, captopril. *Hypertension* 1981, **3:** 18–25.