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The effect of enalapril on baroreceptor mediated reflex function in normotensive subjects

J. F. GIUDICELLI[1], A. BERDEAUX[1], A. EDOUARD[2], C. RICHER[1] & D. JACOLOT[2]
[1]Service de Pharmacologie Clinique et [2]Service d'Anesthésiologie, Hôpital de Bicêtre, 94270 Le Kremlin-Bicêtre, France

1 The effects of enalapril, 20 mg orally, on the responses to baroreflex activation and deactivation by respectively phenylephrine and nitroglycerin were investigated in normotensive subjects on a normal sodium diet, with simultaneous measurement of plasma renin activity (PRA), converting enzyme activity (PCEA), aldosterone and catecholamines.
2 Enalapril, 4 h after administration, lowered arterial blood pressure without modifying heart rate and plasma catecholamines. PCEA was abolished, PRA increased and plasma aldosterone decreased.
3 Enalapril (a) displaced to the left the baroreflex set-point, (b) did not affect baroreflex sensitivity since the slopes of the RR-interval/systolic blood pressure regression lines remained unchanged during both activation and deactivation and (c) did not modify baroreflex efficacy since the maximal RR-interval responses as well as the overall RR-interval-time products to identical blood pressure variations were not modified.
4 Thus, enalapril induced a resetting of the baroreflex, which probably accounts for the lack of reflex tachycardia observed during the drug-induced fall in blood pressure.

Keywords enalapril baroreflex sensitivity baroreflex resetting normotensive volunteers

Introduction

A common feature to all angiotensin I-converting enzyme inhibitors (ACEIs) is that these drugs lower blood pressure without affecting heart rate, both in normotensive subjects and in hypertensive patients (Cody *et al.*, 1979; Brunner *et al.*, 1981; McGregor *et al.*, 1981; Imai *et al.*, 1981; Gavras *et al.*, 1982). The absence of reflex tachycardia during the blood pressure fall has led a number of investigators to study the possible interferences of ACEIs with the arterial baroreflex (BR) function (Mancia *et al.*, 1982; Warren *et al.*, 1983; Ibsen *et al.*, 1983). However, conflicting conclusions have often been reached, that may be accounted for by the fact that the studies were performed either in normotensive or in hypertensive subjects who in addition were often on different types of sodium diets. Since (a) BR function is diminished in hypertensive patients (Bristow *et al.*, 1969; Warren *et al.*, 1983), (b) the effects of ACEIs on BR function are influenced by sodium diet (Hatton *et al.*, 1981), and (c) both BR sensitivity (BRS) and BR set-point modifications may account for the lack of reflex tachycardia with ACEIs (Hatton *et al.*, 1981),

Correspondence: Dr J. F. Giudicelli, Service de Pharmacologie Clinique, Hôpital de Bicêtre, 78, rue du Général Leclerc, 94270 Le Kremlin-Bicêtre, France

in this study investigated the effects of enalapril on arterial baroreflex function in normotensive subjects on a normal sodium diet.

Methods

Subjects

The effects of enalapril on arterial BR were investigated in six normotensive male subjects, aged 22 to 57 years, weighing 60 to 82 kg and on a normal sodium diet (100 mmol Na^+/day for at least 5 days prior to the study). Before their admission at the hospital for a traumatic pathology of mild gravity (four cases of thoracic trauma with rib fractures and two cases of abdominal stab wounds without visceral lesions), these subjects had never suffered any disease interfering with arterial BR function such as hypertension, cardiac and/or renal failure, diabetes mellitus, chronic hypoxia or peripheral neuropathy. They were investigated two days before leaving the hospital, when they had completely recovered from their traumatic pathology and had resumed a normal gastrointestinal function and a normal oral alimentary intake. The supine control blood pressure and heart rate values for the group were 131 ± 7/68 ± 6 mm Hg and 64 ± 5 beats min^{-1}. Biological parameters values were all within the normal range. All subjects had normal chest X-ray and electrocardiogram and none was receiving any medication at the time of the study. All gave informed consent to the investigation which was approved by the hospital ethical committee.

Experimental protocol

The subjects remained in the supine position during the 2 h preceding the onset of the study and then throughout its whole duration. They were continuously infused with dextrose 5% (50 ml h^{-1}) through a catheter placed into the basilic vein. Pulsatile arterial blood pressure was measured by a 18G-catheter inserted percutaneously and under local anesthesia into the controlateral radial artery and connected to a Statham P23Db pressure transducer. Blood samples for plasma renin activity (PRA), converting enzyme activity (PCEA), aldosterone and catecholamines were collected from the same catheter. An electrocardiogram (lead II) was recorded throughout the study for RR-interval calculation and heart rate was measured by means of a cardiotachometer triggered by the ECG. All data were recorded on a Gould Allcograf EN 216 multichannel polygraph.

Systolic arterial blood pressure, heart rate and RR-interval were recorded and BR testing was performed before and 4 h after oral administration of enalapril, 20 mg, i.e. at the time of the peak haemodynamic effects of the drug (McGregor *et al.*, 1981; Gavras *et al.*, 1982). BR testing was performed by sequential intravenous bolus injections of increasing doses (50–150 μg) of phenylephrine and nitroglycerin in order to respectively raise and lower systolic arterial pressure by 20–30 mm Hg. Each injection was followed by a 10–15 min rest period to allow heart rate and blood pressure to return to basal levels.

Arterial blood samples for PRA, PCEA, aldosterone and catecholamines measurements were drawn (a) after 2 h rest in the supine position and just before the first BR testing (S1), (b) 15 min after the end of the first BR testing and just before enalapril intake (S2) and (c) 4 h after enalapril intake and just before the second BR testing (S3).

Baroreceptor reflex analysis

For each individual, control RR-interval values were obtained by averaging over five successive beats immediately before the vasoactive drug was infused. Then, each RR-interval value was plotted as a function of the preceding systolic blood pressure value. Baroreflex set-point was defined as the highest (during activation by phenylephrine) or lowest (during deactivation by nitroglycerin) systolic blood pressure value inducing no variation in RR-interval (Eckberg, 1980). The analysis was then performed beat by beat beginning only after the first noticeable change in RR-interval. A least squares fit regression line was thus obtained in each subject for each vasoactive drug and the corresponding r correlation coefficients were calculated before and after enalapril. Further analysis of the data was performed only when r was 0.80 or greater.

In three and four subjects respectively, the phenylephrine, 50 μg, and nitroglycerin, 50 μg, doses did not increase or lower SBP by 20–30 mm Hg and the 150 μg doses of both phenylephrine and nitroglycerin were used in these three subjects. In the subjects where 2 or 3 doses of phenylephrine and nitroglycerin were used, the slopes of the individual regression lines obtained at the 2 or 3 different doses did not differ from each other or from those obtained after the 100 μg dose (as well before as after enalapril). Thus, in order to preserve homogeneity, only the data obtained with the 100 μg doses of both phenylephrine and nitroglycerin are reported in the Results and BR sensitivity (BRS) was expressed

as the mean ± s.e. mean of the slopes of the individual regression lines for each vasoactive drug before and after enalapril.

In addition, we calculated (a) the mean maximal variations (from control values) of systolic blood pressure and RR-interval induced, before and after enalapril, either by phenylephrine or by nitroglycerin (Goldstein, 1983) and (b) the total magnitude of the mean variations in mean arterial pressure and RR-interval from control values by integrating them over the time taken by these parameters to return to their control levels by planimetry. These products are referred to as 'pressure-time product' (mm Hg s) (McRitchie *et al.*, 1976) and 'RR-interval-time product' (ms s).

Biological parameters determinations

Plasma renin activity (PRA) was assessed by radioimmunoassay according to Ménard *et al.* (1972), plasma converting enzyme activity (PCEA) was measured by the spectrophotometric method described by Cushman & Cheung (1971), plasma aldosterone was determined by radioimmunoassay according to Pham Hu *et al.* (1974) and plasma noradrenaline and adrenaline were measured by the double isotope radioenzymatic method described by Brown & Jenner (1981).

Statistical analysis

Data are expressed as means ± s.e. mean.

Statistical analysis of the data was performed using (a) for clinical data (systolic blood pressure, RR-interval, slopes of RR-interval/systolic blood pressure regression lines, pressure-time product and RR-interval-time product) the Wilcoxon *t*-non parametric test, and (b) for biological data analysis of variance.

Results

On the day prior to the study, the 24 h mean urinary sodium excretion was 167 ± 15 mmol.

Effects of enalapril on cardiovascular and biological parameters

Four hours after its oral administration, enalapril, 20 mg, significantly reduced systolic arterial blood pressure (from 131 ± 7 to 121 ± 8 mm Hg, ($P < 0.05$) without affecting heart rate (63 ± 5 *vs* 64 ± 5 beats min^{-1}) and RR-interval (985 ± 81 *vs* 982 ± 82 ms) (Figure 1). In addition (Table 1), S3 *vs* S2), enalapril almost completely

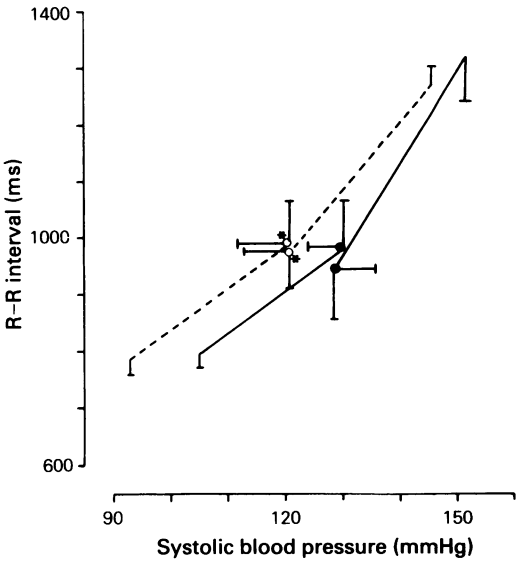

Figure 1 Regression lines between phenylephrine-induced increases in systolic blood pressure and RR-interval and between nitroglycerin-induced decreases in systolic blood pressure and RR-interval before (●—●) and after (○---○) enalapril. Data shown are means ± s.e. mean of individual regression lines obtained in the six subjects. Full and open circles are average control values ± s.e. mean for systolic blood pressure and RR-interval before baroreflex testing. Value significantly different from the corresponding pre-enalapril value: $*P < 0.05$.

abolished PCEA ($P < 0.001$), significantly increased PRA ($P < 0.05$), tended to decrease plasma aldosterone but did not affect plasma noradrenaline and adrenaline levels.

Effects of enalapril on baroreflex activation by phenylephrine (Table 2)

Before enalapril, mean control values of systolic blood pressure and RR-interval were respectively 128 ± 8 mm Hg and 945 ± 90 ms. Set-point was: 130 ± 6 mm Hg (systolic blood pressure)/945 ± 90 ms (RR-interval). The phenylephrine-induced rise in blood pressure caused a progressive lengthening of the RR-interval. The correlation was significant (range of individual *r* values: 0.86–0.95, Table 2). BRS, expressed as the mean of the slopes of the individual regression lines, was 15.4 ± 3.4 ms mm Hg^{-1} (Table 2).

Four hours after enalapril, the mean control value of systolic blood pressure (121 ± 8 mm Hg) was significantly reduced as compared to the corresponding pre-drug control value ($P < 0.05$) but the mean control RR-interval value (979 ± 70 ms) did not differ from the cor-

Table 1 Mean ± s.e. mean values of plasma renin activity (PRA), plasma converting enzyme activity (PCEA), plasma aldosterone, plasma noradrenaline and plasma adrenaline at S1 (after 2 h rest, just before first baroreflex testing), S2 (15 min after first baroreflex testing and just before enalapril administration) and S3 (4 h after enalapril administration).

	S1	*S2*	*S3*	F^2_{15}	
PRA (ng l^{-1} min^{-1})	32 ± 12	34 ± 10	206 ± 79[a]	4.545	S
PCEA (nmol min^{-1} ml^{-1})	13.5 ± 1.6	13.7 ± 1.8	1.4 ± 0.6[c]	22.964	S
Plasma aldosterone (ng 100 ml^{-1})	7.8 ± 1.9	6.9 ± 1.9	3.2 ± 0.5	2.441	NS
Plasma noradrenaline (pg ml^{-1})	505 ± 65	512 ± 117	504 ± 94	0.002	NS
Plasma adrenaline (pg ml^{-1})	152 ± 19	143 ± 24	171 ± 35	0.289	NS

Value significantly different from corresponding S2 value (Anova): [a]$P < 0.05$; [c]$P < 0.001$

Table 2 Individual and mean ± s.e. mean values of control systolic blood pressure (SBP), of control RR-interval (RR), of RR/SBP *r* correlation coefficients and of the slopes of the RR/SBP regression lines observed during baroreflex activation by phenylephrine before and 4 h after oral administration of enalapril, 20 mg

	Before enalapril				*After enalapril*			
Subjects	*Control SBP (mm Hg)*	*Control RR (ms)*	r *values*	*Slopes of regression lines (ms mm Hg^{-1})*	*Control SBP (mm Hg)*	*Control RR (ms)*	r *values*	*Slopes of regression lines (ms mm Hg^{-1})*
1	120	670	0.95	12.6	108	740	0.92	13.6
2	112	720	0.86	13.6	108	815	0.92	15.9
3	148	1190	0.90	6.7	137	1170	0.84	7.7
4	102	960	0.88	31.2	94	980	0.83	6.4
5	147	950	0.91	12.3	145	1030	0.88	13.3
6	135	1180	0.92	16.2	134	1140	0.83	13.2
mean	128	945		15.4	121[a]	979		11.7
± s.e. mean	± 8	± 90		± 3.4	± 8	± 70		± 1.5

Value significantly different from corresponding pre-enalapril value (Wilcoxon *t* test): [a]$P < 0.05$.

responding pre-drug control value. Set-point was 122 ± 6 mm Hg (systolic blood pressure, $P < 0.05$ *vs* pre-enalapril value)/979 ± 70 ms (RR-interval). Mean maximal phenylephrine-induced rises in systolic blood pressure were identical after (25 ± 4 mm Hg) and before (24 ± 5 mm Hg) enalapril and this was also the case for mean maximal RR-interval lengthening (328 ± 50 after and 365 ± 46 before enalapril). The correlation between systolic blood pressure and RR-interval values recorded during phenylephrine injection was significant (range of individual *r* values: 0.83–0.92, Table 2). BRS, expressed as the mean of the slopes of the individual regression lines, was 11.7 ± 1.5 ms mm Hg^{-1} (Table 2), a value which did not differ significantly from the corresponding pre-enalapril one. Finally, while the RR-interval-time product was not modified by enalapril (3550 ± 807 ms s after *vs* 3850 ± 706 ms s before the drug), the pressure-time product was significantly decreased (212 ± 49 mm Hg s after *vs* 310 ± 68 mm Hg s before enalapril, $P < 0.05$).

Effects of enalapril on baroreflex deactivation by nitroglycerin (Table 3)

Before enalapril, mean control values of systolic blood pressure and RR-interval were respectively 131 ± 7 mm Hg and 982 ± 83 ms. These values were also those defining the set-point. The nitroglycerin-induced drop in blood pressure caused a progressive shortening of the RR-interval. The correlation was significant (range of individual *r* values: 0.83–0.94, Table 3). BRS, expressed as the mean of the slopes of the individual regression lines, was 7.2 ± 1.1 ms mm Hg^{-1} (Table 3).

Four hours after enalapril, the mean control and set-point value of systolic blood pressure (121 ± 9 mm Hg) was significantly reduced as compared to the corresponding pre-drug control value ($P < 0.05$) but the mean control RR-interval value (985 ± 81 ms) did not differ from the corresponding pre-drug control value. Mean maximal nitroglycerin-induced decreases in systolic blood pressure were identical after (−28 ± 3 mm Hg) and before (−26 ± 2 mm Hg) enalapril and this was also the case for mean maximal RR-interval shortening (−200 ± 28 ms and −219 ± 35 ms before enalapril). The correlation between systolic blood pressure and RR-interval values recorded during nitroglycerin injection was significant (range of individual *r* values: 0.90–0.97, Table 3). BRS, expressed as the mean of the slopes of the individual regression lines, was 7.2 ± 0.9 ms mm Hg^{-1} (Table 3), a value which did not differ significantly from the corresponding pre-enalapril one.

Table 3 Individual and mean ± s.e. mean values of control systolic blood pressure (SBP), of control RR-interval (RR), of RR/SBP *r* correlation coefficients and of the slopes of the RR/SBP regression lines observed during baroreflex deactivation by nitroglycerin before and 4 h after oral administration of enalapril, 20 mg

	Before enalapril				*After enalapril*			
Subjects	*Control SBP (mm Hg)*	*Control RR (ms)*	*r values*	*Slopes of regression lines (ms mm Hg^{-1})*	*Control SBP (mm Hg)*	*Control RR (ms)*	*r values*	*Slopes of regression lines (ms mm Hg^{-1})*
1	130	720	0.88	6.0	110	720	0.93	4.3
2	117	790	0.94	7.3	107	790	0.97	6.5
3	144	1230	0.83	9.2	137	1260	0.93	5.8
4	105	950	0.91	2.5	90	1030	0.96	7.4
5	155	1030	0.85	9.7	145	1040	0.90	8.1
6	137	1175	0.83	8.6	134	1072	0.95	11.0
mean	131	982		7.2	121[a]	985		7.2
± s.e. mean	± 7	± 83		± 1.1	± 9	± 81		± 0.9

[a] Value significantly different from corresponding pre-enalapril value (Wilcoxon *t* test): $^{a}P < 0.05$.

Finally, while the RR-interval-time product was not modified by enalapril (7310 ± 893 ms s after *vs* 7183 ± 1038 ms s before the drug), the pressure-time product was significantly increased (390 ±76 mm Hg.s after *vs* 272 ± 58 mm Hg s before enalapril, $P < 0.05$).

Discussion

In this study, the effects of enalapril on arterial baroreflex function were investigated in normotensive subjects on a normal sodium diet 4 h after oral administration of a 20 mg dose, i.e. at the time of peak enalaprilic acid plasma levels (Ulm *et al.*, 1982) and of maximal drug-induced reduction in blood pressure in normotensive (McGregor *et al.*, 1981; Reid *et al.*, 1983) as well as in hypertensive patients (Gavras *et al.*, 1982; Johnston *et al.*, 1983). By that time, PCEA was dramatically decreased, PRA was increased and PA tended to decline. Systolic blood pressure was reduced by 9 ± 1 mm Hg ($P < 0.05$), a value in agreement with previous data in normotensive subjects (McGregor *et al.*, 1981; Ibsen *et al.*, 1983), but heart rate was not drug-affected.

This lack of reflex tachycardia, a classical finding with all ACEIs, has led many authors to investigate the possible interference between ACEIs and BR function, since it could be accounted for either by an alteration of the BRS or by a modification of the BR set-point. To date, a number of studies have been performed either in normotensive subjects or in hypertensive patients under various types of sodium diets, which might possibly explain some conflicting results. Thus, in hypertensive patients on a normal sodium diet, Mancia *et al.* (1982) and Warren *et al.* (1983) found with captopril a displacement to the left of the BR set-point but no modification of the BRS during activation by phenylephrine. During deactivation by nitroglycerin or amyl nitrite, BRS was found to be either unchanged (Warren *et al.*, 1983) or slightly increased (Mancia *et al.*, 1982). However, it has clearly been demonstrated that hypertensive patients have a blunted baroreflex function as compared to a normotensive population (Bristow *et al.*, 1969; Warren *et al.*, 1983) and that their reflex tachycardia to any vasodilation is minimized. Hence, only studies in normotensive subjects really allow an assessment of the effects of a given drug on baroreflex function. Recently, Ibsen *et al.* (1983) have shown that in those conditions enalapril displaces to the left the BR set-point and induces a slight potentiation of BRS during activation by phenylephrine. However, the study was conducted in mildly sodium depleted subjects and in addition BRS to deactivation was not investigated. Our data, obtained from normotensive subjects on a normal sodium diet, clearly indicate that enalapril induces a baroreflex resetting since (a) the set-point was significantly displaced to the left, (b) the BR sensitivity was not modified, as evidenced by the fact that BRS curves were only shifted to the left in a parallel fashion, and (c) the BR efficacy was maintained, as shown by the fact that the maximal RR responses as well as the overall RR-interval-time products to identical blood pressure variations were not modified.

A number of arguments could have contributed to ACEIs-induced BRS alteration: (a) ACEIs eliminate angiotensin II vasoconstrictor effects, modify vasomotor tone, as shown in our experiments by a reduction in phenylephrine pressure-time product and an augmentation in nitroglycerin pressure-time product, and increase arterial compliance (Freslon & Giudicelli, 1983; Ibsen *et al.*, 1983; Simon *et al.*, 1983, 1984) which might have led to an increased baroreceptors firing rate (Randall *et al.*, 1978; Mancia *et al.*, 1982) on the afferent portion of the BR; (b) angiotensin II stimulates receptors in the area postrema inducing an increase in blood pressure and antagonizing centrally the BR (Ferrario *et al.*, 1979; Hatton *et al.*, 1981). Hence, ACEIs by preventing angiotensin II formation could have induced the opposite effects, i.e. a centrally mediated potentiation of the BR; (c) ACEIs could also have interfered with the efferent portion of the BR. Major changes in vagal tone apparently do not occur with ACEIs (Mancia *et al.*, 1982; Millar *et al.*, 1982; Warren *et al.*, 1983) but regarding the sympathetic system, there are contradictory data in the literature. Thus a sympatho-inhibitory effect of ACEIs has been demonstrated in a number of experimental (Casellas *et al.*, 1980; Antonaccio & Kerwin, 1981; Richer *et al.*, 1983) and clinical (Imai *et al.*, 1982; De Leeuw *et al.*, 1983; Warren *et al.*, 1983) studies but was not found by others (Mancia *et al.*, 1982; Millar *et al.*, 1982; Ibsen *et al.*, 1983).

That BR sensitivity and efficacy were not affected by enalapril in this study, either during activation or during deactivation, does not imply that the drug does not exert any of the above-mentioned effects on the different parts of the baroreflex arch. It is not inconceivable that some of these actions do indeed develop to some extent, possibly blunting each other and hence resulting in an overall null effect. Additional experiments are needed to ascertain if this hypothesis is founded. But what our data clearly indicate is that the lack of reflex tachycardia during enalapril-induced decrease in blood

pressure can probably be accounted for by the drug-induced baroreflex resetting.

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