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Effects of captopril on plasma endothelin-1 in patients with essential hypertension

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In cultured human endothelial cells, angiotensin converting enzyme-inhibitor (ACE-I) suppressed endothelin-1 (ET-1) release. The aim of this study was to evaluate the acute effect of ACE-I captopril on plasma ET-1 levels in uncomplicated hypertensive patients.

The study group included 5 normotensive subjects (mean age 40.1 ± 12 years) and 15 hypertensive patients (mean age 42.2 ± 15 years) without signs of organ damage (WHO stage I). Blood samples, for determination of ET-1, plasma renin activity (PRA), plasma aldosterone (PA) and serum angiotensin converting enzyme (SACE), were taken before, 30 and 60 min. after captopril (25 mg) intake. At the same time blood pressure and pulse rate were measured. Captopril administration determined a significant reduction (ANOVA 0.000; $p < 0.05$) of systolic and diastolic blood pressure in essential hypertensive patients. The mean baseline SACE level was significantly higher ($p < 0.05$) in the hypertensive group. After captopril administration, PRA value in both groups was increased similarly ($p < 0.05$), while SACE and PA values were decreased ($p < 0.05$). In hypertensives but not in normotensives the captopril intake determined a significant reduction of plasma ET-1 levels ($p < 0.05$).

The current study demonstrates that, while there was no significant difference in the baseline plasma ET-1 levels between normotensive and hypertensive subjects, plasma ET-1 concentrations were significantly suppressed by captopril in essential hypertensive patients. *J Clin Basic Cardiol 1999; 2: 75–7.*

Key words: Captopril, endothelin-1, essential hypertension.

Endothelin-1 (ET-1), a peptide isolated from the media of cultured vascular endothelial cells, exerts marked vasomodulatory, mainly vasoconstrictive effects [1] and may represent a major factor in the regulation of blood pressure.

Using a highly specific and sensitive radioimmunoassay, Ando et al. [2] demonstrated the presence of ET-immunoreactivity in the plasma of normal subjects.

The relation between ET-1 and blood pressure regulation has been extensively explored [3]. In human essential hypertension, some studies reported that plasma ET-1 levels are increased [4–6]. In contrast, normal or low levels of ET-1 were reported in patients with essential hypertension by other investigators [7, 8].

With regard to renin-angiotensin-aldosterone system studies, using pharmacological doses of ET-1 *in vivo,* have demonstrated a significant increase in plasma aldosterone [9, 10]; in contrast *in vitro* studies reported an inhibitory action of endothelin on renin release from juxtaglomerular cells [11, 12] and a stimulation of aldosterone biosynthesis from adrenal cells [13, 14]. In humans, we have recently shown that plasma ET-1 levels are increased in patients with aldosterone-producing adenoma at diagnosis and reduced after surgical therapy [15] and that in patients with low-renin hypertension plasma ET-1 concentrations are significantly increased with respect to those of normal subjects and patients with normal and high-renin hypertension [16]. Although the exact pathophysiological role of ET-1 remains to be established.

The aim of the study is to evaluate the acute effect of captopril, an angiotensin converting enzyme inhibitor (oral administration) on plasma ET-1 levels in essential hypertensive patients without signs of organ damage.

Methods

The current study was conducted in accordance with the principles of the Helsinki II declaration and informed consent was obtained from all subjects.

The study group included 5 normotensive subjects (3 males and 2 females) without a family history of hypertension (mean age 40.1 ± 12 years), recruited from volunteers employed in our hospital and 15 patients with essential hypertension (10 males and 5 females; mean age 42.2 ± 15 years). None of the subjects and patients were overweight (BMI < 27 kg/m^2) and none were smoking.

Hypertension was defined as elevated blood pressure exceeding 150/90 mmHg for three consecutive measurements over a period of two weeks. Secondary causes of hypertension were ruled out through a comprehensive check-up. They did not receive antihypertensive drugs or, if they had, the drug had been stopped for at least two weeks.

The normal subjects and essential hypertensive patients were maintained on normal sodium (Na) and potassium (K) intake (120–140 mEq/day and 50–60 mEq/day, respectively) for two weeks prior to the testing, and 24 h Na-K urine collection evaluation confirmed the adherence to diet.

All hypertensive patients were in stage I (without signs of organ damage) according to the WHO.

On the day of the study, the fasted subjects were studied between 08.00 and 09.00 a.m. A venous cannule was inserted in the antecubital vein in all subjects in the supine position and they remained supine for 60 min. before venous blood samples were drawn.

The subjects received one tablet of captopril (25 mg) (Acepress, Bristol-Myers Squibb, Italy). Blood pressure and pulse rate were measured before and at 30 and 60 min. after captopril intake. At the same time antecubital venous blood was taken for determination of ET-1, plasma renin activity (PRA), plasma aldosterone (PA) and serum angiotensin converting enzyme (SACE). The blood was transferred to three tubes, one containing EDTA (1 mg/ml), one other supplemented with aprotinin (500 U/ml) in addition and the other without additive.

Plasma and serum were separated by centrifugation at 4 °C and stored at –70 °C until assayed. The aprotinin plasma was

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used for the assay of ET-1. Plasma ET-1 concentration was measured by specific RIA as we have previously described [17]. In brief, ET-1 was extracted from samples with C-18 column (Sep-Pak column) after acidification with 1 ml of 0.1 % trifluoroacetic acid and 2 NHCl (pH = 3), and eluted with 60 % acetonitrile. The extracts were evaporated under nitrogen and then the assay with a specific RIA (RIC-6901, Peninsula Laboratories, Belmont, CA, USA) was performed. Cross-reactivity with ET-2 and ET-3 was 7 %. The intra- and interassay coefficients of variation for ET-1 were 9 % and 12 %, respectively. PRA was measured by methods described by Haber et al. [18] using RIA kits (Sorin, Saluggia, Italy). The intraassay coefficient of variation for PRA was 5.5 % and interassay variability was 16.2 %. PA was measured using the McKenzie and Clements [19] RIA method (Sorin, Saluggia, Italy) with intraassay and interassay coefficients of 10.7 % and 8 %, respectively. SACE activity was determined with procedures reported in our previous study [20].

All data are given as mean ± SD. The statistical calculation was performed using Primer software. The individual values were inserted by group on the sheet and were evaluated using ANOVA followed by Bonferroni's t-test, whenever appropriate. Correlation between ET-1 and other variables was determined by means of linear regression. A p value < 0.05 was considered statistically significant.

Results

All participants completed the study. The groups were well matched for age, and baseline blood pressure values were significantly different between hypertensive and normotensive subjects (ANOVA 0.000; $p < 0.05$) Captopril administration determined a significant reduction (ANOVA 0.000; $p < 0.05$) of the systolic and diastolic blood pressure and heart rate in essential hypertensive patients.

Table 1 summarizes the data of captopril effects on PRA, PA, SACE and ET-1 in this study. The mean baseline SACE levels were significantly higher ($p < 0.05$) in the essential hypertensive group, while the baseline PRA and PA values in the hypertensive patients did not differ from that in the normotensive subjects. After captopril administration, PRA in both groups increased similarly, while SACE and PA decreased.

There was no significant difference ($p > 0.05$) of the baseline ET-1 concentration between the normotensive (8.7 ± 2.6 pg/ml) and the hypertensive (8.3 ± 4 pg/ml) group. In hypertensives but not in normotensives, the captopril administration determined a significant reduction of plasma ET-1 levels. In particular, plasma ET-1 concentrations in essential hypertensive patients were significantly reduced after 60 min. of captopril administration with respect to baseline values (6.5 ± 2.1 pg/ml vs 8.3 ± 4 pg/ml; ANOVA 0.000, $p < 0.05$) (Fig. 1).

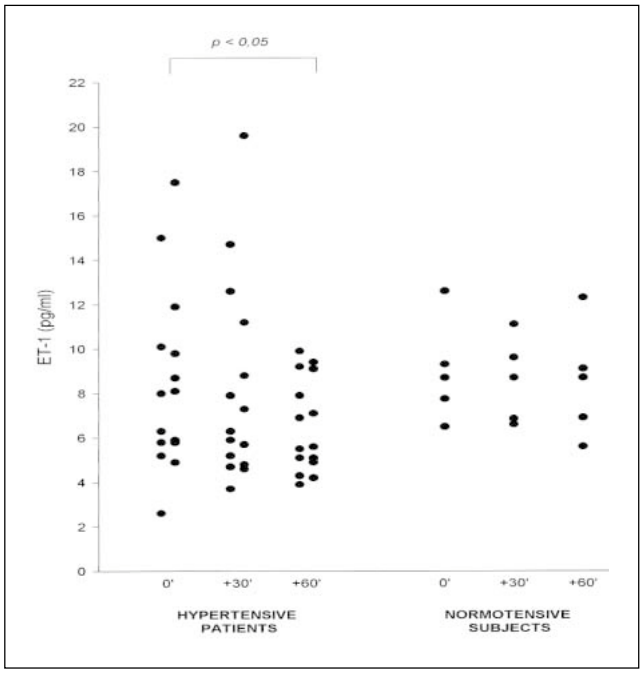

Figure 1. Plasma endothelin-1 levels in both group after captopril administration

There was no significant correlation between ET-1 levels and haemodynamic parameters, PRA, PA and SACE in both groups.

Discussion

The aim of our study was to investigate the potential effects of an angiotensin-converting enzyme inhibitor, captopril, given acutely on ET-1 plasma concentration in essential hypertensive patients and in normotensive subjects.

In the present study we did not observe differences of the baseline plasma ET-1 levels between hypertensives and normotensives. Additionally, in essential hypertensive patients but not in normotensive subjects the acute captopril administration determined a significant drop of plasma ET-1 concentrations. These results confirmed the data reported by Uemasu and coworkers [21]. In fact these authors demonstrated that

Table 1. Effects of captopril on blood pressure, heart rate, plasma renin activity, plasma aldosterone, serum angiotensin-converting enzyme and plasma endothelin-1 in hypertensive and normotensive subjects

Variables	Hypertensive patients (n = 15)			Normotensive subjects (n = 5)		
	Baseline	*+ 30 min*	*+ 60 min*	*Baseline*	*+ 30 min*	*+ 60 min*
SBP (mmHg)	150 ± 15*	141 ± 11.7†	133.6 ± 9.5†	124 ± 11.4	114 ± 6.5	109 ± 4.2††
DBP (mmHg)	98.7 ± 8.2*	88.3 ± 9.6†	84.7 ± 6.9†	81 ± 7.4	80.1 ± 6.1	77.1 ± 5.7
HR (b/min)	74.1 ± 6.4	72.4 ± 5.9	70.9 ± 6.1†	71.1 ± 6.7	72.8 ± 9.2	70.2 ± 9.6
PRA (ng/ml/h)	1.9 ± 1.7	3.2 ± 4.2	5.0 ± 5.9†	2.4 ± 2.1	4.5 ± 5.0	7.6 ± 5.3††
PA (ng/dl)	16.0 ± 7.9	11.9 ± 5.8†	9.1 ± 5.0†	19.6 ± 6.3	11.4 ± 2.1	5.6 ± 1.5††
SACE (nmol/ml/min)	15.1 ± 1.9*	9.9 ± 1.2†	6.2 ± 1.7†	10.0 ± 3.3	7.3 ± 1.9††	4.9 ± 1.6††
ET-1 (pg/ml)	8.3 ± 4	8.2 ± 4.5	6.5 ± 2.1†	8.9 ± 2.3	8.5 ± 1.9	8.5 ± 2.5

SBP = Systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; PRA = plasma renin activity; PA = plasma aldosterone SACE = serum angiotensin converting enzyme; ET-1 = endothelin-1

* $p < 0.05$ vs baseline normotensive subjects; † $p < 0.05$ (ANOVA = 0.000) vs baseline; †† $p < 0.05$ (ANOVA = 0.000) vs baseline.

captopril suppressed the plasma ET-1 levels in essential hypertensive patients with concomitant reduction in blood pressure.

With respect to this study, we explored the response of the SACE and PA to captopril administration and showed that the angiotensin-converting enzyme inhibitor captopril administration significantly reduced these components of the renin-angiotensin system.

ET-1, a peptide isolated from the media of cultured endothelial cells, exerts marked vasomodulatory, with mainly vasoconstrictive effects [1] and may represent a factor in the regulation of blood pressure. Two types of ET-1 receptors have been described: ET-A and ET-B receptors [22, 23]. Both types have been identified in vascular smooth muscle cells and found to mediate vasoconstriction [24], whereas only the ET-B receptor has been identified in endothelial cells.

Plasma levels of ET-1 have been found to be elevated in some but not in all studies of patients with essential hypertension [4–8]. Furthermore, administration of specific endothelin receptor antagonists resulted in reductions in certain animal models of hypertension [25] and in human hypertension [26] suggesting that ET-1 has a role in blood pressure elevation.

The exact mechanism responsible for the drop in ET-1 levels in essential hypertensive patients after acute captopril administration is yet unknown.

Because little is known regarding factors influencing levels of ET-1 in human essential hypertension, it is unclear whether the changes in plasma levels observed after captopril administration reflect direct effects of drug on ET-1 production or whether ET-1 production may be modulated by therapeutic interventions that modify haemodynamic status. In line with this assumption, the administration of captopril resulted in significant reductions in blood pressure values in the present study, and changes in plasma ET-1 levels may reflect these reductions.

Both a sulphydryl (captopril) and non-sulphydryl (enalapril) ACE-inhibitor inhibit ET-1 secretion from cultured human umbilical endothelial cells [27] and enalapril attenuates the increase in ET-1 mRNA levels in the glomeruli of diabetic rats [28]. Mortensen et al. [29] have demonstrated that co-infusion of captopril (1 mg/kg/h) prevented ET-1 induced hypertension in rats, suggesting that an elevation in blood pressure is, in part, caused either by ET-1 induced stimulation of angiotensin II. Since the baseline SACE levels in our essential hypertensive patients were increased with respect to normotensive subjects and the captopril administration determined a significant concomitant reduction of SACE and ET-1 levels, we speculate that the drop in plasma ET-1 concentration might be expected, in part, from blockade of the renin-angiotensin system or through the inhibition of kinin degradation [30] and the release of vasodilatator prostanoids [31]. These endogenous vasodilatators are known to antagonize the vasoconstrictor ET-1. In fact bradykinin inhibited the ET-1 production in cultured human endothelial cells [32].

In conclusion, the current study demonstrates that plasma ET-1 concentrations were significantly suppressed by captopril in the hypertensives but not in normotensives, while there was no difference of the baseline plasma ET-1 levels between normotensive subjects and essential hypertensive patients.

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