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ABSTRACT
The central role of angiotensin II in the pathogenesis of cardiovascular diseases has necessitated the development of pharmacological agents which target the renin-angiotensin-aldosterone system. Angiotensin-converting enzyme (ACE) inhibitors block the conversion of angiotensin I into angiotensin II and have renoprotective and cardioprotective effects in addition to their antihypertensive activity. Blood pressure reduction is achieved with monotherapy with an ACE inhibitor in 35-70% of hypertensive patients. An estimated 20–40% of patients do not respond to and/or tolerate ACE inhibitors. The purpose of this study was to investigate the resistance to ACE-inhibitor therapy caused by ACE-independent generation of angiotensin II. Serum levels of angiotensin II (Ang II) were studied in 30 patients with stage 1 essential arterial hypertension (AH) and 10 healthy controls by commercially available enzyme-linked immunosorbent assay. Hypertensive patients were being treated with lisinopril and only 63.3% had controlled hypertension. Serum levels of angiotensin II were significantly lower in the patients than in the healthy controls (18.7±1.86 pg/ml vs. 20.6±244 pg/ml; p=0.013). Besides, there was no statistically significant difference between the groups with good blood pressure control and with uncontrolled hypertension (18.87 ±1.89 pg/ml vs. 18.4 ±1.86 pg/ml; p=0.53). Previously, we examined the serum chymase levels in the study group and found a significant elevation in the AH patients compared to the healthy controls and similar quantities of serum chymase in the patients with controlled and uncontrolled hypertension. In our current study, a strong positive relationship between chymase and Ang II levels in patients with uncontrolled hypertension(r=0.6518; p=0.03) was observed, in contrast to patients with good blood pressure control (r=0.1113; p=0.65). Our study demonstrated a decrease of angiotensin II serum level in patients with stage 1 essential arterial hypertension treated with an ACE-inhibitor. In addition, a strong positive correlation between chymase and angiotensin II levels in patients with uncontrolled

The effect of ACE-inhibitor therapy on serum level of angiotensin II

Introduction
The renin-angiotensin system has been studied and recognized as one of the major blood pressure–regulating systems for the past century (Arakawa & Urata, 2000).
Angiotensin (Ang) II plays an important role in cardiovascular homeostasis, not only in the systemic circulation but also at the tissue level, and is involved in the remodeling of the heart and vasculature under pathological conditions (Akasu et al., 1998). Several studies with angiotensin I converting enzyme (ACE) inhibitors have demonstrated a remarkable improvement in the morbidity and mortality rates of patients with primary hypertension and congestive heart failure. Since ACE inhibitor therapy not only improves systemic haemodynamics but also provides a better prognosis, the cardiac renin-angiotensin system is apparently one of the major targets of ACE inhibitor therapy (Urata et al., 1994). However, an estimated 20–40% of patients do not respond to and/or tolerate ACE inhibition (Becker et al., 2011). In the last quarter century, many
alternative pathways of angiotensin II formation have been found, and among them, chymase has been a focus of interest because of its specificity and potency in the human cardiovascular system (Arakawa & Urata, 2000). Many studies assume that chymase-dependent Ang II formation as a major molecular mechanism is responsible for the ineffectiveness of ACE inhibition therapy. Company C et al. found that in vivo, Ang II is primarily generated by ACE under basal conditions, but in inflammatory conditions, the release of mast cell chymase amplifies local Ang II concentrations (Company et al., 2011).

The purpose of this study was to investigate the resistance to ACE-inhibitor therapy caused by ACE-independent generation of angiotensin II.

Materials and Methods

Subjects

The study includes 30 patients with stage 1 essential arterial hypertension (AH) (systolic blood pressure of 140–159 mm Hg and/or diastolic blood pressure of 90–99 mm Hg, according to the Guidelines for the management of arterial hypertension). All patients were male, current non-smokers of age between 36 and 69 years. Patients with concomitant diseases of the cardiovascular system or diabetus mellitus were excluded.

All patients had already been diagnosed with hypertension and had been treated with the ACE-inhibitor drug Lisinopril for more than one year. We categorized blood pressure as controlled (systolic blood pressure of <140 mm Hg and diastolic blood pressure of <90 mm Hg) or uncontrolled (systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg). 19 of 30 patients (63.3%) had controlled hypertension. The patients with uncontrolled AH had refused combinatory therapy during that period. The control group consisted of 10 healthy volunteers, age-sex-and-smoking status matched to the patient group.

Informed consent was obtained from all subjects and authorization was given by the Ethics Review Board of the Faculty of Medicine, Trakia University, Stara Zagora. All procedures applied were approved by the Local Ethics Committee of UMHAT "Prof. Soyan Kirkovich", Stara Zagora, Bulgaria.

Serum level of angiotensin II

Quantitative determination of angiotensin II in sera was performed by enzyme-linked immunosorbent assay (ELISA) using a commercially available human angiotensin II ELISA kit purchased from Sigma-Aldrich.

Statistical analysis

Statistical analysis was carried out using statssoft software, version 6. Differences in serum levels of angiotensin II between patients groups and controls were assayed by parametric Student’s t-test and Pearson’s Correlation. In all cases P value less than 0.05 (two-tailed) was considered significant.

Results and Discussion

Our study demonstrated that the serum levels of angiotensin II were significantly lower in the patients than in the healthy controls (18.7±1.86 pg/mL vs. 20.6±2.44 pg/mL; p=0.013) (Figure 1).

Figure 1 Serum levels of angiotensin II were significantly lower in the patients than in the healthy controls (18.7±1.86 pg/ml vs. 20.6±244 pg/ml; p=0.013).

In the total group of patients with arterial hypertension, 17% (5 patients) showed a serum level of angiotensin II higher and 83% (25 patients) showed lower level of Ang II than the average level for the control group (20.6 ± 2.44 pg / mL).

The reduction of angiotensin II (a powerful vasoconstrictor) in the group of hypertensive patients compared to the control group demonstrated effective ACE inhibition therapy. Obviously, the inhibition of the main enzyme (ACE) which converts inactive angiotensin I into
active angiotensin II, results in significant decrease the quantity of Ang II in patients sera.

When the total patients group was subdivided into two subgroups according to the therapy response we observed a prevalence of patients with good response to the ACE-inhibitor therapy. Patients with controlled hypertension were in 63% (n=19) and patients who do not respond to and/or tolerate ACE inhibition were in 37% (n=11). The observed percentage of patients with uncontrolled hypertension in our investigated group was similar to that reported previously (Becker et al., 2011).

The mean serum level of Ang II in both subgroups of patients with controlled and uncontrolled hypertension was similar (18.87 ±1.89 pg/ml vs. 18.4 ±1.86 pg/ml; p=0.53) and significantly lower than control group (p=0.042 and p=0.031, respectively) (Figure 2).

It is well known that other enzymes, such as chymase, kallikrein, cathepsin G, elastase-2 play a role in alternate angiotensin II-generating pathways. Several studies have suggested that chymase might be more important for the formation of angiotensin II on a tissue level, and could be a reason for the resistance to ACE-inhibitor therapy. Previously, we examined the serum chymase levels in the study group and found a significant elevation in the AH patients compared to the healthy controls (99.6±159 vs. 9.34±10pg/ml; p=0.0076). Although the mean serum level of AngII and chymase were similar in the patients with controlled and uncontrolled hypertension, in our current study, a strong positive relationship between chymase and Ang II levels in uncontrolled hypertension (r=0.6518; p=0.03) was observed. In contrast, in patients with good blood pressure control, negligible correlation (r=0.1113; p=0.65) was detected. This result suggests a role of chymase in the formation of Ang II in case of resistance to ACE-inhibitor therapy. However, one limitation of our study is the relatively small number of patients with uncontrolled hypertension. Also, we cannot exclude the role of other enzymes of ACE-independent pathways for generation of Ang II for resistance to ACE-inhibitor therapy.

Conclusion

Our study demonstrated a decrease of angiotensin II serum level in patients with stage 1 essential arterial hypertension treated with an ACE-inhibitor. In addition, a strong positive correlation between chymase and angiotensin II levels in patients with uncontrolled hypertension suggests a role of chymase in the formation of Ang II in case of resistance to ACE-inhibitor therapy.

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References


