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Determinants of increased angiotensin II levels in severe chronic heart failure patients despite ACE inhibition

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Abstract

Introduction: The beneficial effects of ACE inhibitors are generally ascribed to blockade of neurohormonal activation. However, especially in chronic heart failure (CHF) patients plasma angiotensin II and aldosterone levels can be elevated despite ACE inhibition, the so-called ACE escape. In the present study, we aimed to identify the frequency and determinants of ACE escape in CHF patients.
Methods: We studied 99 stable chronic heart failure patients (NYHA class III and IV, 66% ischemic etiology) receiving long-term therapy with ACE inhibitors. In all patients, cardiac, renal, and neurohormonal parameters were measured. ACE escape was defined as plasma angiotensin level $\geq$16 pmol/L.
Results: Mean ($\pm$SD) left ventricular ejection fraction of our 99 patients (79 men and 20 women, age 69 $\pm$ 12 years) was 28 $\pm$ 10%. In addition to an ACE inhibitor, 93% of patients received diuretics, 71% a β-blocker, and 49% spironolactone. None of the patients used an angiotensin receptor blocker. In our population, 45% of the patients had an angiotensin II plasma concentration higher than 16 pmol/L (median concentration was 14.1 pmol/L). Spironolactone use was an independent predictor of elevated plasma angiotensin II levels. Furthermore, spironolactone users had significantly higher plasma active renin protein and aldosterone levels. Plasma angiotensin II concentration was positively correlated to active renin, plasma angiotensin I and plasma aldosterone. No correlation was found between plasma angiotensin II levels and serum ACE activity, dose of ACE inhibitor, or duration of use.
Conclusion: In a group of severe chronic heart failure patients, 45% had elevated plasma angiotensin II levels independent of serum ACE activity despite long-term ACE inhibitor use. Although a causal link could not be proven, an association was found between spironolactone use and active renin protein, angiotensin II and aldosterone levels, suggesting that escape from ACE is mainly caused by a feedback mechanism.

Keywords: Angiotensin II; Chronic heart failure; ACE inhibition

1. Introduction

Inhibition of the renin angiotensin system with ACE inhibitors proved to be beneficial in patients with CHF [1,2]. The clinically favorable outcome of CHF patients using an ACE inhibitor is mainly explained by reduction of angiotensin II formation. However, in patients on chronic ACE inhibition the angiotensin II and aldosterone levels will often rise again, even though plasma ACE level remains suppressed and the antihypertensive effect does not disappear [3–6]. Escape from ACE inhibition occurs particularly in patients with an activated RAS. Activation of the RAS depends on several factors such as medication, salt intake, physical activity, posture and genetic preposition [7–9]. In addition, activity of the RAS is observed in CHF patients and

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in these patients it is related to the severity of CHF. Plasma angiotensin II levels under ACE inhibition vary from less than 10 pg/mL in mild CHF patients to 70 pg/mL in patients with severe CHF [10,11]. Angiotensin II has been viewed as a primary factor causing target organ damage in the cardiovascular system, and aldosterone exacerbates its tissue-damaging properties [12,13]. Moreover, both elevated angiotensin II concentrations and elevated plasma aldosterone levels are associated with poorer prognosis [14,15].

However, predictors of ACE and aldosterone escape have not been well described. Therefore, the present study was designed to measure plasma angiotensin II levels and other neurohormones in heart failure patients on chronic ACE inhibitor therapy in a routine clinical setting, and to identify which factors are related to ACE escape.

Table 1
ACE inhibitor characteristics

	Angiotensin II < 16 pmol/L ($n=54$)	Angiotensin II ≥ 16 pmol/L ($n=45$)	Significance (two-tailed) p-value
Captopril (%, mmd)	27.8 (94 mg)	15.7 (59 mg)	<0.001*
Enalapril (%, mmd)	33.1 (18 mg)	37.8 (13 mg)	0.677*
Fosinopril (%, mmd)	1.9 (10 mg)	6.7 (23 mg)	0.327*
Lisinopril (%, mmd)	27.8 (13 mg)	20.0 (15 mg)	0.481*
Perindopril (%, mmd)	3.7 (2 mg)	17.8 (3.7 mg)	0.040*
Quinapril (%, mmd)	5.6 (23 mg)	2.2 (30 mg)	0.624*
Dose ACE inhibitor (% of recommended daily dose)	72 ± 37	68 ± 37	0.568#
Duration of ACE inhibitor use (months)	46 ± 28	36 ± 30	0.110#

#Independent samples t-test; *chi-square test.
MMD: median daily dose.

2. Methods

2.1. Patients

Between February 2003 and November 2003, we evaluated 106 patients with congestive heart failure New York Heart Association (NYHA) functional class III or IV, as a result of idiopathic dilated cardiomyopathy, ischemic or valvular heart disease, who presented at the Heart Failure Clinic of St Antonius Hospital (Nieuwegein), University Hospital Groningen (Groningen), and Deventer Hospital (Deventer). All had been followed by the outpatient clinic of one of the participating hospitals and all subjects were being treated with stable doses of ACE inhibitor for at least three months. Diagnosis had been made on the basis of medical history, ongoing symptoms and physical examination. All patients had a left ventricular ejection fraction (LVEF) <45%, as assessed by echocardiography or radionucleotide measurement. Every patient had been in a stable clinical condition for at least three months before the study.

Patients who used an angiotensin II receptor blocker were excluded from this study. Various ACE inhibitors were used and the dose of each ACE inhibitor was expressed as a percentage of the maximum recommended dose (Table 1) [16].

The study was approved by each hospital's ethics committee and written informed consent was obtained from all patients.

2.2. Hormonal measurements

Venous blood samples and urine samples were taken at the outpatient clinic while the patient was in an upright position. The blood and urine samples were transported to the local laboratory immediately and each aliquot was processed and stored according to protocol for later batched analysis. The concentration of aldosterone was measured by a sandwich radioimmunoassay (Diagnostic Products Corporation, Breda, The Netherlands). Active renin protein was measured by an immunoradiometric assay (Nichols Institute Diagnostics, Middlesex, United Kingdom) and serum ACE activity was measured by an enzymatic assay (Bühlmann Laboratory AG, Schünenbuch, Swiss). Analyses were performed in a routine setting according to the guidelines of the manufacturer. Angiotensin I and II were measured by specific radioimmunoassays after SepPak extraction of plasma as described previously [17]. ACE escape was defined as an angiotensin II plasma concentration of ≥16 pmol/L (≥16.7 pg/mL), which is twice the upper limit of the reference value used in our laboratory, and comparable to the definition used by Roig et al. [14].

NT-probrain natriuretic peptide (NT-proBNP) was measured by an Elecsys NT-proBNP immunoassay (Roche Diagnostics, Mannheim, Germany).

2.3. Statistics

Values are expressed as mean values ± SD, and neurohormone levels or activity are expressed as median values (25th–75th percentile). Differences between groups were investigated by using the unpaired t-test for independent samples and the chi-square test, when appropriate. Stepwise multiple regression analysis was performed to identify the independent predictors of increased plasma angiotensin II levels. Neurohormonal data were log-transformed before statistical comparison in order to correct for skewness. Linear and logistic regression analysis were performed to identify relations between variables. A p-value <0.05 was considered statistically significant.

3. Results

Of the 106 patients in our study, seven patients were excluded because they either failed to give informed consent ($n=2$), because inadequate venous blood samples were