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The 1166 A/C Polymorphism of the Angiotensin II Type 1 Receptor Gene does not Correlate with the Blood Pressure Response to Angiotensin II in Patients with CHF

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Whether the 1166 (A/C) polymorphism of the Angiotensin II (AII) type 1 receptor (AT1R) gene does correlate with increased vascular reactivity to AII is unclear. Accordingly we measured the blood pressure response to exogenous AII and determined the 1166A/C AT1R gene polymorphism in patients with Chronic Heart Failure (CHF).

40 patients with CHF and functional capacity compatible with NYHA class II-III were studied. All patients were genotyped for the 1166 A/C polymorphism. The frequency of the C allele was 0.2. Radial Artery Systolic Pressure (RASP) was non-invasively monitored using a Colins Pilot Monitor 9200. Ascending doses of AII were administered intravenously to increase RASP by 20 mmHg (AII Pd 20). Patients with CHF exhibited a 10-fold variability in their response to AII with Pd 20 ranging from 2.5 to 25 ng/kg. Patients with AA or AC/CC genotype, had similar AII Pd 20: 11.35 ± 1.18 vs. 13.21 ± 2.2 respectively (p = 0.42). Similarly, among the patients with decreased vascular reactivity who required ≥ 10 ng/kg of AII to achieve Pd 20 (n = 29), RASP response to 10 ng/kg of AII was comparable among patients with AA and AC/CC genotype 22.5 ± 2.8 vs. 21.9 ± 3.3 mmHg respectively (p = 0.9).

In patients with CHF, the doses of AII required to increase BP by 20 mmHg demonstrate a 10-fold variability. The 1166A/C polymorphism of the AT1R gene does not account for the wide range of AII Pd 20. Factors other than 1166A/C polymorphism of the AT1R gene are likely to determine BP response to exogenous AII in CHF patients. J Clin Basic Cardiol 2001; 4: 75–77.

Key words: angiotensin receptor, gene, polymorphism, blood pressure

Angiotensin II (AII) exerts its hemodynamic and tissue remodeling effects via the activation of various signaling and transduction pathways modulated by AII type 1 and 2 receptors [1–3]. Most of the known effects of AII in adult cardiovascular tissues are attributable to the AT1 receptor [4]. A single nucleotide substitution (1166 A/C) in the 3’ non-coding region of the AT1 receptor gene has been described and associated with hypertension (HTN) [5]. Subsequently, the AT1 1166A/C polymorphism was associated with increased aortic stiffness [6], left ventricular mass [7, 8], vascular reactivity [9] and coronary artery vasoconstriction [10]. The AT-1R 1166 A/C polymorphism may identify the patients with high risk vascular disease [11–13] and the need for aggressive therapy, although this is disputed by some investigators [8, 14–18]. Recently in healthy volunteers AT-R1 1166 A/C polymorphism could not be linked to the greater pressure response [9]. The present study was undertaken to determine whether the 1166 A/C AT-1R gene polymorphism affects vascular reactivity in patients with CHF.

Methods

Patient population
25 men and 15 women with CHF were studied. All patients were treated with angiotensin converting enzyme (ACE) inhibitors (lisinopril 40 mg QD or monopril 40 mg QD) and none with AII receptor blockers. Other medication included; furosemide in 89 % of patients, digoxin in 68 %, beta-adrenergic blockade in 55 % and alldactone in 5 %. Mean age and left ventricular ejection fraction was 58 years and 35 % respectively.

The ethnic background was African-American in 12, Hispanic in 13 and Caucasian in 15 patients. The etiology of CHF was hypertension in 22 patients and coronary artery disease in the remaining 18 patients. In addition, 20 patients were diabetic. Functional capacity was compatible with NYHA class III in 29 patients and class II in 11.

Non invasive continuous monitoring of radial artery pressure
Right radial artery waveform was continuously recorded using a Colins Pilot Monitor 9200 (Colins Instruments Corp., San Antonio, TX). Data were stored on the notebook computer using TDA program version 2 from Colins. Analysis of RASP response to ascending dose of AII was completed prior to knowledge of the 1166 A/C AT-1R gene polymorphism.

Drug administration
Angiotensin II: Ascending doses of exogenous AII were administered intravenously to increase RASP by 20 mmHg. The first dose of AII was 2.5 ng/kg. Providing that RASP had not increased by 20 mmHg, the dose was increased by 2.5 ng/kg increment every 10 minutes until desired RASP response had been obtained.

Genotyping
Genomic DNA was extracted from 1 ml of whole blood by standard methods using commercially available kit (S.N.A.P)
from Invitrogen. The genotyping was performed as described by Schmidt et al. [18]. Briefly: the C base substitution at the position 1166 creates restriction site, which can be detected by digestion with the Dde I, enzyme. A-519 bp fragment of the AT-1 gene was amplified by PCR as described [18]. The PCR product was subjected to restriction digestion with 10 U of enzyme Dde I (New England Biolabs, Inc) at 37 °C for 4 hours, followed by analysis using 1.5 % agarose gel electrophoresis. The product derived from the undigested wild-type (A) allele was visible as a fragment of 519 bp, while the product representing the C allele occurred with two bands at 134 and 384 bp. To assure restriction quality of DNA all products were digested completely with 10 U of Hind III enzyme, which generated two bands of 310 bp and 209 bp. All digestions were repeated twice for each sample by two independent investigators.

**Statistical analysis**

Values are expressed as mean ± SEM. To increase the power to detect smaller differences, comparisons were made between AA homozygotes and pooled C allele carriers (AC/CC) by a two sample t-test assuming equal variances. A 2 tailed value of $p < 0.05$ was considered significant.

**Results**

All patients underwent genotyping for the 1166 A/C polymorphism of the AII AT-1R gene. The frequency of the C allele was 0.2; 25 patients had the AA genotype and 15 had AC or CC genotype (AC-13, CC-2). Age, sex, ethnic background, underlying pathology, pharmacological treatment and haemodynamic parameters were equal in both groups at the beginning of the AII infusion. Pd 20 dose of AII varied from 2.5 to 25 ng/kg with the median of 10 ng/kg (Figure 1). The Pd 20 dose of AII were similar in patients with AA and AC/CC allele; 11.35 ± 1.18 vs. 13.21 ± 2.2 respectively ($p = 0.42$) (Figure 2). Twenty-nine patients with low vascular reactivity to AII required ≥ 10 ng/kg of AII to achieve Pd 20. Among these 29 patients, patients with the AA and AC/CC genotype had comparable RASP response to 10 ng/kg of AII: 22.5 ± 2.8 vs. 21.9 ± 3.3 mmHg respectively ($p = 0.9$) (Figure 3).

**Discussion**

Our data indicate that the vascular reactivity of patients with CHF to AII is extremely variable and that the 1166 A/C polymorphism does not account for this variability.

The frequency of the C allele is 0.2 in patients with CHF. It is comparable to that noted in normal controls and patients with hypertension [5, 9, 10, 19, 20]. The 1166 A/C AT1 receptor gene polymorphism was previously associated with increased; aortic stiffness [6], left ventricular mass [7, 8] vascular reactivity [21], coronary artery vasoconstriction [10] and increased risk of myocardial infarction (in synergy with an ACE gene deletion polymorphism) [20]. The association may be due to either an AT1 gene variant or an effect of a still unidentified gene locus in linkage disequilibrium with the AT 1 polymorphism [22]. More recently, the pressure response to AII could not be related to the AT1 gene C polymorphism in young white male subjects [9]. Thus, our observation in older and more diverse (gender and ethnic background) patients with CHF corroborates the experience in healthy white males. As expected, in view of the decreased vascular reactivity to AII reported in patients receiving ACE inhibitors, the dose of AII required to reach Pd 20 was greater in our patients [23].

In summary, our study suggests that the 1166A/C polymorphism of the AT1R gene does not account for the wide range of AII Pd 20. Factors other than 1166A/C polymorphism of the AT-1R gene are likely to determine BP response to exogenous AII in CHF patients.
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