Relation Between Severity of Coronary Artery Disease and Influence of the Angiotensin II Type-1 Receptor Gene Polymorphisms

Koroner Arter Hastalığının Şiddeti ile Anjiyotensin-II Tip 1 Reseptör Gen Polimorfizmi Arasındaki Ilişki

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Geliş Tarihi/*Received:* 26.04.2008
Kabul Tarihi/*Accepted:* 21.08.2008

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ABSTRACT Objectives: Angiotensin II acts mainly via the angiotensin II type 1 receptor (AGT1R). In association studies the C allele has been related to coronary vasoconstriction and endothelial proliferation. We investigated the relationship between the AGT1R gene polymorphism and severity of coronary artery disease in patients with a first anterior acute myocardial infarction (AMI). **Material and Methods:** The subjects were 132 patients (106 men, 26 women, 59 ± 12 years) with a first anterior AMI. Based on the polymorphism of the AGT1R gene, they were classified into two groups: Group 1(AA genotype) of 91 patients and group 2 (AC and CC genotype) of 41 patients. The coronary artery disease extent score was defined by the number of coronary arteries exhibiting a stenosis > 50% diameter reduction. **Results:** There was no significant difference in the baseline characteristics of patients ($p > 0.05$). The coronary artery disease extent score was significantly greater in patients who have AGT1R AC/CC genotype (1.93 ± 0.82) than AGT1R AA genotypes (1.41 ± 0.58) ($p < 0.05$). **Conclusion:** According to our data the existence of a slight association of the AGTR1 gene polymorphism and the coronary artery disease extent in patients with a first anterior acute myocardial infarction can be supposed. We suggested that a slight evidence on the association between the AGTR1 gene polymorphism and the coronary artery disease extent.

Key Words: Polymorphism, genetic; coronary artery disease; myocardial infarction; coronary angiography

ÖZET Amaç: Anjiyotensin II başlıca anjiyotensin-II tip 1 reseptör (AGT1R) üzerinden etki gösterip, C allel ile ilgili çalışmalar koroner vazokonstriksiyon ve endoteliyal proliferasyon ile ilişkili bulunmuş. İlk kez anteriyor akut miyokard infarktüsü (AMİ) geçiren hastalarda, AGT1R gen polimorfizmi ile koroner arter hastalığı şiddeti arasındaki ilişkiyi araştırdık. **Gereç ve Yöntemler:** İlk kez anteriyor AMİ geçiren 132 hasta (106 erkek, 26 kadın) çalışmaya alındı. AGT1R gen polimorfizmine göre hastalar 2 gruba ayrıldı. Grup 1 (AA genotip) 91 hastadan, grup 2 (AC ve CC genotip) 41 hastadan oluşmaktaydı. Koroner arter hastalığı yaygınlık skoru, %50'den fazla daralmaya yol açan koroner arter sayısı olarak tanımlanmaktadır. **Bulgular:** Klinik özellikleri bakımından iki grup arasında anlamlı fark yoktu ($p > 0.05$). Koroner arter hastalığı yaygınlık skoru AGT1R AC / CC genotipli hastalarda (1.93 ± 0.82), AGT1R AA genotipli hastalara (1.41 ± 0.58) göre anlamlı düzeyde daha yüksek bulundu ($p < 0.05$). **Sonuç:** Verilerimize göre, ilk kez anteriyor akut miyokard infarktüsü geçiren hastalarda koroner arter hastalığının yaygınlığı ile AGTR1 geni arasında zayıf bir ilişkinin varlığı öne sürülebilir.

Anahtar Kelimeler: Genetik polimorfizm, koroner arter hastalığı, myoakard infarktüsü, koroner anjiyografi

Turkiye Klinikleri J Cardiovasc Sci 2008;20(3):151-6

Coronary artery disease (CAD) is a multifactorial disorder, influenced by environmental and genetic factors. Experimental studies and clinical trials has shown that the renin-angiotensin system (RAS) affects the patogenesis of CAD and prognosis of myocardial infarction (MI). Three major components of the renin-angiotensin system are renin substrate angiotensinogen; angiotensin-II, which is a crucial biologically active product of the renin-angiotensin system; and the angiotensin-II type-1 receptor (AGTR1). The cellular effects of angiotensin II are mediated by three structurally distinct receptor subtypes, AT_1, AT_2 and AT_4. AT_4 receptors are postulated to have an antifibrinolytic effect. AT_2 receptors inhibition of growth in the late fetal phase. In adult life AT_2 receptors being upregulated in hypertrophy and in heart failure. Angiotensin II acts mainly via the angiotensin II type 1 receptor (AGTR1) as an acute vasoconstrictor that regulates systemic blood pressure and vascular tone. Furthermore, angiotensin II is involved in cardiac and vascular growth processes.[1] A polymorphism in the 3' untranslated region of the AGTR1 has been described, corresponding to an A-C transversion at nucleotide position 1166 of the mRNA sequence. The polymorphism consists of an A or C variant, giving three different possible genotypes: AA, AC, or CC.[2]

A polymorphism in the AGTR1 (an adenine/cytosine [A/C] base substitution at position 1166) has been associated with essential hypertension,[3] increased arterial vasoconstriction,[4,5] and cardiac hypertrophy.[6] The severity of coronary atherosclerosis positively correlates with levels of AGTR1 expression in coronary arteries.[7] In association studies the C allele has been related to coronary vasoconstriction and stenosis.[4,8] Tiret and coworkers[2,9] found an association with the risk of developing hypertension and ischemic heart disease, whereas others have been unable to confirm these findings.[10,11]

Atherosclerosis is a systemic disease and a close correlation is found between coronary artery disease (CAD) and peripheral endothelial dysfunction.[12,13] The severity of coronary atherosclerosis positively correlates with levels of AGTR1 expression in coronary arteries.[7]

In this study, we tested the hypothesis that the AGTR1 gene polymorphism could modify the impact of the coronary anatomy in patients with a first acute anterior myocardial infarction.

MATERIAL AND METHODS

SUBJECT POPULATION

The subjects were 132 consecutive patients (106 men, 26 women, 59±12 years) with a first acute anterior myocardial infarction. The diagnosis of anterior AMI was established with typical chest pain lasting ≥ 30 minutes, diagnostic increase in serum creatine kinase-MB, and the presence of at least two of ECG criteria (ST elevation ≥ 2 mm in precordial derivations, and ≥1 mm in limb derivations). The study protocol was approved by the ethics committee of our department, and informed consent was obtained from all patients. Based on the polymorphism of the AGTR1 gene, they were classified into two groups: Group 1 (AA genotype) of 91 patients and group 2 (AC and CC genotype) of 41 patients.

QUANTITATIVE CORONARY STUDY

Coronary angiograms were performed 132 consecutive patients who were admitted to a coronary angiography laboratory with acute anterior MI. Cardiac catheterisation was performed according to routine procedures. Coronary angiograms were recorded on CD, and analyzed.[14] The coronary arteries were independently analyzed by 2 experienced cardiologists throughout the study who were unaware of clinical and genetic data. Vessel diameters were assessed by caliper reading. CAD was defined as stenosis ≥50% in a major coronary artery or in a major branch. Severity of CAD was classified as 1-, 2-, or 3-vessel disease. The coronary artery disease extent score was defined by the number of coronary arteries exhibiting a stenosis > 50% diameter reduction. Left ventricular ejection fraction (LVEF) was assessed by ventriculography.

DETERMINATION OF THE GENOTYPES

Genomic DNA was extracted from white blood cells. The AGTR1 gene polymorphism was identi-

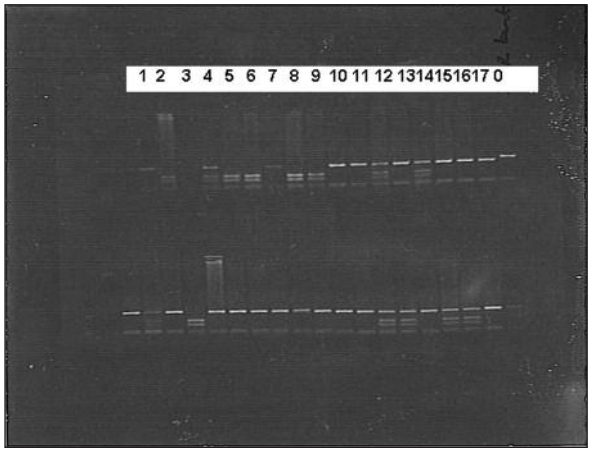

FIGURE 1: Gel electrophoresis of the AGTR1 polymorphism. 0: a DNA size marker (100bp) ,1:AA, 2:CC, 3:AA, 4:AC, 5:CC, 6:CC, 7:AA, 8:CC, 9:CC, 10:AA, 11:AA, 12:AC, 13:AA, 14:AC, 15:AA, 16:AA, 17:AA.

fied by a mismatch-polymerase chain reaction/restriction fragment length polymorphism strategy by a laboratory staff member who was unaware of the clinical details.[15] Digested products were separated with agarose gel electrophoresis (Figure 1).

STATISTICAL ANALYSIS

All data were expressed as mean ± SD. Based on the results of AGTR1 gene polymorphism analysis, the patients were classified into two groups: Group 1; AGTR1 AA genotype, group 2; AGTR1 AC / CC genotype. The various parameters mentioned above were compared between these two groups. The statistical analysis was performed with SPSS for Windows.

Mean, standard deviation and median values were computed for variables. Chi-square and t tests were used for comparisons between groups for categorical and continuous variables, respectively. Pearson or Spearman correlation analyses were used to determine possible correlations between different variables. A p-value less than 0.05 was considered significant.

RESULTS

CLINICAL PARAMETERS

Age, distribution of gender, smoking, hypertension, diabetes mellitus, hyperlipidemia showed no significant differences between the groups (Table 1).

ANGIOTENSIN-II TYPE-1 RECEPTOR GENE POLYMORPHISM

Analysis of AGTR1 gene polymorphism showed that 91 patients belonged to the AGTR1 AA genotype, 36 patients belonged to the AGTR1 AC genotype and 5 patients belonged to the AGTR1 CC genotype. Genotype was not available in 18 cases because of uninterpretable restriction digest. Overall genotype frequencies for wild type (AA), heterozygous (AC), and homozygous (CC) polymorphisms were 91 (69%), 36 (27%), and 5 (4%) among cases. Table 2 shows the genotype distribution and allele frequency of the AGTR1 gene polymorphism in patients with a first anterior AMI. The observed prevalences of the AGTR1 genotypes agree with the frequencies predicted by Hardy-Weinberg equilibrium.

TABLE 1: Clinical characteristics of patients according to AGTR1 gene polymorphism..

	AGTR1 AA Genotype (n= 91)	AGTR1 AC / CC Genotype (n= 41)	p Value
Age (yr)	58±12	60±13	NS
Gender (F/M)	20 / 71	6 / 35	NS
HT	27 (29%)	10 (24%)	NS
DM	9 (9%)	3 (7%)	NS
Smoking	51 (56%)	25 (60%)	NS
Hyperlipidemia	24 (26%)	10 (24%)	NS

AGTR1 : Angiotensin II Type 1 Receptor, F : Female, M : Male,
HT : Hypertension, DM : Diabetes Mellitus, NS : Not significant.

TABLE 2: Angiotensin-II type-1 receptor (AGTR1) genotypes and allele frequencies in patients with a first acute anterior myocardial infarction.

AGTR1 Genotype	Genotype Frequency
AA	91 (69%)
AC	36 (27%)
CC	5 (4%)
AGTR1 Alleles	Allele Frequency
A Allele	218 (83%)
C Allele	46 (17%)

TABLE 3: Angiographic characteristics of patients according to AGTR1 gene polymorphism.

	AGTR1 AA Genotype (n= 91)	AGTR1 AC/CC Genotype (n= 41)	p value
Coronary Score	1.41±0.58	1.93±0.82	< 0.05
LV EF	43.6%	37.3%	< 0.05

AGTR1 : Angiotensin II Type 1 Receptor, LV EF : Left ventricular ejection fraction.

RESULTS OF QUANTITATIVE CORONARY STUDY

The coronary artery disease extent score was significantly greater in patients who have AGTR1 AC/CC genotype than AGTR1 AA genotypes. Also, left ventricular ejection fraction (LVEF) was significantly lower in patients who have AGTR1 AC/CC genotype than AGTR1 AA genotypes (Table 3, p< 0.05). In the correlation analysis age (r= 0.278, p= 0.021), LVEF (r= 0.176, p= 0.04) and AGT1R gene (r= 0.315, p= 0.03) correlated with coronary artery disease extent score (r= 0.278, p= 0.021).

DISCUSSION

Provided that LV function is partly determined by the anatomy of the coronary vessels, at least after myocardial infarction, the study of possible associations between biologic or genetic markers and LV function warrants taking into account these anatomic factors.[16]

Renin-angiotensin system (RAS) was proposed to be involved in the genesis of atherosclerosis, an increasing number of reports have focused on the association of polymorphisms of the RAS and coronary artery disease (CAD).[8,14,17,18]

Angiotensin II, generated at the end of the enzymatic cascade of the RAS, is a powerful vasoconstrictor and a growth-promoting factor for vascular smooth muscle cells.[7,19-21] Because the resulting vascular hypertrophy could play a role in development of arterial wall thickening, it has been proposed that polymorphisms of the angiotensin II type 1 receptor (AGTR1), which appears to be the primary receptor mediating the effects of angiotensin II in human beings, are associated with CAD.[22, 23]

The severity of coronary atherosclerosis positively correlates with levels of AGTR1 expression in coronary arteries.[24] Atherosclerosis is a systemic disease and a close correlation is found between coronary artery disease (CAD) and peripheral endothelial dysfunction.[12,25] Patients who have anterior AMI have a severe coronary atherosclerosis. Therefore we studied patients who have anterior AMI. In the CORGENE study, no relation between the magnitude of coronary atherosclerosis and the presence of the AGTR1 polymorphism.[13] However, Nakauchi et al. have suggested that the AGTR1 polymorphism in Japanese patients was related to severity of coronary stenosis.[8] Also, we have found that significantly greater coronary artery disease extent in patients with AGTR1 AC/CC gene polymorphism. It was an important finding in our study that, in contrast to previous reports.[8,13,17] The AGTR1 A1166C polymorphism tended to be associated with higher CAD risk.

In the present study, it has been shown that there was a relationship between AGTR1 genotypes and CAD severity. CAD severity was higher in AC and CC than AA genotypes. In cases with C allele it can be claimed that have high Ang II level, and complex structural changes related atherosclerosis and/or arteriosclerosis.

A possible physiological mechanism of the presence of a C allele in the AGTR1 gene polymorphism has not been clarified. Several G protein-coupled receptors exhibit down-regulation due to increased agonist stimulation. Miller et.al have suggested that the C allele of the AGTR1 gene polymorphism is related to augmented angiotensin II activity.[26]

Peng et al. have reported that there is no association between AGTR1 gene A1166/C polymorphism and occurrence of early-onset CHD. AGTR1 gene A1166/C polymorphism has no effect on plasma lipid levels.[27] Also, we have found that there is no relationship between AGTR1 gene polymorphism and plasma lipid levels.

Liu et.al have reported that the A1166C polymorphism neither represents a risk factor for adverse events complicating coronary interventions

nor seems to have significant impact on further long-term processes such as development and severity of CAD.[24] Furthermore, Hamon et.al have reported that the subjects homozygous for the AGTR1 CC mutation had a significantly lower ejection fraction than those with allele A (AC+AA).[28] In addition, we found that ejection fraction was significantly lower in patients with AGTR1 CC and AGTR1 AC than AGTR1 AA.

Nevertheless Gurchala et.al have reported that, their study does not support the role of the ACE I/D and AGTR1 A1166C polymorphisms in the determination of the left ventricular size and performance in patients with significant coronary atherosclerosis. However, it indicates that the influence of polymorphisms may be present in specific patient populations.[29] However, in a previous study, we found that ACE I/D gene polymorphisms may affect right ventricular myocardial performance index after a first acute anterior myocardial infarction.[30]

A1166C mutation is located in a nontranslated region of the gene, and it has been shown that the frequency of the C allele is increased in patients with hypertension.[3] However, we found that there is no relationship between AGTR1 gene polymorphism and hypertension. Also, an adenine/cytosine (A/C) base substitution at position 1166 in the AGTR1 gene is associated with the incidence of essential hypertension and increased coronary artery vasoconstriction. These results indicate increased responses to angiotensin II in patients with the CC genotype. The mechanism is preserved during ACE inhibition, which in itself also increased the response to angiotensin II. This reveals that the A1166C polymorphism may be in linkage disequilibrium with a functional mutation that alters angiotensin II responsiveness, which may explain the described relation between this polymorphism and cardiovascular abnormalities .[31] Also, Hindorff et.al have reported that there was a suggestion of increased risk of incident CHF and ischemic stroke associated with the CC genotype, relative to the AA genotype, in white participants with treated hypertension at baseline.[32]

Xue et.al have reported that AGTR1 gene contributed to type-2 Diabetes Mellitus complicated by hypertension, but is only associated with cases of elevated systolic blood pressure.[33] Coll et.al have reported that susceptibility to faster progression to end stage renal disease is associated with the AGTR1 A1166C polymorphism.[34] Moreover, Miller et.al have reported that these results suggest that there is a relationship between the AGTR1 A1166C polymorphism and the humoral and renal hemodynamic responses to AGTR1 blockade and to Angiotensin II infusion in the sodium-replete state, and that the C allele is associated with enhanced intrarenal and peripheral Angiotensin II activity. Further studies are required to determine the genetic locus for this effect.[26] However, the A1166—>C polymorphism in the angiotensin-II type 1 receptor gene does not contribute to the genetic susceptibility to diabetic nephropathy or proliferative retinopathy in caucasian Insulin Dependent Diabetes Mellitus.[35]

There are, however, some limitations of this study that should be noted. As the AGTR1 CC genotype homozygotes are infrequent in the general population, large study groups are required to establish significant associations with diseased phenotype.

CONCLUSION

Our data provide evidence for an association of the AGTR1 gene polymorphism and the coronary artery disease extent in patients with a first anterior acute myocardial infarction. Therefore, we suggested that significantly greater coronary artery disease extent in patients with AGTR1 AC/CC gene polymorphism. However, further studies are required to establish a relation.

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