Association Between A/C1166 Gene Polymorphism of the Angiotensin II Type 1 Receptor and Biventricular Functions in Patients With Acute Myocardial Infarction

Mehmet S Ulgen, MD; Onder Ozturk, MD*; Mehmet Yazici, MD; Mehmet Kayrak, MD; Sait Alan, MD*; Fatih Koç, MD; Selahattin Tekes, MD**

**Background** Although there have been several association studies of angiotensin II type 1 receptor (AT1R, A/C1166) gene polymorphism in clinical endpoints such as myocardial infarction (MI), hypertension, aortic stiffness, and left ventricular mass, the relationship between AT1R polymorphism and biventricular function in acute anterior MI has not been studied before.

**Methods and Results** The study group comprised 132 consecutive patients who were admitted to the coronary care unit with their first acute anterior MI. Systolic and diastolic diameters, volumes, inflow properties, ejection fraction and myocardial performance index of both ventricles were measured. AT1R polymorphism was determined using polymerase chain reaction amplification. Based on A/C1166 polymorphism of AT1R, the patients were classified into 3 groups: group 1, A/A (n=91) genotype, group 2 A/C (n=28), and group 3 C/C (n=13) genotype. When the left ventricular and right ventricular echocardiographic functions were compared, all parameters of the 3 groups were found to be similar. No difference was detected in either the genotype distribution or allele frequencies between the patients and the controls for AT1R.

**Conclusions** The results suggest that A/C1166 polymorphism of AT1R did not influence the risk of either acute MI or biventricular function after anterior MI. (*Circ J* 2006; 70: 1275–1279)

**Key Words:** Gene polymorphism; Myocardial infarction; Ventricular function

A cute myocardial infarction (AMI) is characterized by loss of contractile tissue and changes in ventricular geometry. The presence of congestive heart failure or left ventricular (LV) systolic dysfunction is probably the most important risk factor in patients with AMI. The development of right ventricular (RV) dysfunction has been reported following LV myocardial infarction (MI), and is also associated with increased risk of shock, arrhythmia, and death.

After MI, the process of LV remodeling begins rapidly, usually within the first few hours after an infarct, and continues to progress. Furthermore, it is known that the renin–angiotensin–aldosterone system (RAS) and angiotensin-converting enzyme (ACE) activity contribute to the remodeling process.

Angiotensin II (ATII) is the final effector of the RAS. It is a vasoactive peptide and leads to growth promotion, fibroblast proliferation, and the most potent vasoactive and salt-retaining effector peptide of the RAS, which is involved in blood pressure homeostasis and cardiovascular pathophysiology. Two subtypes of cell surface receptors, ATII type 1 receptor (AT1R) and ATII type 2 receptor (AT2R), have been identified. Most of the actions of ATII are mediated by AT1, which is particularly prominent in the myocardium. Although a number of polymorphisms of the AT1R gene have been identified, one of the most widely studied is an A–C substitution at position 1166 (A/C1166).

Two-dimensional (D) and Doppler echocardiography is a reliable tool for the diagnosis of systolic and diastolic dysfunction. The Doppler echocardiographic myocardial performance index (MPI) called the “Tei index”, combining time intervals of LV contraction and relaxation, has been shown to be a powerful predictor of death and congestive heart failure after MI. This index can be obtained easily, is reproducible and independent of the ventricular geometry, and has been shown to have potential for clinical application in the assessment of overall cardiac function in various disorders. Poulsen et al recently reported that the LVMPI was a powerful predictor of death or congestive heart failure after MI and Moller et al showed that the RVMPI was increased in the acute phase of MI and was significantly correlated with indices of RV systolic dysfunction. In a previous study, we reported higher LVMPI and RVMPI in patients with the DD genotype than in patients with the ID genotype of the ACE gene after anterior AMI.

Although there have been several association studies of the polymorphism of AT1R (A/C1166) in clinical endpoints, such as MI hypertension, aortic stiffness and LV mass to our knowledge the relationship between AT1R polymorphism and biventricular function in anterior MI has not been studied before.
Using the parasternal long-axis view to longitudinally and apically in examination were performed using the parasternal long-axis view with continuous wave or pulsed wave Doppler, with the sample volume positioned just below the aortic valve. The MPI was calculated as the sum of the isovolumic relaxation and contraction times divided by ejection time, which was measured from mitral inflow and LV outflow recordings (Fig 1). Echocardiography was performed by 1 examiner. Five consecutive beats were measured and averaged for each Doppler parameter. The absolute difference for the observer was 0.02±0.03 for MPI.

Assessment of RV Function

The RV inflow was recorded with the transducer in the apical 4-chamber view, aligning the Doppler beam as perpendicular as possible to the plane of the tricuspid annulus. The sample volume was placed at the tips of the tricuspid leaflet during diastole. The RV outflow velocity curve was recorded from the parasternal short-axis view, with the sample volume placed just below the pulmonary valve.

Genetic Analysis

Genomic DNA was isolated from peripheral leukocytes using a commercially available kit. The A1166–C variant of AT1R was identified by polymerase chain reaction (PCR) and restriction fragment length polymorphism analysis, using the primers 5’-GCT TTG TCT TGT TGC AAA AGG-3’ and 5’-CCC ACT CAA ACC TTT CAA-3’ according to the PCR conditions described by Miller et al.

Statistical Analysis

The data were analyzed statistically by computer software (SPSS version 11.0; Chicago, IL, USA) and presented as mean±standard deviation. One-way ANOVA or chi-square tests were used where appropriate to compare groups. 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

Patient Characteristics

There were no significant differences among the 3 different genotype groups in terms of age, hypertension, hypercholesterolemia, other factors of coronary artery disease or peak CK-MB concentrations (p>0.05). At baseline, blood pressure levels and heart rates were similar in all groups (p>0.05) (Table 1). There were no significant differences among the 3 groups with regard to the treatments (thrombolytic agent, β-blocker, nitrate, ACE inhibitor agents) (p>0.05).

Genetic Analysis and Echocardiographic Examination Results

Genetic analysis was performed in all 132 patients.

AMI has not been studied before.

Methods

Patient Selection

We studied 132 consecutive patients (males 106, females 26; mean age 59±12 years, range 42–78) who were admitted to the coronary care unit with their first anterior AMI, defined as: (1) creatine kinase (CK) ≥210 IU and CK-MB ≥20 IU; or (2) electrocardiographic evidence of MI (ST elevation >1 mm); and (3) typical chest pain. The patients were excluded if they fulfilled one of the following criteria: (1) history or ECG findings of previous MI, (2) previous coronary angioplasty or aortocoronary bypass surgery or (3) hypertensive or valvular heart disease. The study protocol was approved by the departmental ethics committee, and informed consent was given by all patients. In the control group, there were 100 healthy blood donor adults without any prior history of disease (70 males, 30 males), who were included to determine the distribution of gene polymorphism in the general population.

Treatment

All patients were treated with thrombolytic therapy (streptokinase 1.5 million units/30 min or tissue type plasminogen activator 100 mg according to the accelerated protocol), acetylsalicylic acid-100, β-blocker (metoprolol 25–50 mg) or angiotensin-receptor blocker (valsartan 80–160 mg) was added to the treatment in the first 24 h, if there was no contraindication.

Echocardiography

Echocardiographic examinations were performed in all patients within 24 h of onset using a Vingmed CFM 800 system equipped with 3.5- and 2.5-MHZ transducers. All examinations were performed using the parasternal long-axis view to assess the ventricular dimensions, the ejection fraction (EF) was calculated by the modified Simpson formula.

Assessment of LV Function

Using conventional echo-Doppler methods, the following parameters were assessed: peak velocities of early (E) and late (A) diastolic filling, the E/A ratio, deceleration time (DT), and isovolumic relaxation time. To obtain mitral flow velocities, a Doppler sample volume was placed between the tips of the mitral leaflets during diastole. LV outflow was recorded from the apical long-axis view with continuous wave or pulsed wave Doppler, with the sample volume positioned just below the aortic valve. The MPI was calculated as the ratio of the isovolumic relaxation and contraction times divided by ejection time, which was measured from mitral inflow and LV outflow recordings (Fig 1). Echocardiography was performed by 1 examiner. Five consecutive beats were measured and averaged for each Doppler parameter. The absolute difference for the observer was 0.02±0.03 for MPI.

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Genetic Analysis and Echocardiographic Examination Results

Genetic analysis was performed in all 132 patients.
Table 1  General Characteristics of the Patient Groups According to A/C1166 Genotype

<table>
<thead>
<tr>
<th></th>
<th>AA (n=91)</th>
<th>AC (n=28)</th>
<th>CC (n=13)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57±13</td>
<td>62±11</td>
<td>56±17</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>16/75</td>
<td>7/21</td>
<td>3/10</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>120.7±23</td>
<td>129.0±26.3</td>
<td>125.0±20.7</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>82.0</td>
<td>81.2±13.1</td>
<td>76.6±8.1</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>87.6</td>
<td>86.3±14</td>
<td>87.1±16.6</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (24%)</td>
<td>8 (29%)</td>
<td>2 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18 (20%)</td>
<td>7 (25%)</td>
<td>3 (24%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>57 (65%)</td>
<td>16 (57%)</td>
<td>8 (61%)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9±3.4</td>
<td>25±2.9</td>
<td>25±3.0</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>29 (32%)</td>
<td>8 (28.6%)</td>
<td>4 (30%)</td>
<td>NS</td>
</tr>
<tr>
<td>CK-MB peak (IU/L)</td>
<td>501±197</td>
<td>490±155</td>
<td>512±179</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td>74 (81%)</td>
<td>24 (85%)</td>
<td>9 (69.0%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Difference with 1-way ANOVA.

Table 2  Angiotensin II Type 1 Receptor (A/C1166) Genotype Distribution and Allele Frequency in Patients and Controls

<table>
<thead>
<tr>
<th>AT1R genotypes, n (%)</th>
<th>AA</th>
<th>AC</th>
<th>CC</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>91 (68.9%)</td>
<td>28 (21.2%)</td>
<td>13 (9.8%)</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>61 (61.0%)</td>
<td>32 (32.0%)</td>
<td>7 (7.0%)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.326</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3  Echocardiographic Data of the Patient Groups According to A/C1166 Genotype

<table>
<thead>
<tr>
<th></th>
<th>AA (n=91)</th>
<th>AC (n=28)</th>
<th>CC (n=13)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral E/A</td>
<td>1.02±0.37</td>
<td>0.91±0.31</td>
<td>0.99±0.33</td>
<td>NS</td>
</tr>
<tr>
<td>Mitral DT</td>
<td>148.2±44.33</td>
<td>153.9±41.7</td>
<td>156.5±41.9</td>
<td>NS</td>
</tr>
<tr>
<td>LVMPI</td>
<td>92.59±20.74</td>
<td>87.2±26.7</td>
<td>90.8±32.2</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDV</td>
<td>0.43±0.23</td>
<td>0.46±0.19</td>
<td>0.40±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>LVEV</td>
<td>98.54±36.50</td>
<td>105.0±38.5</td>
<td>100.5±30.7</td>
<td>NS</td>
</tr>
<tr>
<td>LVESV</td>
<td>64.30±18.37</td>
<td>62.2±24.9</td>
<td>59.1±16.2</td>
<td>NS</td>
</tr>
<tr>
<td>LVDD</td>
<td>0.48±0.55</td>
<td>4.9±0.5</td>
<td>4.9±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>LVSD</td>
<td>3.9±0.63</td>
<td>3.2±0.5</td>
<td>3.2±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Tricuspid E/A</td>
<td>40.3±6.9</td>
<td>41.8±6.4</td>
<td>39.3±4.0</td>
<td>NS</td>
</tr>
<tr>
<td>Tricuspid DT (ms)</td>
<td>1.12±0.33</td>
<td>1.08±0.31</td>
<td>1.13±0.17</td>
<td>NS</td>
</tr>
<tr>
<td>Tricuspid DT (ms)</td>
<td>177.5±98.8</td>
<td>176.5±84.8</td>
<td>163.3±81.6</td>
<td>NS</td>
</tr>
<tr>
<td>RVMPI</td>
<td>0.38±0.24</td>
<td>0.36±0.20</td>
<td>0.35±0.19</td>
<td>NS</td>
</tr>
<tr>
<td>RVDD</td>
<td>3.0±0.41</td>
<td>3.2±0.5</td>
<td>3.2±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>RVSD</td>
<td>2.56±0.44</td>
<td>2.9±0.4</td>
<td>2.7±0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

No significant difference was found among three genotypes in all measured variables by 1-way ANOVA (p>0.05).

Discussion

We found that the LV and RV functions in the early phase of anterior AMI did not differ among the AA, AC, and CC genotypes of AT1R. In addition, we found that the genotype distribution of A/C1166 polymorphism did not differ between the patients and the controls. Our results suggest that A/C1166 polymorphism did not have a clear effect on the LV or RV function in the early phase of anterior AMI.

Previous studies have reported that A/C1166 polymorphism is associated with hypertension, increased arterial
stiffness\textsuperscript{10} and increased risk of cardiovascular disease\textsuperscript{19,20} but others have not confirmed these associations\textsuperscript{23–25}. No evidence of an association was detected between cardiovascular structural phenotype, either LV mass or carotid artery wall thickness, and A/C1166 polymorphism\textsuperscript{23}. Hindorff et al have reported that A/C1166 polymorphism was not associated with blood pressure control or incident cardiovascular events\textsuperscript{26}. Castellano et al found A/C1166 polymorphism to be possibly associated with arterial blood pressure but not to show any relationship with cardiac or vascular structures\textsuperscript{23}. These authors did not advocate a major role for this gene polymorphism as a marker of cardiovascular phenotypes associated with increased cardiovascular risk\textsuperscript{23}. Although Canavy et al found that the genotype distribution of AT1R polymorphism was significantly different between controls and patients\textsuperscript{27} studies of the association between the C allele and coronary disease have been inconclusive\textsuperscript{28,29}. Our data are in agreement with these reports, demonstrating that A/C1166 polymorphism was not associated with AMI.

Positive associations between this polymorphism and disease may be the result of linkage disequilibrium with another polymorphism of functional importance, either within the AT1R gene or one nearby\textsuperscript{23}. The A/C transversion does not characterize per se any functional diversity. Although there is no evidence to support this hypothesis, this polymorphism can be considered solely as a possible marker, in linkage disequilibrium with other functionally relevant genetic variants affecting the structure or expression of the AT1R\textsuperscript{23}.

It was recently shown in some studies that some gene polymorphism has a protective effect against MI, whereas some contribute to susceptibility for MI\textsuperscript{30,31}. Some of the contradictory findings concerning AT1R polymorphism and the risk of MI and hypertension may due has not been found as an independent risk factor for MI or hypertension in either sex\textsuperscript{33,34}. Our results are consistent with these reports and we found no difference in the distribution of the A/C1166 genotype or allele frequency between the patients and the control group in either sex.

**Ventricular Dysfunction in MI**

LV volumes and EF have provided insight into long-term prognosis and mortality rates\textsuperscript{35,36}. In the post-MI population, LV volumes, particularly LV end-systolic volumes, are the strongest prognostic indicators. LVEF measured within the initial 24 h after AMI predicts prognosis throughout the subsequent years\textsuperscript{35,36}.

Subjects homozygous for the AT1R CC mutation may have a lower LVEF compared with those with allele A (AC + AA)\textsuperscript{2}. However, in a recent study, LVEF did not differ among patients with or without the AA or CC genotype. These data question the role of the studied genotypes in the pathogenesis of AMI and contradict the previously supported hypothesis that these genotypes influence prognosis\textsuperscript{37}. Andrikopoulos et al\textsuperscript{37} in their multicenter prospective study of MI patients argued against a measurable effect of I/D polymorphism of ACE and A/C1166 polymorphism of AT1R on early prognosis after AMI. They also showed that carriers of the AT1R-CC genotype did not display either lower LVEF or altered short-term prognosis after MI\textsuperscript{37}. In agreement with that report, in our study LVEF did not differ among patients carrying the AA, AC or CC genotypes.

In many patients, RV dysfunction is due to RV infarction, but in some patients, it may be secondary to LV dys-

function\textsuperscript{38}. RV systolic function appears to be normally maintained, even when anteroseptal wall motion is severely impaired; however, even in the presence of mild anteroseptal wall motion abnormality, RV filling may be impaired without reduced RV systolic function\textsuperscript{2}. In a previous study, Tei et al demonstrated that MPI correlates closely with +dP/dt, –dP/dt, and tau\textsuperscript{39}. This finding indicates that MPI is a measure of overall ventricular function\textsuperscript{16}. MPI is less affected by age and by changes in heart rate and preload than are conventional Doppler measurements\textsuperscript{16} and the index needs no correction for blood pressure, heart rate, or age.

It has been found that LVMPI increases after MI compared with healthy controls\textsuperscript{16} and in these patients LVMPI shows a significant correlation with indices of LV systolic and diastolic function\textsuperscript{5,16}. The RVMPI was increased in the acute phase of MI in patients with or without echocardiographic signs of RVMI compared with controls\textsuperscript{16} and resolved rapidly during follow-up. These findings can be explained by the fact that an infarction that involves the interventricular septum affects LV as well as RV function, which, in theory, produces an increase in MPI\textsuperscript{16}. In our study, we found no significant differences among the AA, AC or CC genotypes, or tricuspid DT or mitral DT. Furthermore, in addition to LVEF, tricuspid and mitral DT, other echocardiographic parameters such as LVMPI, systolic and diastolic volumes, and systolic and diastolic diameters did not differ among the 3 genotype groups. Our results support the hypothesis that this polymorphism cannot be considered solely as a possible marker of ventricular function\textsuperscript{33}.

**Study Limitations**

Our study is the first to investigate the relationship between AT1R polymorphism and biventricular function, assessed by 2-D echocardiography and Doppler indices, on the first day after anterior AMI. For this reason, there are no data in the literature with which to compare our results. Angiography with assessment of infarct-related artery patency was not performed routinely, and reperfusion rates were not measured.

In conclusion, the present study results suggest that A/C1166 polymorphism did not influence the risk of AMI development, or biventricular function after anterior AMI. Because our measurements were performed within the first 24 h after infarction, these results cannot be generalized to a later period after MI.

**References**


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