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Angiotensin-converting Enzyme Gene Polymorphisms, Blood Pressure and Pulse Pressure in Subjects with Essential Hypertension in a South Sulawesi Indonesian Population

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ABSTRAK

Tujuan: meneliti hubungan potensial antara polimorfisme gen ACE, hipertensi esensial dan tekanan nadi. Metode: penelitian ini melibatkan 99 subjek tanpa hipertensi dan 104 subjek dengan hipertensi. Hipertensi didefinisikan sebagai tekanan darah sistolik ≥140 mmHg dan/atau tekanan darah diastolik ≥90 mmHg. Tekanan nadi diukuk pada perbedaan antara tekanan darah sistolik dan tekanan darah diastolik. Amplifikasi DNA untuk menentukan polimorfisme ACE I/D dilakukan dengan metode PCR modifikasi Rigat. Hasil: penelitian ini menunjukkan bahwa tidak ada perbedaan distribusi genotipe dan frekuensi alel yang bermakna antara kedua kelompok. Penelitian ini menemukan bahwa tekanan nadi >60 mmHg berbeda antar genotipe gen ACE. Genotipe DD berisiko 1,8 kali mengalami tekanan nadi >60 mmHg dibandingkan genotipe ID; sedangkan genotipe DD berisiko 4,4 kali mengalami >60mg daripada genotipe II. Kesimpulan: penelitian ini tidak mendukung dugaan bahwa polimorfisme I/D pada locus gen ACE berhubungan dengan hipertensi di Makasar, Sulawesi Selatan, Indonesia. Meskipun demikian, terdapat hubungan yang bermakna dengan tekanan nadi dan tidak tergantung pada tekanan darah.

Kata kunci: polimorfisme gen ACE, tekanan darah, hipertensi, tekanan nadi.

ABSTRACT

Aim: to investigate the potential association between the ACE gene polymorphism, essential hypertension and pulse pressure. Methods: the study included 99 non-hypertensive and 104 hypertensive subjects. Hypertension is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Pulse pressure refers to the differences between the systolic blood pressure and diastolic blood pressure. DNA amplification to examine ACE I/D polymorphism was conducted by Rigat-modification PCR method. Results: this study showed no significant difference in genotype distribution and allele frequency between two groups. We found PP >60 mmHg is different between ACE gene genotype. Genotype DD has a risk of 1.8 times of having PP >60 mmHg than ID genotype while DD genotype has a risk of 4.4 times of having PP >60mg than II genotype. Conclusion: this study does not support that the I/D polymorphism at ACE gene locus associated with hypertension in Makasar, South-Sulawesi, Indonesia. However, there were a significant correlation with pulse pressure independent from blood pressure.

Key words: ACE gene polymorphism, blood pressure, hypertension, pulse pressure.
INTRODUCTION

The renin angiotensin system (RAS) is one of the important factors regulating blood pressure (BP) as well as fluid and electrolyte balance and may have an important role in the pathogenesis of hypertension and target organ damage. Target organ damage is not only positively correlated with level of blood pressure, but also pulse pressure (PP). Pulse pressure >60 are independently associated with CV risk. A genetic variability in the degree of expression of one of the components of its pathway may account for variability in BP as well as PP or may play a role in mediating high BP.¹

Angiotensin-I converting enzyme (ACE) gene is one of the most intensely studied genes because of the key role it plays in the renin–angiotensin system (RAS). ACE catalyses the conversion of angiotensin I to angiotensin II, a vasoactive and aldosterone-stimulating peptide, and inactivates bradykinin. ACE gene is located on chromosome 17q23 and consists of 26 exons and 25 introns. The insertion deletion (I/D) polymorphism in this gene refers to an Alu repetitive sequence 287 bp long, in intron 16, resulting in three genotypes, DD and II homozygotes and ID heterozygotes.²

The I/D polymorphism is reported to determine circulating and tissue ACE levels, such that individuals homozygous for the D allele have higher tissue and plasma ACE concentrations than heterozygotes and II homozygotes.³ This polymorphism has recently been implicated in the pathogenesis of essential hypertension. However, controversial results have been reported from studies on different ethnic groups suggesting that the ACE I/D polymorphism association with essential hypertension might be population dependent.⁴

In the present study we determined the ACE genotype in a South Sulawesi population, to investigate the potential association between the ACE gene polymorphism, essential hypertension and pulse pressure.

METHODS

Subjects

The study included a total of 203 subjects of both sexes, consisting of 99 subjects non-hypertensive and 104 patients with hypertension. The hypertensive individuals were recruited from the Internal Medicine outpatient clinic of the Wahidin Sudirohusodo Hospital and Labuang Baji Hospital in Makassar, South Sulawesi, Indonesia. They had no prior or current use of antihypertensive agents. Arterial BP (systolic and diastolic) was measured twice and the lower value was taken into account. The measurement was performed on the right upper arm by auscultation method after the subject had been seated for at least 5 min. Mercury sphygmomanometers were used and the appropriate adult cuff size was applied.

Hypertension was defined as a sustained diastolic blood pressure ≥90 mmHg that is accompanied by an elevated systolic blood pressure ≥140 mm Hg. Secondary hypertension was minimized using detailed health questionnaire and clinical evaluation, and none had evidence of cardiac or renal failure. The normotensive control subjects were recruited from employee in both hospital. They had no history of hypertension and were not on anti-hypertensive drug therapy. They were between the ages of 40 to 70 years. Pulse pressure was expressed in absolute value (mmHg). Pulse pressure refers to the differences between the systolic and diastolic blood pressure. Based on epidemiological studies, PP above the level of 60 mmHg cause particular risk in patients, therefore we use 60 mmHg as cut off point in this study.⁵

Body mass index was determined for all patients. It was calculated by dividing body weight in kilograms by the square of the height in meters. Patients were categorized as normal (BMI, <25 kg/m²), overweight (BMI, 25–29.9 kg/m²), or obese (BMI, >30 kg/m²).

DNA Studies

Genomic DNA was isolated from peripheral leukocytes as previously reported. The genotype of the ACE gene was determined by the polymerase chain reaction (PCR) according to Rigat et al.² The sense oligonucleotide primer was 5'-CTG GAGACC ACT CCC ATC CTT TCT-3' (1st Base Singapore), and the antisense primer was 5'-GAT GTG CCC ATC ACATTC GTC AGAT-3' (1st Base Singapore). These primers allowed detection of a genomic DNA segment with 490 bp corresponding to the insertion allele (I) as well as a segment with 190 bp corresponding to the deletion allele (D). Reactions were performed in a final volume of 25 ~1, containing 10 pmol of each primer, 20 mmol/l MgCl₂, 100
mmol/l KCl, 500 mmol/l Tris-HCl (pH 8.3) and 2 U Taq DNA polymerase (FastStart Taq DNA Polymerase, Roche Applied Science, German). The amplification profile included a denaturation at 95°C for 30 s and 32 cycles of denaturation at 95°C for 30 s, annealing at 59°C for 60 s, and extension at 72°C for 90 s. The PCR products were resolved in 2% agarose gels (Promega) and visualized with ethidium bromide staining (Promega). To avoid the possibility of mistyping the ID heterozygotes as DD homozygotes, all DD genotypes were reamplified by using a second primer pair specific for the inserted sequence.

**Statistical Analysis**

The values of the data on clinical characteristics of the subject groups were expressed as means. Allele and genotype frequencies in hypertensive and non-hypertensive subjects were analysis by chi-square test. All statistical analysis was performed using Statistical Package for Social Sciences (SPSS) for windows version 17.

**RESULTS**

The characteristics of the 104 hypertensive patients and 99 non-hypertensive subjects who met the criteria are summarized in Table 1.

**Table 1. Clinical characteristic of the non-hypertensive and hypertensive subjects**

<table>
<thead>
<tr>
<th></th>
<th>Hypertensive (104)</th>
<th>Non-hypertensive (99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52.7±7.9</td>
<td>49.5±7.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2±3.2</td>
<td>24.6±3.4</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>154.7±20.7</td>
<td>121.0±9.2</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>98.4±11.4</td>
<td>79.8±4.2</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>56.3±13.9</td>
<td>41.2±8.0</td>
</tr>
</tbody>
</table>

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure

Polymorphism was detected as a 490 bp PCR product corresponding to the insertion allele (I) and/or as a 190 bp corresponding to the deletion allele (D). Genotype and allele frequencies are shown in Table 2 indicating that there was no significant difference in genotype distribution between the hypertensive and non-hypertensive subjects and there was also no significant differences in allele frequency between the groups.

**Table 2. Frequency of ID Polymorphisms of angiotensin-converting enzyme in hypertensive and non-hypertensive subjects**

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Hypertensive (104)</th>
<th>Non-hypertensive (99)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>21 (50.0%)</td>
<td>21 (50.0%)</td>
<td>0.903</td>
</tr>
<tr>
<td>ID</td>
<td>34 (50.0%)</td>
<td>34 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>49 (52.7%)</td>
<td>44 (47.3%)</td>
<td></td>
</tr>
</tbody>
</table>

**Alleles**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.36</td>
<td>0.38</td>
<td>0.802</td>
</tr>
<tr>
<td>D</td>
<td>0.64</td>
<td>0.62</td>
<td></td>
</tr>
</tbody>
</table>

Nevertheless, current study (Table 3) found significant relationship in genotype distribution of pulse pressure between two groups. We found PP >60 mmHg is different between ACE gene genotype. Genotype DD has a risk of 1.8 times of having PP >60 mmHg than ID genotype while DD genotype has a risk of 4.4 times of having PP >60 mg than II genotype.

**Table 3. Frequency of pulse pressure in ACE gene genotypes**

<table>
<thead>
<tr>
<th></th>
<th>Pulse pressure</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;60 mmHg</td>
<td>≤60 mmHg</td>
</tr>
<tr>
<td>Genotypes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>7 (7.5%)</td>
<td>86 (92.5%)</td>
</tr>
<tr>
<td>ID</td>
<td>11 (16.2%)</td>
<td>57 (83.8%)</td>
</tr>
<tr>
<td>DD</td>
<td>11 (26.2%)</td>
<td>31 (73.8%)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The distribution of ACE genotypes is different among ethnic groups all over the world. Therefore, it is important that studies of ACE gene polymorphism be conducted in genetically homogenous populations. The differences in the distribution of ACE genotype may be an important factor in the relative risk of cardiovascular morbidity and mortality in different populations. Nevertheless, evidence that the RAS is an important determinant of BP, and the complimentary findings on the benefit of ACE inhibition, a direct relationship between the I/D ACE polymorphism and hypertension has been difficult to demonstrate. Various reports described the D Allele as a risk factor for essential hypertension in various populations whereas other studies disagree with that hypothesis.46
Our results are consistent with some reports describing that there is no association of I/D polymorphism of ACE gene with hypertension based upon casual blood pressure. Nevertheless, other studies show that the I/D polymorphism of ACE gene is associated with hypertension based upon casual blood pressure. Negative association was also shown in Chinese population, Italian, Greek, Japan and Indian. Whether the controversy is due to ethnic or inclusion criteria variances is unknown and merits further investigation. However, one substantial reason for the controversy could be due to the methodological problems in blood pressure measurement.

However, we found a significant association of I/D polymorphism of ACE gene with pulse pressure. Few animal and clinical study have addressed the relationship between PP and gene polymorphism related to the renin-angiotensin system. The current results suggest that the DD variant of the ACE gene polymorphism is associated with PP. Association of DD variant of ACE gene polymorphism with PP could explain one of the pathomechanisms of target organ damage.

The main limitation of this study is relatively small sample size. Our subjects are not homogenous, because patients are often referred to our hypertension clinic for specific reasons.

**CONCLUSION**

In summary, our cross sectional study does not support that the I/D polymorphism at the ACE gene locus associated with hypertension in Makassar, South Sulawesi, Indonesia. However, we found a significant correlation of I/D polymorphism with pulse pressure independent from blood pressure.

**REFERENCES**