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The Effect of Angiotensin-Converting Enzyme Gene Polymorphisms in the Coronary Slow Flow Phenomenon at South Sumatra, Indonesia Population

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Abstract

BACKGROUND: The coronary slow flow phenomenon (CSFP) is believed to be affected by endothelial dysfunction ruled by renin, angiotensin, aldosterone, and the angiotensin-converting enzyme (ACE). The gene of ACE has been characterized in humans by a major insertion (I)/deletion (D) polymorphism. Serum ACE levels were associated with I/D polymorphism in the ACE-encoding gene.

AIM: This study explored and analyzed the role of ACE gene polymorphism risk factors with the incidence of CSFP in the population of South Sumatra, Indonesia.

METHODS: This study was a cross-sectional analytic observational study. A total of 112 CSFP and non-CSFP patients participated in this study. Blood was obtained from the study subjects then processed. Angiotensin I and aldosterone levels were examined using the enzyme-linked immunosorbent assay. The Judkins method was used in the assessment of coronary angiography, which was carried out through the femoral artery. For the examination of ACE I/D polymorphisms, genome deoxyribonucleic acid was extracted from blood cells (leukocytes), using the Wizard's purification system and examined using the polymerase chain reaction method. All data were evaluated using the Chi-square test, two samples t-test, and Mann-Whitney U-test. All tests used two-sided significance and $p < 0.05$ was considered statistically significant.

RESULTS: ACE I/D gene polymorphism possessed a significant effect in increasing the risk of CSFP. Genotype II polymorphism increased the risk of CSFP as much as 6.9 times compared to individuals with ID/DD genotype. The existence of allele I increased the risk of CSFP 5.7 times compared to allele D. Levels of angiotensin I and aldosterone were increased significantly in patients with CSFP.

CONCLUSION: ACE I/D gene polymorphism possessed a significant effect in increasing the risk of CSFP. Genotype of II was the risk factor for the development of CSFP in population of South Sumatra, Indonesia.

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Keywords: Angiotensin-Converting enzyme; Renin-Angiotensin-Aldosterone system; Gene polymorphisms; Coronary slow flow phenomenon

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Introduction

The coronary slow flow phenomenon (CSFP) is a clinical angiographic disorder that is characterized by late filling of the distal coronary artery during catheterization of the coronary artery using contrast, which causes symptoms of coronary artery stenosis. Although this angiographic disorder has been known for almost five decades, the pathological mechanism is still unclear and not yet comprehensively known. CSFP has serious clinical implications related to the initiation of myocardial ischemia, arrhythmias, cardiac death, and recurrent acute coronary syndromes. Cardiovascular disorders caused by CSFP will cause problems and require substantial funds for the management and rehabilitation of patients. This is further exacerbated by the late diagnosis of CSFP. In general, patients are

known to experience CSFP after coronary syndrome disorder is encountered and after an invasive action in the form of cardiac catheterization. Exploration of pathomechanism and molecular markers related to CSFP is required, to determine the biological changes of this disorder that occurs before the emergence of cardiovascular disorders [1].

Endothelial dysfunction of coronary artery is believed to play an important role in the pathomechanism of CSFP. Increased coronary microvascular tone and vasomotor dysregulation are the basis for coronary endothelial dysfunction. The renin-angiotensin-aldosterone system (RAAS) plays a role in the regulation of vascular and microvascular tone, including coronary artery. This system consists of several proteins, namely, renin, angiotensin, aldosterone, and the angiotensin-converting enzyme (ACE). ACE is one of the important regulators in the RAAS system. This enzyme plays a role

in the conversion of angiotensin I protein to angiotensin II, then aldosterone activation occurs which will be followed by sodium and water retention in the kidney tubules. This will cause an increase in intravascular volume, an increase in cardiac output, an increase in blood pressure, and an increase in vascular and microvascular tone, including coronary artery [2], [3].

Central dogma states that in every expression of a protein, it will definitely be preceded by the process of transcription of the protein-coding gene, then followed by the translation process to produce the target protein. The same applies to ACE enzymes. The expression of this enzyme is influenced by the enzyme-coding gene. Changes that occur in the enzyme-coding gene will cause changes in enzyme levels, which of course greatly affect the function and role associated with the ACE enzyme. The gene of ACE is located on chromosome 17 and has been characterized in humans by a major insertion (I)/deletion (D) polymorphism consisting of the presence of I or an absence of D of a 287-base pairs repeat sequence with 25 intron 16. Serum ACE levels were associated with I/D polymorphism in the ACE-encoding gene. The genotype of DD is associated with increased serum ACE level, compared to genotype of II. The increasing level of ACE increases conversion of angiotensin I to angiotensin II and activates signaling pathway from inflammation, oxidative stress, and increased vascular and cardiovascular tone. Aldosterone is one of the other proteins that regulated the rigidity of vascular tone by increasing the accumulation of fibrotic tissue and is responsible in endothelial dysfunction [4], [5], [6], [7], [8].

This study explored and analyzed the role of ACE gene polymorphism risk factors with the incidence of CSFP in the population of South Sumatra, Indonesia. In addition, this study was the pilot study related to the exploration of the role of ACE gene polymorphisms in the population of South Sumatra, Indonesia.

Methods

Study design

This study was a cross-sectional analytic observational study. Analysis of the role of the ACE gene polymorphism, sociodemography, and history of metabolic and laboratory related metabolic disorders with the incidence of CSFP was carried out in this study.

Study subjects

A total of 112 study subjects (CSFP = 54 subjects and non-CSFP = 58 subjects) participated in this study. The study subjects were patients undergoing coronary angiography with suspected coronary arterial disease, within the period of May 2018–December

2018, at Dr. Moh. Hoesin General Hospital, Palembang, Indonesia. All study subjects possessed normal coronary angiographic result and no atherosclerotic lesions were found in coronary arteries; however, there was a slowdown in coronary flow rates. Each study subject had a history of chest pain that resembled angina symptoms based on myocardial perfusion or treadmill test. Subjects who were taking vasoactive drugs were not included in this study. Every patient had taken informed consent related to the willingness to participate in the study and various risks that might occur during the study. This study had obtained ethical approval from the Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya/Dr. Moh. Hoesin General Hospital (No.231/kptfkunsri-rsmh/2018). Every study subject who had agreed to take part in this study underwent anamnesis, physical examination by cardiologist followed by laboratory examination and coronary angiography by cardiologist were performed.

Biochemical parameters assay

Blood was obtained from each study subject after 10 h of fasting. In the process, the serum was first separated by centrifuge (Biorad®) at a speed of 5000 rpm, temperature of 25°C, for 20 min. Then, the supernatant was separated from the pellet, stored at -80°C. Angiotensin I and aldosterone levels were examined using the enzyme-linked immunosorbent assay (ELISA) method using the human ELISA kit (Cloud-Clone®). A total of 10 µl samples from each study subject were included in the microplate well, then incubated for 30 min, at 37°C. The microplate was then washed with a washing solution on Immuno Washer (Biorad®). Next, conjugated horseradish peroxidase was added to each microplate and incubation was again performed. The microplate was then added with chrom A and chrom B and reincubated for 15 min. Then, a stop solution was added to the microplate and an optical density (OD) value was read from the microplate on the ELISA reader (Biorad®). The next step was to convert OD values into angiotensin I and aldosterone levels using standard curves.

Angiographic examination

The Judkins method was used in the assessment of coronary angiography, which was carried out through 19 femoral artery. All study participants were given iopromide (Ultravist 370, Schering AG, Berlin, Germany) as a contrast medium. All participants underwent assessment for slow coronary flow through coronary angiography; total frame cine (TFC) was used to measure the coronary flow rate of each patient. To ensure that coronary flow was objectively quantified, two separate doctors with no information of the patients determined coronary flow through TFC. With TFC, the operator recorded the number of cine frames (taken at 30 frames per second) needed so that the contrast

was at the level of the normal distal coronary landmark in the follow²⁶ arteries: Left circumflex artery (LCX), descending left anterior (LAD), and right coronary artery (RCA). Predetermined distal landmarks were distal bifurcations of LAD, commonly referred to as “pitchfork” or “whale’s tail,” distal bifurcation segments with the longest total distance for LCX, and the first branch of the posterolateral artery for RCA. The accepted mean for normal coronary arteries was 22.2 ± 4.1 frames for LCX, 36.2 ± 2.6 frames for LAD, and 20.4 ± 3 frames for RCA. TFC for LAD is often the highest of the coronary arteries because it is the longest; therefore, TFC for LAD must be corrected by dividing it by 1.7.

ACE gene polymorphism assay

For the examination of ACE I/D polymorphisms, genome deoxyribonucleic acid (DNA) was extracted from blood cells (leukocytes), using the Wizard’s purification system (Promega Ir²⁰) following the manufacturer’s instructions. ACE I/D polymorphisms were examined using the polymerase chain reaction (PCR) method.

Briefly, ACE was obtained through a separate reaction, using oligonucleotides. The primary PCR was 5’GCCCTGCAGGTGTCTGCAGCATGT3’ (forward primer) and 5’GGATGGCTCTCCCCGCTTGTCTC3’ (reverse primer). The final volume of the PCR reaction mixture was 70 µL containing 1 mM of each primer (Invitrogen[®]), 1.5 mM MgCl₂, 0.2 mM of 17th deoxynucleoside triphosphate – dNTP, 2.5 µL of 10 × PCR buffer, and 0.5 U of Taq polymerase (Invitrogen[®]). Amplification was carried out in a thermocycler (Biorad[®]) with an initial denaturation step at 94°C for 2 min followed by 40 cycles consisting of denaturation at 94°C for 10 s, annealing at 60°C for 30 s, and extension at 72°C for 30 s. PCR products were separated in 8% polyacrylamide gels and DNA was visualized with silver nitrate. This gel was made with 15 mL of polyacrylamide solution, 129 µL of ammonium persulfate, and 15 µL of N,N,N¹¹-Tetramethylethylenediamine. DNA fragments were 190 bp for D allele and 490 bp for I allele. Fragments displayed in the gel were permitted to verify if the patient was heterozygous (ID: 490 bp/190 bp) or homozygous (II: 490 bp and DD: 190 bp). DNA from previously typed individuals was included in each set of samples analyzed as control of enzyme activity.

Statistical analysis

All data were evalu¹⁰ using the SPSS software (version 24.0 for Windows, Inc., Chicago, Illinois, United States). Continuous variables were presented as mean and standard deviation, while categorical variabl¹⁶ were presented as percentages and analyzed through the Chi-square test. The Kolmogorov–Smirnov test was used to determine whether the data were normally distributed. Continuous, numerical, and normal distributed variables

underwent univariate analysis with two samples t-test, while those without normal dis⁸ruption were analyzed with the Mann–Whitney U-test. All tests used two-sided significance and p<0.05 was considered statistically significant.

Results

Clinical characteristics

All import²⁹ clinical parameters of the study subjects are listed in Table 1. There were no significant differences between CSFP and non-CSFP regarding gender, age, presence of hypertension, smoking

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Table 1: Demographic and clinical characteristics of the study participants

| Variables | CSFP (n=54) | Non-CSFP (n=58) | p value |
|--|-------------|-----------------|---------|
| Age, years | 53±12 | 54±11 | 0.84 |
| Male gender, n | 29 (53.7%) | 31 (53.4%) | 0.79 |
| BMI, kg/m ² | 31±8 | 29±9 | 0.71 |
| Hypertension, n | 19 (35.2%) | 22 (37.9%) | 0.81 |
| Diabetes mellitus, n | 21 (38.9%) | 23 (39.7%) | 0.76 |
| Hyperlipidemia, n | 10 (18.5%) | 12 (20.7%) | 0.83 |
| Cigarette smoking, n | 16 (29.6%) | 17 (29.3%) | 0.68 |
| Family history of CAD, n | 10 (18.5%) | 9 (15.5%) | 0.77 |
| Fasting glucose, mg/dL | 112±21 | 100±19 | 0.61 |
| Total cholesterol, mg/dL | 178±23 | 182±21 | 0.73 |
| Triglycerides, mg/dL | 147±67 | 135±56 | 0.67 |
| HDL cholesterol, mg/dL | 45±11 | 43±12 | 0.68 |
| LDL cholesterol, mg/dL | 117±21 | 120±19 | 0.54 |
| TIMI frame count measurements | | | |
| LAD | 60±28 | 29±7 | 0.001 |
| LAD (corrected) | 35±17 | 17±4 | 0.001 |
| LCX | 29±11 | 19±3 | 0.001 |
| RCA | 41±23 | 19±5 | 0.001 |
| Mean | 35±12 | 19±3 | 0.001 |
| The length of epicardial coronary arteries | | | |
| LAD, mm | 170±20 | 170±19 | 0.73 |
| LCX, mm | 127±30 | 124±29 | 0.67 |
| RCA, mm | 183±39 | 166±32 | 0.87 |
| Diameters of coronary arteries | | | |
| LAD, mm | 3.96±0.66 | 3.58±0.66 | 0.021 |
| LCX, mm | 3.66±0.61 | 3.23±0.62 | 0.041 |
| RCA, mm | 3.71±0.81 | 3.11±0.31 | 0.003 |
| Coronary flow velocities | | | |
| LAD, mm/s | 102.8±47.0 | 186.8±57.0 | 0.001 |
| LCX, mm/s | 148.7±59.6 | 203.7±60.6 | 0.001 |
| RCA, mm/s | 165.9±73.9 | 281.9±76.9 | 0.001 |

Data were presented as mean±SD, median (interquartile range) and as number (percentage). *Student’s t-test, Mann–Whitney U-test and Chi-square test. CSFP: Coronary slow flow phenomenon, Non-CSFP: Non-coronary slow flow phenomenon, BMI: Body mass index, CAD: Coronary artery disease, HDL: High-density lipoprotein, LDL: low-density lipoprotein, TIMI: Thrombosis in myocardial infarction, LAD: Left anterior descending artery, LCX: Left circumflex artery, RCA: Right coronary artery.

history, and the presence of diabetes (p > 0.05). In addition, there were no differences in lipid parameters or glucose values (after fasting) between the two groups (p > 0.05).

TFC

CSFP patients significantly displayed increased TFC in all three main coronary arteries compared to controls (p < 0.05). While there was no difference in blood vessel length between CSFP and non-CSFP, CSFP patients possessed coronary arteries that were significantly larger in size than non-CSFP, whereas non-CSFP showed significantly increased coronary flow rates compared to CSFP group (p < 0.05).

Table 2: Distribution of ACE I/D, angiotensin I, and aldosterone in CSFP

| Distribution of ACE I/D | CSFP (n=54), n (%) | Non-CSFP (n=58), n (%) | OR (95% CI) | p value |
|--|------------------------------|----------------------------------|------------------|---------|
| DD | 5 (9.2) | 6 (10.3) | 0.08 (0.03–0.28) | 0.001 |
| ID | 11 (20.4) | 29 (50) | 0.29 (0.19–0.46) | 0.001 |
| II | 38 (70.4) | 23 (39.7) | 6.9 (4.4–10) | 0.001 |
| I | 87 (80.5) | 75 (64.6) | 5.7 (3.6–7.8) | 0.001 |
| D | 21 (19.5) | 41 (35.4) | | |
| Level of angiotensin I and aldosterone | CSFP (n=54), Mean (pg/mL)±SD | Non-CSFP (n=58), mean (pg/mL)±SD | | p value |
| Angiotensin I | 234.6±25.7 | 102.5±11.6 | | 0.001 |
| Aldosterone | 367.9±3.7 | 231.6±27.9 | | 0.001 |

Data were presented as mean±SD, and number (percentage); ACE I/D: Angiotensin-converting enzyme insertion/deletion, I: Insertion, D: Deletion, Non-CSFP: Non-coronary slow flow phenomenon, CSFP: Coronary slow flow phenomenon, OR: Odds ratio, CI: Confidence interval.

Role of ACE gene polymorphism, level of angiotensin I and aldosterone

This study showed that the ACE I/D gene polymorphism possessed a significant effect in increasing the risk of CSFP. Genotype II polymorphism increased the risk of CSFP as much as 6.9 times compared to individuals with ID/DD genotype. The existence of allele I increased the risk of CSFP 5.7 times compared to allele D (Table 2). The PCR was shown in Figure 1.

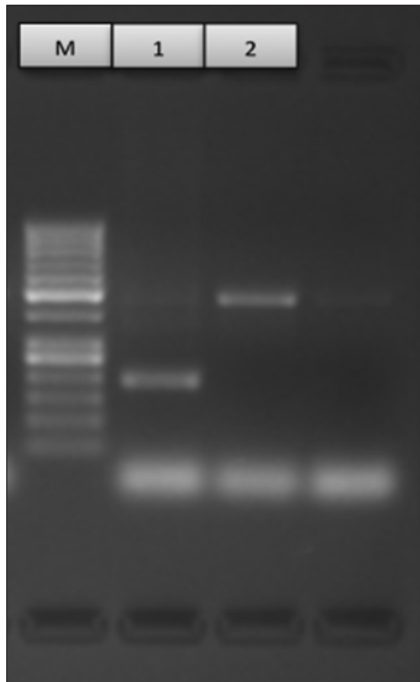


Figure 1: Angiotensin-converting enzyme gene polymerase chain reaction. M: Marker; 1: Genotype DD; 2: Genotype II

Levels of angiotensin I and aldosterone were increased significantly in patients with CSFP. These results indicated increased activity of the RAAS activity in patients with CSFP (Table 2).

Discussion

Coronary artery disease is a polygenic disease that involves complex interactions between

several pathophysiological pathways with several genes and environmental risk factors. This study analyzed several cardiovascular risk factors in patients with CSFP. Abnormal processes such as damage to the arterial wall, metabolic disorders, oxidative stress, and endothelial dysfunction can cause arterial sclerosis, coronary artery lesions, and an increased risk of developing atheromatous plaque. This study revealed a strong association between ACE I alleles, in general, and genotype II, in particular, with CSFP risk. Other studies related to the role of ACE I/D gene polymorphisms were quite varied. Some studies showed no significant association of ACE I/D gene polymorphism, while other studies showed different results from this study. Other studies related to ACE I/D gene polymorphism exhibited that the D allele increased the risk of CSFP. These ethnic and racial differences affected the genotypic variation of each individual. This finding became interesting, due to in Indonesia's South Sumatra population, the ACE I/D gene polymorphism that acted as a risk factor was allele I, not D. Various studies suggested that the main coronary risk factor was associated with coronary endothelial dysfunction even before stenosis lead to the concept that endothelial dysfunction occurred in the early stages of atherosclerosis [3], [9], [10], [11]. The ACE I/D polymorphism has been implicated in the pathogenesis of atherosclerosis and plays an important role in endothelial function. ACE, a key enzyme in the RAAS system, converts angiotensin I into a powerful angiotensin II vasoconstrictor. The chronic effect of higher angiotensin II levels in the ACE D allele carrier compared with angiotensin I allele carriers may associate with the development and/or progression of atherosclerosis. Increased ACE activity will increase angiotensin II, affecting cell growth and proliferation by stimulating various cytokines and growth factors that cause endothelial dysfunction by reducing the bioavailability of nitric oxide. Increased ACE expression in macrophages and smooth muscle cells of coronary artery plaque was previously reported to indicate that ACE activity in the lesion contributed greatly to the development of atherosclerosis [11], [12].

CSFP possibly occurs in coronary vessels with no atherosclerotic change in coronary angiography. The coronary blood flow may be normal in patients with atherosclerotic changes. Other studies showed DD genotype might influence

the development of CSFP. The ACE activity was higher in patients with DD genotype. Serum ACE level was associated with I/D polymorphism in the ACE-encoding gene. Genotype of DD exhibited increased serum ACE level, compared than genotype of II. The increasing level of ACE was associated with activated conversion of angiotensin I to angiotensin II and activated signaling pathway from inflammation, oxidative stress, and increased vascular and cardiovascular tone. Aldosterone is one of the other proteins that regulate the rigidity of vascular tone by increasing accumulation of fibrotic tissue and is responsible in endothelial dysfunction. The result of this study was different with the previous studies [1], [13], [14]. The study showed II genotype was the risk factor in CSFP patients. The ACE activity was lower in patients with II genotype. Serum ACE levels were associated with I/D polymorphism in the ACE-encoding gene. Genotype of II exhibited decreased serum ACE level, compared to genotype of DD. The decreasing level of ACE was associated with deactivated conversion of angiotensin I to angiotensin II. However, we hypothesized that there was another signaling pathway that would be responsible for the development of CSFP. A non-ACE pathway probably played a role in a conversion of angiotensin I to angiotensin II and increment of aldosterone [15], [16].

Conclusion

ACE I/D gene polymorphism possessed a significant effect in increasing the risk of CSFP. Genotype of II was the risk factor for the development of CSFP in population of South Sumatra, Indonesia.

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Authors' Contributions

Authors equally contributed in design, data compiling and analysis, and the composing of the manuscript.

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