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The Role of AT1R A1166C Gene Polymorphism in Coronary Slow Flow Phenomenon of Undergoing Coronary Angiography Patients

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Abstract

BACKGROUND: The presence of gene polymorphisms in the renin-angiotensin-aldosterone system associated with an impaired endothelial function that causes atherosclerosis and also myocardial fibrosis such as the polymorphism of the angiotensin-converting enzyme gene and the angiotensin I receptor (AT1R) gene.

AIM: This research was aimed to explore the role of AT1R A1166C gene polymorphism in the in**cidence of coronary** slow flow phenomenon (CSFP) in the Malay population, South Sumatra, Indonesia.

METHODS: This study is a comparative analysis using a case-control study design to analyze the effect of the AT1R A1166C gene polymorphism on the incidence of slow flow phenomenon in patients undergoing elective coronary angiography at Mohammad Hoesin Hospital Palembang, Indonesia. Examination of AT1R gene polymorphism was carried out with several steps starting from deoxyribonucleic acid extraction, polymerase chain reaction process, followed by restriction fragment length polymorphism stages with Ddel restriction enzymes and visualization.

RESULTS: Thirty-two patients participated in these study-baseline characteristics between homogeneous coronary regular flow groups and homogeneous coronary slow flow groups. There is no difference between genotype distribution, allele frequency, and genotype between the CSFP and the coronary standard flow group.

CONCLUSION: There is no influence of AT1R A1166C gene polymorphism on the CSFP in patients undergoing coronary angiography.

Introduction

The phenomenon of angina chest pain without significant epicardial coronary artery stenosis but accompanied by a slowing of coronary blood flow attracts cardiologists since the era of invasive coronary angiography [1]. The phenomenon of slow coronary blood flow is commonly known as the coronary slow flow phenomenon (CSFP) [2]. In 1972, Ghanie *et al*. at Dr. Mohammad Hoesin Hospital began to observe this phenomenon starting in 2003 intensively [3]. Most of the published research defines CSFP using the thrombolysis in myocardial infarction criteria introduced by Gibson. Categorized as CSFP if the time needed to contrast to pass at least one of the three branches of the coronary arteries to the distal marker is more than twenty-seven frames without a significant stenosis lesion (<40%) [4]. In contrast, Ghanie *et al*. took the CSFP limit using the time blanking criteria contrast (clearance) in the left anterior descending (LAD) artery. CSFP is categorized if the time of the entry of the contrast media starts from the LAD artery estuary until the disappearance of the contrast in the distal branch is more than 45 frames (in <3 s) [3].

Various studies that reported the prevalence of CSFP varied between 17% [4], [5], [6], [7] The majority of CSFP was relatively high, at 38.3% reported by Ghanie *et al*. at Dr. Moh Hoesin general hospital, Palembang, Indonesia [3], [4]. About 80% of CSFP patients experienced recurring or persistent symptoms such as discomfort in the chest, tightness, and chest pain. Some clinical studies report that the long-term prognosis of most CSFP patients is quite good, but some patients develop acute myocardial infarction, rhythm disorders, and sudden cardiac death [5], [8].

So far, the pathophysiology of CSFP is not exact; it is thought to be caused by various causes in blood vessels, in the form of coronary microvascular disease, inflammation and endothelial dysfunction [9], [10], [11]. The pathogenesis of CSFP also involves a vital role of the renin-angiotensin-aldosterone system (RAAS). This system consists of hormones and enzymes, which include angiotensinogen, angiotensin-converting enzyme (ACE), angiotensin I (AT1), angiotensin II (AT2), and aldosterone. AT2 has two receptor subtypes, namely, type 1 receptor (AT1R) and type 2 receptors (AT2R) [10]. The function of AT2 not only to stimulating aldosterone secretion but also to constrict blood vessel,

stimulates various growth factors, initiates hypertrophy and smooth muscle hyperplasia of blood vessels, making the condition of arterial stiffness. Besides, AT2 also oxidizes low-density lipoproteins cholesterol particles so that it starts absorption into the endothelium which will cause endothelial dysfunction, which results in atherosclerosis of the epicardial coronary arteries as well as small arteries and capillaries that connect with small veins [5], [12].

Several studies indicate the presence of gene polymorphisms in RAAS associated with an impaired endothelial function that causes atherosclerosis and also myocardial fibrosis such as the polymorphism of the ACE gene and the AT1R gene. So that the ACE gene and the AT1R gene become candidate genes as a cause of cardiovascular disease, including CSFP [12], [13], [14], this study is the first study that seeks to explore the role of AT1R A1166C gene polymorphism in the incidence of CSFP in the population of Malay, South Sumatra, Indonesia.

Methods

This study is a comparative analysis using a case-control study design to analyze the effect of the AT1R A1166C gene polymorphism on the incidence of CSFP in patients undergoing elective coronary angiography at Mohammad Hoesin Hospital Palembang, Indonesia. The study subjects were all patients indicated to have coronary angiography that fulfilled the inclusion and exclusion criteria, where the sampling was done in a consecutive sampling method until groups with CSFP and without CSFP were collected, respectively, 32 people, with matching for age and sex. Inclusion criteria were aged more than 18 years old, willing to participate in the study and signed informed consent, the group of cases obtained slowing down of coronary blood flow based on clearance criteria of more than 45 frames (more than 3 s) in the LAD artery, the control group found coronary blood flow ≤45 frames (≤3 s) in the LAD artery. Exclusion criteria were subjects with systolic heart failure (ejection fraction <50%), valvular heart disease, patients with connective tissue disease and autoimmune disease, patients with liver disease, and severe renal impairment. The ethics committee approved this study of the Faculty of Medicine of Sriwijaya University No. 234/kptfkunsri-rsmh/2019.

Examination of AT1R gene polymorphism was carried out with several steps starting from deoxyribonucleic acid (DNA) extraction, polymerase chain reaction (PCR) process, followed by restriction fragment length polymorphism (RFLP) stages with Ddel restriction enzymes and visualization. DNA extraction begins with as much as 200 uL of blood inserted in a sterile 1.5 mL tube. Washed with phosphate-buffered saline (PBS) pH 7.4 of 1000 uL then centrifuged at a speed of 5000 rpm for 5 min. Supernatant removed, this stage is repeated up to 2–3 times. Supernatant removed and then added 500 μL of saponin 0.5% mixed using a vortex—deep incubation for 24 h in the refrigerator –20°C. Vortex returns to melt immediately, then centrifuge at 12,000 rpm for 10 min, discard the supernatant. Add PBS 10,000 uL, centrifuge at 5000 rpm for 10 min, and remove the supernatant. They were repeated 2 times until the supernatant is clear.

The supernatant is removed then added 50 μL of Chelex (chelating agent) and added 100 μL of dd H_2O. Incubated/boiled in boiling water for 5 min then homogenized. Centrifuge with a speed of 1000 rpm for 1 min. Set in boiling water for 10 min. Centrifuge at 12,000 rpm for 10 min. DNA will be in the supernatant (DNA containing water), then the supernatant part is removed in a sterile tube and stored at –20°C until PCR examination. The PCR stage is an initial process of denaturation for 5 min at a temperature of 95°C. Then, it will be followed by denaturation at 94°C for 30 s for 34 cycles, annealing at 58°C for 1 min, and extension at 72°C for 35 s. The results of the products which have been applied were visualized with agarose gel 2% dipped with ethidium bromide. The next step is making RFLP mix with ingredients such as dd H2O 3.5 mL, a buffer of 1 ML, enzyme 0.5 ML, 10 ML amplicon with a total of 15 ML. Furthermore, incubation was carried out for 3 h, and the results of the product carried out by cutting the Ddel enzyme were visualized with agarose gel 2% dipped with ethidium bromide.

Genetic analysis of the AT1R A1166C gene polymorphism in the 3'UTR region used 5'AAT GCT TGT AGC CAA AGT CAC CT 3 as primary sense (F) and 5'GGC TTT GCT TTG TCT TGT TG 3' as primary antisense (R). The PCR results are 856 base pairs (bp) cuts. After being cut with the Ddel RFLP enzyme for 3 h, the PCR product was detected in the presence of electrophoretic spots on the 2% agarose gel with ethidium bromide. A homozygous allele produces two fragments referring to the size of 600 bp and 256 bp. The mutant C allele has three fragments, 600 bp, 146 bp, and 110 bp. Individual homozygous A alleles will produce two bands, 600 bp and 256 bp. Individual homozygous C alleles will have three rounds, namely 600 bp, 146 bp, and 110 bp. AC heterozygous individuals produce four bands, namely, 600 bp, 256 bp, 146 bpm, and 110 bp.

Data management and analysis are performed using the SPSS 25.0 for Windows program. Data are presented in the form of narratives and tables. To determine the normality of the data, the Shapiro–Wilk distribution test was conducted. Information is generally distributed if the value of $p > 0.05$. Hypothesis testing in this study was carried out using the Chi-square test if the Chi-square test requirements were not met; it was carried out by the Fisher's exact test.

Results

Table 1 shows that clinical and laboratory characteristics between the CSFP group and the coronary normal flow (CNF) group were not statistically significant differences, p > 0.05. Table 1 shows that the subjects used in this study are homogeneous to minimize the presence of confounding factors that will influence the genetic analysis of AT1R gene polymorphisms.

Table 1: Baseline characteristics

Characteristics	CSFP	CNF	p
Age (Mean ± SD)	50.6 ± 7.7	52.5 ± 12.4	0.31**
Gender			
Male, n (%)	20 (62.5)	18 (56.3)	0.35*
Female, n (%)	12 (37.5)	14 (43.7)	
Smoking			
Yes, n (%)	9 (28.1)	14 (43.7)	0.37*
No, n (%)	23 (71.9)	18 (56.3)	
Hypertension			
Yes, n (%)	18 (56.2)	18 (56.2)	0.9*
No, n (%)	14 (43.8)	14 (43.8)	
Diabetes mellitus			
Yes, n (%)	7 (21.9)	7 (21.9)	0.9*
No, n (%)	25 (78.1)	25 (78.1)	
Body mass index			
<25 kg/m^2	18 (56.2)	18 (56.2)	0.9*
≥25 kg/m^2	14 (43.8)	14 (43.8)	
ACEI/ARB consumption			
Yes, n (%)	9 (28.1)	9 (28.1)	0.9*
No, n (%)	23 (71.9)	23 (71.9)	
Anti-diabetic drugs			
Yes, n (%)	3 (9.4)	2 (6.3)	0.7*
No, n (%)	29 (90.6)	30 (92.7)	
Statin consumption			
Yes, n (%)	6 (18.8)	5 (15.6)	0.7*
No, n (%)	26 (81.2)	27 (84.4)	
Aspirin consumption			
Yes, n (%)	12 (37.5)	18 (56.3)	0.5*
No, n (%)	20 (67.5)	14 (42.8)	
Clopidogrel consumption			
Yes, n (%)	5 (15.6)	8 (25)	0.6*
No, n (%)	27 (84.4)	24 (75)	
Hb (Mean ± SD)	13.9 ± 1.8	13.36 ± 1.5	0.6**
Leukocyte (Mean ± SD)	8.2 ± 1.1	8.3 ± 1.5	0.6**
Thrombocyte (Mean ± SD)	293.8 ± 55.3	289.9 ± 57.8	0.6**
Ureum (Mean ± SD)	23.9 ± 5.8	25.3 ± 5.5	0.5**
Creatinine (Mean ± SD)	0.89 ± 0.41	0.83 ± 0.45	0.6**
Blood glucose (Mean ± SD)	113.9 ± 45.5	112.4 ± 34.8	0.6**
Cholesterol (Mean ± SD)	153.9 ± 23.8	154.4 ± 18.3	0.3**

CSFP: Coronary slow flow phenomenon, CNF: Coronary normal flow, *Chi-square test, p < 0.05; **Independent t-test, p < 0.05

The genetic analysis presented in Table 2 shows that the distribution of genotypes, allele frequencies, and genotypes between the CSFP and CNF groups was not different. This difference is increasingly seen where the statistical tests show that there is no significant difference between the CSFP and CNF groups in the AC/CC and AA genotype frequencies.

Table 2: Genetic analysis of AT1R gene polymorphism

Genetic analysis	CSFP, n (%)	CNF, n (%)	p*
Genotype distribution			
AA	25 (78.1)	26 (81.25)	
AC	6 (18.8)	6 (18.75)	
CC	1 (3.1)	0	
Allele Frequency			
A	56 (87.5)	58 (90.6)	
C	8 (12.5)	6 (9.4)	
Genotype			
AC/CC	7 (21.9)	6 (18.75)	0.76
AA	25 (78.1)	26 (81.25)	

CSFP: Coronary slow flow phenomenon, CNF: Coronary normal flow, *Chi-square test, p < 0.05. AT1R: Angiotensin I receptor

Discussion

The condition of CSFP is the interaction of various pathophysiological pathways involving traditional risk factors, genetic factors, and RAAS components. The role of RAAS in the pathogenesis of CSFP is quite significant. The variation of genes encoding functional proteins plays a role in influencing the activity of the RAAS pathway. Several studies have reported that the RAAS gene encoding component is a candidate gene in cardiovascular disease, the presence of RAAS gene polymorphisms associated with coronary artery disease, including CSFP events [15], [16], [17]. The effect of AT1R gene polymorphisms on CSFP events is not yet apparent, and research has limited the influence of AT1R A1166C gene polymorphism on coronary microvascular circulation, which causes CSFP [18], [19], [20], [21]. There are genetic variations on the tendency to experience CSFP in various ethnic groups. Several studies report the presence of gene polymorphisms in groups with coronary artery disease and experiencing microvascular dysfunction with groups that have healthy coronary arteries both anatomically and functionally. These studies conclude that there may be a relationship between gene polymorphisms with ischemic heart disease in this case against vessel disease coronary blood and microvascular dysfunction. In several studies, it is suspected that the presence of C allele in the AT1R gene will increase the detrimental effects of AT2 [22], [23], [24], [25].

In this study, the dominant genotype AA and allele A distribution were obtained. There is not much difference in genotype distribution and allele frequency of CSFP groups and CNF groups. From the analysis, there was no correlation between AT1R A1166C gene polymorphism and CSFP events. As is known, AT1R gene expression in individuals with A allele is not too large. In contrast, in this study, the dominant allele A frequency is obtained so that the adverse effects of AT2 in the form of vasoconstriction, hypertrophy, and hyperplasia and extracellular matrix deposition are not so significant. It is suspected that the influence of aldosterone is the leading cause of CSFP events; the study of Ghanie *et al*. supports this. In which a significant relationship was found between aldosterone levels and the incidence of CSFP. This relation is evidenced by the high prevalence of diastolic dysfunction in this study, but unfortunately, in this study, we did not examine aldosterone and AT2 levels [26], [27], [28], [29]. Ghanie also reported, based on genotype analysis, the majority of CSFP patients had genotype ii, which showed that ACE enzyme activity was low, so it cannot explain high aldosterone concentrations via the ACE pathway. The non-ACE pathway may have a role in the conversion of AT1 to AT2 and elevated aldosterone [3]. Besides, the coronary microvascular at the capillary level, it is only covered by the endothelium and basement membrane

where there is no AT1R receptor. Distribution of AT1 receptors were mostly in smooth muscle, and tunica adventitia of arteries. If CSFP disturbance is suspected to occur at the level of capillaries that are only covered by the endothelium, there is no role of AT2 through type-1 [30], [31], [32] receptors. The study of Ghanie *et al*. also supports this (homocysteine and adiponectin) in both CSFP and NSF patients, so the possible cause is not in the presence of endothelial dysfunction [3].

While in the myocardium, the AT1 receptor distribution is found with low density in the atria and ventricles so that the role of AT1R makes hypertrophy, hyperplasia, and pro-fibrosis less pronounced large so that can be used as an excuse is an increase in aldosterone levels through the non-ACE pathway [3], [33] Besides, the existence of treatment with ACE-inhibitors can affect due to an increase in the effects of bradykinin [34].

The research reported by Yalcin *et al*. also found no association between AT1R A1166C gene polymorphisms and CSFP events, Yalcin *et al*. could not conclude the role of AT1R on CSFP events [15]. Other studies looked at the effect of AT1R A1166C gene polymorphisms with cardiovascular events, as reported by Delshad *et al*. the relationship between the AT1R A1166C gene polymorphism and the incidence of acute coronary syndromes [35], [36]. The study reported by Araujo *et al*. found no relationship between the polymorphism of the AT1R A1166C gene with the incidence of acute myocardial infarction or the severity of coronary artery disease [36].

The study reported by Mishra *et al*. AC and CC were significantly higher in patients who experienced impaired left ventricular function compared with those who did not experience impaired left ventricular function. Further analysis showed that there was a significant relationship between the polymorphism of the AT1R A1166C gene with the dimensions of left ventricular (LV) end-diastole and LV end-systole and LV ejection fraction.[20] Based on these studies, the influence of genetic factors did not stand on CSFP or cardiovascular events, but other factors contributed to the CSFP incident [30], [31], [32].

Besides the influence of RAAS, the mechanical condition of myocardial hypertrophy also contributes to the high level of resistance at the microcirculation level as found in the mean height experienced hypertrophy in the CSFP group. The presence of comorbid in the form of traditional risk factors contributes to the destruction of endothelium physiology and the perivascular environment, which activates complex molecular pathways. This condition ultimately contributes to myocardial fibrosis which results in ventricular stiffness and diastolic dysfunction that is often found in CSFP patients [33]. Besides, these other pathophysiological processes may underlie CSFP is an increase in coronary microvascular resistance caused by microvascular endothelial dysfunction associated with atherosclerosis diffuse, thus resulting in stiffness in arterioles and coronary capillaries [34], [35].

Due to its difficulty in histology examination, the coronary microvascular circulation is still a mystery outside the epicardial arteries. With an understanding of the interaction between genetic influences, RAAS, metabolic disorders, and humoral components in the microvascular circulation that play a role in the mechanism of CSFP could assist in the development of diagnostic and therapeutic strategies. Until now, not many studies have tried to find the correlation of genetic factors and biochemical components with the incidence of CSFP. Ghani's research shows the influence of ACE gene polymorphisms on CSFP events, but there is no relationship with inflammation [3]. Since the pathophysiology and role of genetic factors in CSFP are not yet fully known, so far, the treatment of CSFP has not been satisfactory.

The target of therapy is aimed at functional obstruction in arterioles (<200 μm), such as dipyridamole, which has a vasodilator effect on coronary microvascular. Furthermore, administration of long-acting mibefradil (calcium T-channel antagonist group) gives a good response to microvascular. Provision of statins (such as simvastatin and atorvastatin) which have anti-inflammatory effects on blood vessels to improve endothelial function can relieve symptoms in CSFP. Administration of potentiation beta-blocker nebivolol 5 mg daily for 12 weeks can improve endothelial function in CSFP patients. The administration of anti-angina nicorandil drug, which has a vasodilator effect by increasing cGMP 5 mg three times a day can reduce episodes of chest pain and improve left ventricular function in CSFP patients. This effect may be due to an increase in NO expenditure and a decrease in endothelin-1 levels. Besides, trimetazidine antianginal drugs which work to inhibit the oxidation of beta fatty acids can reduce the symptoms of angina in CSFP patients [35]. Prognosis of CSFP patients at the age of 50 years with comorbid hypertension and dyslipidemia is not right. Therefore CSFP should be considered a separate disease and CSFP quite dangerous [6], [36].

Conclusion

There is no influence of AT1R A1166C gene polymorphism on the CSFP in patients undergoing coronary angiography.

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