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Original Article

Angiotensin type 1 receptor A1166C gene polymorphism is associated with endothelial dysfunction and in-stent restenosis after percutaneous coronary intervention

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Abstract: Background and purpose: Percutaneous coronary intervention (PCI) has been commonly used in the treatment of ischemic cardiovascular diseases, but the postprocedural in-stent restenosis (ISR) associated with altered endothelial functions has limited the clinical application of it; preventive medication with aspirin and statins has underlying adverse effects despite lowered risk of ISR. The purpose of this study was to investigate the role of angiotensin type 1 receptor (AT1R) A1166C gene polymorphisms in the development of endothelial dysfunction and ISR after PCI. Methods: A total of 483 ST-segment elevation myocardial infarction (STEMI) patients undergoing PCI were prospectively genotyped using polymerase chain reaction (PCR) and restriction fragment length polymorphism assay. The demographic, clinical, laboratory and angiographic parameters were recorded peri-procedurally and the patients were followed within 3 years. The flow-mediated dilation (FMD) was used to reflect the short-term changes in endothelial functions among different genotypes. The significance of AT1R gene polymorphisms in the development of ISR was analyzed using univariable and multivariable models. Results: Amongst 483 patients, the distribution of the AT1R genotypes (AA, AC and CC) was associated with the levels of blood biomarkers of oxidative stress and deteriorated FMD after PCI ($P<0.05$). In univariable and multivariable logistic regression analysis, it was shown that AT1R CC genotype is strongly associated with the development of restenosis within 3 years after PCI (OR=3.736; $P<0.001$; calibrated OR=4.104; $P<0.001$). Conclusion: The CC AT1R genotype was associated with deteriorated endothelial functions in the target vessels of PCI and intermediate to long-term ISR. Our findings contribute to the foundation of genome-based prevention for high risk groups of cardiovascular diseases and pretreatment for the patients undergoing PCI.

Keywords: Angiotensin type 1 receptor, polymorphism, percutaneous coronary intervention, in-stent restenosis

Introduction

Percutaneous coronary intervention (PCI) is commonly used in the treatment of ischemic cardiovascular diseases, including unstable angina pectoris, ST-segment elevation myocardial infarction (STEMI) and non-STEMI, and chronic coronary heart disease (CHD). PCI is effective in quickly increasing the blood supply to myocardial tissues and lowering the risk of major adverse cardiac events (MACEs), especially in those patients that are not anatomically suitable for surgical therapies. However, PCI has been associated with a series of vascular complications, which are usually considered to result from altered endothelial functions, ever since it was clinically applied [1-3]. The patients undergoing PCI are very likely to suffer postprocedural endothelial dysfunction in target vessels, exposed to high risk of in-stent stenosis (ISR), myocardial infarction and even death. In order to modulate the endothelial functions in target vessels and lower the risk of postprocedural cardiovascular events, statins have been clinically used and considered to significantly lower the risk of thrombosis and inflammatory injuries [4-9].

Although the related clinical data is never too sparse to ground the beneficial effects of

statins in the patients undergoing PCI, the complex pharmacological mechanisms of statins have never been entirely clarified and some underlying influence on the cardiovascular system or other organs and systems are usually unpredictable. As the worldwide application of PCI, the cases of PCI-related hemorrhage have also accumulated; these postprocedural hemorrhagic complications are mainly associated with the preoperative use of anticoagulants such as warfarin and statins except for some iatrogenic injuries [10-13]. When hemorrhagic complications occur, it is a dilemma between the withdrawal of anticoagulants and the prevention of thrombosis. In addition, the clinical application of statins does also have its limitations because many of the MACEs do not have subjective premonitory symptoms, thus intermediate to long-term pretreatment is often impossible. Obviously, genome-based therapies, which are more targeted and controlled, can overcome the shortcoming of statins and other traditional preventive medications and provide long-term protection from endothelial dysfunction following PCI, but the genotypes involved in the onset and progression of endothelial dysfunction and ISR are still unclear. Therefore, the purpose of this prospective 3-year observational study was to investigate the significance of angiotensin type 1 receptor (AT1R) A1166C gene Polymorphism in the development of endothelial dysfunction among STEMI patients undergoing PCI.

Methods and materials

Study cohort

A total of 483 STEMI patients were treated with PCI and followed for 3 years. The patients were at the ages between 65 and 79 years, including 223 males and 260 females. On the basis of genotyping results, the patients were divided into AT1R AA (n=216), AC (n=155) and CC groups (n=112). The inclusion criteria were: 1) STEMI patients undergoing successful PCI; 2) complete clinical records; 3) signing informed consent; 4) consistent results from AT1R genotyping twice. The exclusion criteria were: 1) past history of cardiovascular diseases treated with invasive modalities; 2) medication with traditional Chinese medicine; 3) life-threatening comorbidities such as malignant tumors; 4) serious hepatic or renal dysfunction; 4) chronic inflammatory diseases or systemic autoimmune diseases; 5) coagulation defects; 6) loss to follow-up. During follow-ups, 307 patients were diagnosed as ISR based on the coronary angiographic results.

PCI procedure

Each patient was preprocedurally administered with aspirin, 200 mg/d, and clopidogrel, 300 mg. The bare metal stents were deployed according to the results of quantitative coronary angiography. A successful PCI procedure was defined as a residual stenosis less than 20% and TIMI flow grade III. Each patient was postprocedurally administered with aspirin, 200 mg/d, along with clopidogrel, 75 mg/d, for 4 weeks, and then asked to take aspirin, 100 mg/d, for a lifetime unless otherwise advised during follow-ups. A definite diagnosis of ISR was defined as a restenosis no less than 50% within a distance of 5 mm to the stented site, which was detected using coronary angiography.

Genotyping and detection of blood biomarkers

The AT1R genotyping of STEMI patients was performed using polymerase chain reaction (PCR) restriction fragment-length polymorphism assay [14]. All of the samples were genotyped twice; the samples delivering inconsistent results were discarded and the corresponding cases were excluded from the study cohort. For each patient, fasting peripheral venous blood was drawn before and one day after the procedure, and immediately tested for the levels of Ang II, vWF, hs-CRP and IL-6. The attending physicians were blinded from these results so the management was not affected for any of the patients.

Statistical analysis

For the comparison of baseline demographic and clinical parameters, and genotypes between ISR and non-ISR groups, measurement data was analyzed using independent samples t-test while enumeration data was analyzed using chi-square test. For the comparison of pre- and postprocedural blood biomarkers, student's t-test was used; for the comparison of blood biomarkers among different genotypes, one-way ANOVA analysis was used. For the investigation into the association

Table 1. Comparison of demographic and clinical data: ISR versus non-ISR cases

Characteristics	ISR	Non-ISR	*P*
Number	307	176	-
Age (yr)	72.2±4.2	72.2±4.1	0.976
Gender			0.478
Male	138	85	
Female	169	91	
Hypertension			0.654
Yes	147	88	
No	160	88	
Smoker			0.300
Yes	170	106	
No	137	70	
Diabetes			0.692
Yes	96	52	
No	211	124	
BMI (kg/m^2)	26.5±2.1	26.3±2.0	0.214
ACS			0.102
Yes	203	129	
No	104	47	
SA			0.083
Yes	57	22	
No	250	154	
HbA1c	6.06±0.57	6.06±0.57	0.973
TC	4.44±0.49	4.42±0.50	0.607
TG	2.18±0.64	2.15±0.65	0.611
HDL	1.14±0.24	1.15±0.22	0.593
LDL	3.16±0.82	3.12±0.81	0.594
Lipoprotein (a)	0.50±0.03	0.49±0.04	0.195
Involved branches			<0.001
1	51	60	
2	146	47	
3	110	69	
Primary stenosis degree (%)	91.60±3.65	86.79±3.19	<0.001
Target lesion (mm)	17.13±3.44	15.73±2.80	<0.001
Stent diameter (mm)	2.89±0.24	3.02±0.34	<0.001
Releasing pressure (kPa)	1146.56±112.66	11.44.28±103.78	0.825
AT1R genotype			<0.001
AA	116 (37.8)	100 (56.8)	
AC	100 (32.6)	55 (31.3)	
CC	91 (29.6)	21 (11.9)	

between AT1R genotypes and ISR, univariate and multivariate Logistic regression analyses were performed with odds ratio (OR) and the 95% confidence interval (95% CI) were used to reflect relative risk. $P<0.05$ was considered statistically significant.

Results

Demographic and clinical data

Sex, age and body mass index (BMI) distribution was similar between ISR and non-ISR groups ($P>0.05$). The percentages of hypertension, smoker, diabetes, acute coronary syndrome (ACS) and stable angina (SA) were also similar between the two groups ($P>0.05$). Hemoglobin A1c (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and Lipoprotein (a) were also evenly distributed between the two groups ($P>0.05$). Involved branches, primary stenosis degree, target lesion and stent diameter were different between the two groups ($P<0.01$), which reflected the significance of primary lesion severity and stenting degree in the prognosis of PCI, except that 2 involved branches had a higher rate of postoperative ISR. Most importantly, ISR and non-ISR groups have significantly different compositions of AT1R genotypes ($P<0.001$); the percentage of 3-year ISR was respectively 53.7%, 64.5% and 81.3% in AT1R AA, AC and CC cases. See **Table 1** for details.

Flow-mediated dilation (FMD) decreased after PCI procedure, which reflected the influence of PCI on endothelial functions; ISR and non-ISR cases were not significantly different in preprocedural FMD ($P=0.257$), but ISR cases showed a more significant decrease in FMD than non-ISR cases when the PCI was completed ($P<0.001$). The blood biomarkers of inflammatory reactions, vWF, hs-CRP and IL-6, increased

Table 2. Comparison of pre- and postprocedural FMD and blood biomarkers in different genotypes

	ISR	non-ISR	*P*
FMD (%)			
Before	6.43±1.13	6.56±1.24	0.257
After	4.32±1.48	5.52±1.34	<0.001
vWF (IU/dL)			
Before	156.10±50.30	150.65±50.40	0.253
After	202.46±55.88	174.32±50.86	<0.001
Hs-CRP (mg/L)			
Before	2.16±0.97	2.25±0.93	0.345
After	3.74±1.26	2.89±0.96	<0.001
IL-6 (pg/dL)			
Before	2.76±0.14	2.75±0.14	0.658
After	3.22±0.25	3.12±0.21	<0.001
Ang II (pmol/L)			
Before	15.36±0.86	13.12±0.75	<0.001
After	16.82±1.14	14.30±0.94	<0.001

Table 3. Comparison of Blood biomarkers among different AT1R genotypes

	AA	AC	CC	*P*
FMD (%)				
Before	6.66±1.14	6.32±1.19	6.35±1.18	0.008
After	5.12±1.38	4.50±1.60	4.43±1.62	<0.001
vWF (IU/dL)				
Before	155.15±50.43	149.33±52.50	158.72±46.95	0.297
After	189.69±56.12	189.11±59.51	201.33±48.56	0.141
hs-CRP (mg/L)				
Before	2.18±0.96	2.15±0.99	2.27±0.91	0.603
After	3.32±1.23	3.40±1.25	3.71±1.17	0.023
IL-6 (pg/mL)				
Before	2.75±0.15	2.75±0.14	2.78±0.14	0.249
After	2.95±0.32	3.25±0.33	3.55±0.31	<0.001
Ang II (pmol/L)				
Before	14.36±1.43	14.55±1.38	14.87±1.14	0.006
After	15.69±1.71	15.86±1.62	16.37±1.33	0.001

after PCI procedure, as suggested that stenting contributed to the activation of inflammatory factors; ISR and non-ISR cases were not significantly different in levels of blood biomarkers of inflammation ($P>0.05$), but ISR cases showed a more significant increase after PCI in comparison with the non-ISR cases ($P<0.001$). Interestingly, ISR and non-ISR cases were significantly different in pre- and postprocedural level of Ang II ($P<0.01$). See **Table 2** for details.

To investigate the association between endothelial functions and PCI, the comparison of FMD, vWF, hs-CRP, IL-6 and Ang II were performed among three AT1R genotypes (**Table 3**). Before PCI, the three AT1R genotypes were significantly different in FMD and Ang II ($P<0.01$), with the AT1R CC genotype showing the lowest FMD and highest level of Ang II, but no significant difference was found in levels of blood biomarkers of inflammation among the three genotypes ($P>0.05$). However, after PCI, the three AT1R genotypes were significantly different in all the parameters above ($P<0.01$), with the AT1R CC genotype showing the lowest FMD, and highest level of Ang II and the blood biomarkers of inflammation.

To investigate the prognostic significance of AT1R polymorphisms among STEMI patients undergoing PCI, logistic regression was performed. The model including AT1R genotypes only indicated that the risk of postprocedural ISR was significantly associated with AT1R AC and CC genotypes; with sex and age included, the calibrated model 1 gives the OR values of 1.567 and 3.764 for AC and CC; with all the demographic and clinical parameters included, the calibrated model 2 gives the OR values of 1.651 and 5.352 for AC and CC. In the calibrated model 2, AT1R AC genotype was no longer a significant factor ($P=0.094$), but AT1R CC genotype was still significant ($P<0.001$). See **Table 4** for details.

All the demographic and clinical parameters were included into the final multivariable regression model with forward method (likelihood ratio) and the Hosmer-Leme-show test gave a *p*-value of 0.834. The independent risk factors to suffer postprocedural ISR were AT1R CC [OR=4.104 (2.174-7.748); $P<0.001$], primary stenosis degree [OR=1.515 (1.396-1.644); $P<0.001$], target lesion [OR=1.208 (1.112-

Table 4. Logistic regression for 3-year risk of post-procedural ISR among elderly STEMI patients

Independent factors	OR	95% CI	*P*
Univariable model			
AT1R AA	1.000	-	-
AT1R AC	1.567	1.026-2.395	0.038
AT1R CC	3.736	2.167-6.440	<0.001
Calibrated model 1			
AT1R AA	1.000	-	-
AT1R AC	1.567	1.027-2.401	0.037
AT1R CC	3.764	2.181-6.496	<0.001
Calibrated model 2			
AT1R AA	1.000	-	-
AT1R AC	1.651	0.918-2.970	0.094
AT1R CC	5.352	2.643-10.839	<0.001

Table 5. Multivariable logistic regression for 3-year risk of postprocedural ISR among STEMI patients

Independent factors	OR	95% CI	*P*
AT1R CC	4.104	2.174-7.748	<0.001
Primary stenosis degree	1.515	1.396-1.644	<0.001
Target lesion	1.208	1.112-1.311	<0.001
Stent diameter	0.143	0.059-0.347	<0.001

1.311); *P*<0.001] and stent diameter [OR= 0.143 (0.059-0.347); *P*<0.001] (**Table 5**).

Discussion

For the patients with serious ischemic cardiovascular diseases such as STEMI, conservative treatment is not actually a good option. The progression of ischemic myocardial injuries is usually accelerated as the abnormal anatomic structure remains untreated, leading to life-threatening MACEs. In comparison with surgical therapies, PCI is less invasive and most of the patients can be peri-procedurally compliant. Although surgical treatment is still reserved for those patients with complex and severe cardiovascular lesions, PCI has been increasingly used in the treatment of different ischemic cardiovascular diseases. However, one of the most prominent limitations of PCI is the high risk of ISR and subsequent MACEs associated with altered endothelial functions. However, a recent large-scale multi-center study has shown that a considerable number of patients undergoing PCI without pretreatment of statins did not suffer higher risk of in-hospital complications and mortality [15]; it suggested that not all of the patients undergoing serious endothelial dysfunction after PCI and that those patients suffering post-procedural ISR might be attributed to some gene-level mechanisms.

The concrete mechanisms of post-procedural endothelial dysfunction amongst the patients undergoing PCI have not been entirely clarified, although past reports have identified a number of risk factors for ISR and MACEs. A study enrolling 687 acute coronary syndrome (ACS) or stable angina pectoris patients undergoing successful PCI showed that high low-density lipoprotein cholesterol (LDL-C)/high-density lipoprotein cholesterol (HDL-C) ratio predicts a high risk of MACEs after PCI [16]. A recent study examining 238 patients who suffered recurrent cardiac ischemia after PCI also suggested that LDL-C/HDL-C ratio contributes to the onset of newly developed coronary artery diseases induced by restenosis [17]. The prognostic significance of C-reactive protein (CRP) has also been mentioned in many reports regarding the patients undergoing PCI. According to a large-scale study including 1800 stable or unstable angina patients, the difference between baseline and peaked CRP values during treatment, rather than the baseline values, was closely associated with the risk of in-stent restenosis amongst the patients undergoing PCI, which suggested that restenosis is mainly attributed to the inflammatory reactions induced by stenting [18]. A long-term follow-up performed amongst 850 angina pectoris patients undergoing PCI suggested that CRP levels reflect the inflammatory reactions triggered by stenting and predict the risk of restenosis [19]. Similarly, a retrospective study examined 513 patients undergoing PCI and coronary angiography showed that preprocedural CRP levels were associated with in-stent restenosis and a diabetic milieu, LDL-C, non-HDL-C and total cholesterol (TC) levels also play roles in the progression of coronary lesions [20]. Some past reports have also pointed that obstructive sleep apnea (OSA) leads to a hypoxic milieu which contributes to the risk of post-PCI restenosis [21, 22]. Regular physical exercise has been considered protective for those patients undergoing PCI from restenosis since it promotes lipid metabolism and increases aerobic capacity [23, 24]. Many reports have provided direct implications in the significance of altered glucolipid metabo-

lism in the development of post-PCI restenosis [25-28]. Thus, it is very likely that oxidative stress and related inflammatory reactions play an essential role in the onset and progression of endothelial functional disorders.

Existing literature has suggested that the endothelial functional disorders after PCI are associated with oxidative stress. AT1R A1166C polymorphisms play a key role in the oxidative stress during the progression of myocardial degeneration. A large-scale study including 3416 patients undergoing successful PCI has suggested that AT1R 1166CC genotype is significantly associated with intermediate-term post-PCI restenosis [29]; our study made further investigation into the long-term outcomes of the patients undergoing PCI and showed similar associations between AT1R 1166CC genotype and ISR. That is to say, our results have suggested that AT1R 1166CC genotype was not only strongly associated with intermediate-term post-PCI restenosis, but also with long-term post-PCI restenosis. In addition, our study cohort included STEMI patients only and guaranteed the homogeneity to some extent. Considering the significance of other gene polymorphisms, which has been analyzed in some of the past reports [30, 31], gene-gene interactions may also play a role in the pathogenesis of post-PCI restenosis; it is a promising research direction in the future.

Our study does still have some limitations. For example, it was a single-center observational study, so the sample size is limited and the participants were at a relatively high age (≥65 y). However, our study has suggested AT1R gene polymorphisms as a long-term prognostic factor for ISR among the patients undergoing PCI for the first time and primarily provided some evidence on the significance of AT1R gene polymorphisms in the future genome-based therapies, as a supplement to the existing research. Our study may also have some implications in the future investigation into other types of gene polymorphisms associated with post-procedural ISR among the patients undergoing PCI.

Conclusion

Our study has delivered the first report on the significance of AT1R CC genotype in the deterioration of endothelial functions and the development of ISR in the long term, contributing to the foundation of genome-based prevention for high risk groups of cardiovascular diseases and pretreatment for the patients undergoing PCI. In the future, other types of gene polymorphisms should be investigated to clarify the gene-gene interactions in the development of ISR among the patients undergoing PCI and a genome-based therapy will be made possible.

Disclosure of conflict of interest

None.

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