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Original Article

Correlation of ApoE gene polymorphism with acute myocardial infarction and aspirin resistance after percutaneous coronary intervention

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Abstract: Objective: To determine the correlation of Apolipoprotein E (ApoE) gene polymorphism with acute myocardial infarction (AMI) and aspirin (APC) resistance after percutaneous coronary intervention (PCI). Methods: In this randomized controlled trial (The Second People's Hospital of Lianyungang Ethics Committee No.L1719), a total of 120 AMI patients admitted to the Second People's Hospital of Lianyungang from January 2019 to June 2020 were enrolled into the research group (Res group) and 120 healthy individuals during the same time period into the control group (Con group). ApoE gene polymorphism was detected by gene microarray and analyzed statistically. The occurrence of APC resistance after PCI was recorded, and the relationship between ApoE gene polymorphism and APC resistance was analyzed. Results: The Res group showed a significantly lower level of ε3/ε3 gene and significantly higher levels of ε3/ε4 and ε4/ε4 genes than the Con group (all P<0.05), but no notable difference was found in the distribution of ApoE ε2 between the two groups (P>0.05). ApoE ε3 carriers were the main carriers in both groups. However, the Res group showed a lower frequency of ApoE ε3 and a higher frequency of ApoE ε4 compared to the Con group (both P<0.05), and patients with more severe AMI had a significantly higher frequency of ApoE ε4 genotype (P<0.05). According to logistic regression analysis, carrying ApoE ε4 allele (ε3/ε4, ε4/ε4) was a risk factor for AMI (P<0.05). Additionally, patients with APC resistance had a significantly higher frequency of ApoE ε4 allele than those without it (P<0.05). A higher frequency of ApoE ε4 allele was also a risk factor of APC resistance in AMI patients after PCI, and its adjusted risk ratio (OR) was 2.26 times (P<0.05). Moreover, no significant difference was observed among patients with different ApoE genotypes in the incidence of adverse events (P>0.05). Conclusion: ApoE gene polymorphism is correlated with AMI and APC resistance after PCI, and ApoE ε4 genotype is probably the risk allele for AMI.

Keywords: Apolipoprotein E, acute myocardial infarction, polymorphism, aspirin resistance

Introduction

Cardiovascular disease is a primary cause of death in middle-aged and elderly people worldwide, and its incidence is gradually increasing. According to a survey, on average, 1 out of every 10 people over 60 years old suffers cardiovascular disease [1]. Among all cardiovascular diseases, acute myocardial infarction (AMI) is a frequently seen disease with the characteristics of sudden attack rate, high mortality, and disability rate, rapid disease development, and high recurrence rate. In the United States alone, over 1.5 million patients die every year due to AMI on average [2]. At the current stage, there are few preventive measures for AMI in clinical practice, and AMI is still mainly treated through timely percutaneous coronary intervention (PCI) after onset, which has some limitations [3].

In response to the growing morbidity and mortality of AMI, efforts must be made to find new diagnosis and treatment. The molecular study of pathogenic mechanisms is the topic of current research [4]. Apolipoprotein E (ApoE), a glycoprotein composed of 299 amino acids, is mainly implicated in the transportation, storage, utilization, and excretion of lipoproteins [5]. It is usually found in chylomicrons (CM),

high density lipoprotein (HDL), low density lipoprotein (LDL) and very low-density lipoprotein (VLDL) [6]. ApoE alleles can be classified into three categories, ε2, ε3, and ε4. Correspondence of each allele to the main isomer generates three homozygotes (ε2/2, ε3/3, ε4/4) and three heterozygotes (ε2/3, ε2/4, ε3/4) [7]. ApoE can regulate the secretion of inflammatory mediators and resist oxidative stress, with antioxidant and anti-inflammatory effects, and has different anti-inflammatory abilities based on different alleles [8]. As we all know, mechanisms including oxidative stress, inflammatory reaction, and charge structure remodelling are strongly related to the occurrence and persistence of AMI, which can greatly accelerate the processes of vascular endothelium and myocardial cell injury, myocardial fibrosis, and myocardial ischemia and induce AMI [9]. Kritharides et al. [10] pointed out that ApoE was strongly associated with myocardial aortic stenosis, and Zhu et al. [11] found that ApoE gene therapy might be a breakthrough in the future therapy of atherosclerosis. Accordingly, based on the correlations of ApoE with the above mechanisms, we infer that the ApoE gene polymorphism has crucial effects on the development of AMI. Additionally, aspirin (APC), the commonly used antithrombotic drug in AMI after PCI, often gives an obvious decrease in the inhibition rate of platelet aggregation due to individual differences of patients, that is, APC resistance, which seriously lowers the rehabilitation chances of patients after PCI [12]. However, Kraus et al. [13] have discovered the ability of APC to alleviate early atherosclerosis in ApoE knockout mice, suggesting that ApoE has a strong association with APC resistance in AMI patients.

Accordingly, this study probed the clinical value of the ApoE gene in AMI by analyzing the association of ApoE gene polymorphisms with AMI and APC resistance after PCI.

Materials and methods

Research objects

In this randomized controlled trial (The Second People's Hospital of Lianyungang Ethics Committee No. L1719), totally 120 AMI patients admitted to the Second People's Hospital of Lianyungang from January 2019 to June 2020 were enrolled into the research group (Res group) and 120 healthy individuals during the same time period into the control group (Con group). The former group consisted of 63 males and 57 females (mean age: 74.26±8.27 years old), and the latter group consisted of 59 males and 61 females (mean age: 64.53±11.90 years old). All participants provided their informed consent in written form.

Inclusion and exclusion criteria

The inclusion criteria: Patients diagnosed with AMI in our hospital; patients whose complete medical records and blood samples could be acquired; patients ≥18 years old; patients who had not received APC before admission; patients with no recent history of surgery and active bleeding; and those who received PCI after admission. Exclusion criteria: Patients with left ventricular dysfunction; pulmonary heart disease; rheumatic heart disease; dilated cardiomyopathy; hypertrophic cardiomyopathy; viral myocarditis; history of cardiac surgery; secondary hypertension; hyperthyroidism; electrolyte disorder; malignant tumour or liver or kidney insufficiency; patients with severe infection, tuberculosis, metabolic syndrome or diseases that may give rise to abnormal inflammatory mediators or blood lipid metabolism.

Recording of clinical baseline data

The data about age, gender, height, weight, body mass index (BMI), smoking history, hypertension history, and diabetes history were acquired, and left atrial diameter (LAD) and left ventricular ejection fraction (LVEF) were obtained by echocardiography. AMI classification: A spontaneous AMI from thrombosis in one or more coronary arteries caused by primary coronary events such as atherosclerotic plaque rupture, ulcer, fissure, or dissection is type 1 AMI. Secondary AMI caused by decreased myocardial oxygen supply or increased oxygen consumption rather than non-coronary artery disease, is type II AMI.

Methods

Detection of ApoE gene polymorphism: Fasting morning peripheral venous blood (2 mL) was sampled from each participant, followed by anticoagulation with EDTA. The sampled blood was kept in a refrigerator (4°C). The cells were extracted by the protease salting-out method. The genomic DNA of leukocytes was extracted with a whole blood genomic DNA extraction kit

Table 1. Clinical baseline data

	Research group (n=120)	Control group (n=120)	t/χ^2	*P* value
Gender			0.267	0.606
Male	63 (52.50)	59 (49.17)		
Female	57 (47.50)	61 (50.83)		
Age	74.26±8.27	64.53±11.90	7.355	<0.001
Height (cm)	165.66±7.35	164.24±9.74	1.275	0.204
Weight (kg)	69.22±12.14	70.35±9.99	0.787	0.432
Body mass index	24.98±3.64	25.85±3.77	1.819	0.070
Smoking			0.194	0.660
Yes	33 (27.50)	30 (25.00)		
No	87 (72.50)	90 (75.00)		
Type 2 diabetes mellitus			0.303	0.582
Yes	8 (6.67)	6 (5.00)		
No	112 (93.33)	114 (95.00)		
Hypertension			8.185	0.004
Yes	34 (28.33)	16 (13.33)		
No	86 (71.67)	104 (86.67)		
LAD (mm)	41.96±10.92	36.66±4.77	4.872	<0.001
LVEF (mm)	53.95±9.77	58.85±9.29	3.981	<0.001

Note: LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

(Invitrogen, USA, K182104A), and the genotypic distribution of ApoE gene was detected by PCR-RFLP. PCR premix, primers (F: 5'-AACAACTGACCCCGGTGGCG-3, R: 5'-ATGGCGCTGAGGCCGCGCTC-3) and deionized water were added to genomic DNA for amplification in PCR instrument (Invitrogen, USA, VeritiPro PCR) (reaction conditions: 50°C for 2 min, followed by 45 cycles of 95°C for 15 min, 94°C for 30 s, and 65°C for 45 s) to acquire PCR products. After restriction endonuclease reaction and agarose gel electrophoresis, the digested products were visualized by a gel imager (Nanjing Shiyan Instrument Co., Ltd., K8500), and the polymorphic sites of ApoE gene were interpreted according to the images.

APC resistance determination: After PCI, patients with AMI were given oral aspirin (ORIGINAL PHARMACOLABO Corporation, State Food and Drug Administration (SFDA) approval no.: H20065051). The dose was 300 mg/time, once a day, in the first day, and it was adjusted to 100 mg/time the second day and lasted for 4 weeks. Arachidonic acid (AA) was given to induce platelet aggregation, and AA-induced platelet aggregation rate ≥20% was deemed as APC resistance. Additionally, the patients were followed up for 3 months, and the incidence of postoperative adverse events (including cardiovascular events such as angina pectoris, myocardial infarction, myocardial enzyme inheritance, and postoperative bleeding) was recorded.

Statistical analyses

SPSS 21.0 was used for statistical analyses. Comparison of measured data (χ±s) was conducted using the independent-samples T test, and data not in a normal distribution were analyzed by a nonparametric test. Comparison of counted data (%) was performed using the χ^2 test. By logistic regression analysis, the associations of ApoE genotype with AMI and APC resistance were determined, and the confounding risk factors were adjusted step by step. Risk prediction intensity was presented as odds ratio (OR) and 95% CI. P<0.05 was deemed a significant difference.

Results

Comparison of clinical baseline data

The Res group and the Con group had no notable difference in gender, height, weight or body mass index (BMI) (all P>0.05), but had differences in age, hypertension history, LAD, and LVEF (all P<0.05, **Table 1**).

ApoE microarray test results

Six genotypes, ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4, were detected.

Analysis of ApoE gene polymorphism

The Res group showed a significantly lower level of ε3/ε3 gene and significantly higher levels of ε3/ε4 and ε4/ε4 genes than the Con group (all P<0.05, **Table 2**).

Distribution of ApoE allele

No significant difference was found in the distribution of ApoE ε2 between the two groups

Table 2. Analysis of ApoE gene polymorphism

	Research group (n=120)	Control group (n=120)	χ^2	*P* value
ε2/ε2	2 (1.67)	1 (0.83)	0.338	0.561
ε2/ε3	16 (13.33)	15 (12.50)	0.037	0.847
ε2/ε4	4 (3.33)	3 (2.50)	0.147	0.701
ε3/ε3	62 (51.67)	88 (73.33)	12.020	<0.001
ε3/ε4	31 (25.83)	13 (10.83)	9.017	0.003
ε4/ε4	5 (4.17)	0 (0.00)	5.106	0.024

Note: ApoE, Apolipoprotein E.

Table 3. Distribution of ApoE allele

	Research group (n=120)	Control group (n=120)	χ^2	*P* value
ε2	18 (15.00)	16 (13.33)	0.137	0.711
ε3	66 (55.00)	91 (75.83)	11.510	<0.001
ε4	36 (30.00)	13 (10.83)	13.570	<0.001

Note: ApoE, Apolipoprotein E.

Table 4. Association of ApoE genotype with the severity of AMI

		Research group (n=120)	Control group (n=120)	χ^2	*P* value
Type 1 AMI	ε2	4 (3.33)	6 (5.00)	1.230	0.541
	ε3	26 (21.67)	37 (30.83)		
	ε4	9 (7.50)	7 (5.83)		
Type 2 AMI	ε2	14 (11.67)	10 (8.33)	15.400	<0.001
	ε3	40 (33.33)	54 (45.00)		
	ε4	27 (22.50)	6 (5.00)		

Note: ApoE, Apolipoprotein E; AMI, acute myocardial infarction.

Table 5. Association of ApoE with AMI

	Uncorrected model			Corrected model		
	OR	95% CI	*P* value	OR	95% CI	*P* value
ε2	0.874	0.424-1.24	0.642	0.744	0.624-1.341	0.451
ε3	1	-	-	1	-	-
ε4	1.429	1.142-1.984	0.003	1.524	1.084-1.763	<0.001

Note: ApoE, Apolipoprotein E; AMI, acute myocardial infarction.

(P>0.05), and ApoE ε3 carriers were the primary carriers in both groups. However, the Res group showed a lower frequency of ApoE ε3 and a higher frequency of ApoE ε4 than the Con group (both P<0.05, **Table 3**).

Correlation of ApoE genotype with severity of AMI

Patients with different severities of AMI were not different in the distribution of ApoE ε2 and ApoE ε3 genotypes (P>0.05), but were different in ApoE ε4 genotype, among which the frequency of ApoE ε4 genotype was significantly higher in patients with more severe AMI (P<0.05, **Table 4**).

Correlation of ApoE with AMI

Logistic regression analysis was performed to show an association of ApoE alleles with AMI. According to the results, ApoE ε2 and ApoE ε3 genotypes were not significantly related with AMI (P>0.05). According to logistic regression analysis before and after adjustment of related risk factors, carrying an ApoE ε4 allele (ε3/ε4, ε4/ε4) was a risk factor for AMI (P<0.05, **Table 5**).

Association of ApoE gene polymorphism with APC resistance

Among the 120 AMI patients, 37 patients developed APC resistance, and the detection rate was 30.83%. According to comparison of the ApoE gene polymorphism between APC-resistant patients and non-APC-resistant patients, there was no difference in the genotypes of ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε4/ε4 and the alleles of ApoE ε2 and ApoE ε3 (P>0.05), but there was a significantly higher frequency of ApoE ε4 allele in APC-resistant patients than in non-APC-resistant patients (**Table 6**). Logistic regression analysis revealed that before and after the correction, the ApoE ε2 and ApoE ε3 alleles were not associated with APC resistance (all P>0.05), while the ApoE ε4 allele was also a risk factor for APC resistance in AMI patients after PCI (P<0.05), with adjusted risk ratio (OR) of 1.897 times (**Table 7**).

Association of ApoE with adverse events after PCI

Three months after PCI, 41 patients suffered adverse events, showing a total incidence of

Table 6. Association of ApoE gene polymorphisms with APC resistance

	APC resistance (n=37)	No APC resistance (n=83)	χ^2	*P* value
Genotype				
ε2/ε2	1 (2.70)	1 (1.20)	0.350	0.554
ε2/ε3	5 (13.51)	11 (13.25)	0.002	0.969
ε2/ε4	1 (2.70)	3 (3.61)	0066	0.797
ε3/ε3	18 (48.65)	44 (53.01)	0.195	0.659
ε3/ε4	9 (24.32)	22 (26.51)	0.064	0.801
ε4/ε4	3 (8.11)	2 (2.41)	2.081	0.149
Allele frequency				
ε2	4 (27.03)	14 (16.87)	0.736	0.391
ε3	16 (43.24)	50 (60.24)	2.987	0.084
ε4	17 (45.95)	19 (22.89)	6.477	0.011

Note: ApoE, Apolipoprotein E; APC, aspirin.

Table 7. Association of ApoE gene polymorphism with APC resistance

	Uncorrected model			Corrected model		
	OR	95% CI	*P* value	OR	95% CI	*P* value
ε2	0.475	0.042-1.74	0.424	0.734	0.414-3.841	0.614
ε3	1	-	-	1	-	-
ε4	3.741	1.554-3.614	0.018	1.897	1.124-3.551	<0.001

Note: ApoE, Apolipoprotein E; APC, aspirin.

Table 8. Association of ApoE with adverse events after PCI

	Adverse events occurred (n=41)	No adverse events occurred (n=79)	χ^2	*P* value
ε2	5 (12.20)	9 (11.39)	0.017	0.897
ε3	21 (51.22)	45 (56.96)	0.360	0.549
ε4	15 (36.59)	21 (26.58)	1.286	0.257

Note: ApoE, Apolipoprotein E; PCI, percutaneous coronary intervention.

34.17%. Among them, 24 patients suffered cardiovascular events and 17 patients had bleeding events. However, no significant difference was observed in the incidence of adverse events among patients with different ApoE genotypes (P>0.05, **Table 8**).

Discussion

Acute myocardial infarction (AMI) is the most threatening cardiovascular disease.I Its pathogenesis is still under investigation, but coronary atherosclerosis is the most crucial cause [14]. The pathogenic molecular mechanisms will give us breakthroughs for the future prevention and therapy of AMI [15]. ApoE encodes 6 variants of the protein and adjusts lipid metabolism through various ways, thus playing a crucial role in tissue repair, inhibition of platelet aggregation and immune regulation, and it is correlated with diseases including atherosclerosis and high lipoproteinemia [16, 17]. ApoE impacts the secretion of inflammatory mediators and resists oxidative stress, but the ApoE ε4 allele can activate the nuclear transcription factor NF-κB which is pro-inflammatory, giving rise to TNF-α, TGF-β1, MCP-1, hs-CRP, IL-1, IL-6, and the expression of inflammatory mediators [18-20], resulting in myocardial electrical remodelling [21], structural remodelling, and atrial arrhythmia. As a crucial factor in fibrosis, ApoE gives rise to TGF-β1 expression and thus induces myocardial fibrosis. TGF-β1 infiltration can be found in muscle biopsies along with an increase in angiotensin II (AngII) [22, 23]. Myocardial fibrosis is also one crucial cause of AMI, which also preliminarily indicates the potential correlation between ApoE and AMI to some extent. When the function of cardiovascular endothelial cells is damaged, the active substances in blood vessels will be secreted abnormally, which will increase the impact of blood flow on the blood vessel wall, and lead to the decline and damage to endothelial function and promote atherosclerosis [24]. Wisniewski et al. [25] have pointed out that the abnormal expression of the ApoE gene is likely to result in endothelial injury, infiltration of lipid inflammatory cells, and peroxidation and further results in atherosclerosis, which once again verifies the strong association of ApoE with AMI.

Our study revealed no significant difference between the two groups in gender, height, BMI, or smoking, which indicates that the general population would not face a higher incidence of AMI because of these factors. However, the two groups were significantly different in age, hypertension, LAD and LVEF, suggesting that elderly people with hypertension, larger LAD, and lower

LVEF may face a greater risk of AMI. At the current stage, reportedly, the increase of LAD and decrease of LVEF can cause different degrees of myocardial electrical remodelling, structural remodelling and fibrosis, and these pathogenic factors are also the key to coronary atherosclerosis [26]. For patients with hypertension, continuous pressure increase will result in endothelial cell injury and increased release of endothelin, and further give rise to the expression of hs-CRP, TNF-α and interleukin, and promote the infiltration of inflammatory factors to destroy the normal atrial structure [27]. The correlation of ApoE with inflammation has been reported before [28, 29], and our results also support the hypothesis about the correlation of AMI with ApoE. Subsequently, we detected six genotypes of ApoE, namely, ε2/ε2, ε2/ε3, ε3/ε3, ε3/ε4 and ε4/ε4. Among them, the frequency of ε3/ε3 genotype is the highest in both groups, which is basically consistent with prior research on the genotype distribution of ApoE [30]. We also found a significantly higher frequency of ApoE ε4 gene in the Res group than in the Con group, which may be correlated with the strong pro-inflammatory impact of ApoE ε4 allele [31]. Additionally, analysis of the distribution frequency of ApoE alleles and the severity of AMI in our study revealed a higher frequency of ApoE ε4 in patients with more severe disease, which was similar to the research results of Lin et al., and might be associated with a higher degree of atrial fibrillation, inflammation, and endothelial damage [32]. However, other alleles besides ApoE ε4 may exert anti-inflammatory effects. For example, Angelopoulou et al. [33] have pointed out that ApoE ε2 might be correlated with a reduced risk of atrial fibrillation. However, in our study, no significant difference was found in ApoE ε2 and ApoE ε3 between AMI patients with different disease degrees, but this may need further confirmation with a larger sample size. Correlation analysis of ApoE with AMI revealed that carrying ApoE ε4 allele was a risk factor for AMI, which further illustrated the significance of the ApoE ε4 gene for AMI, and also revealed the possibility of adopting the ApoE ε4 gene for future prevention and treatment of AMI.

In addition, PCI is a preferred option for the therapy of AMI at the current stage, and postoperative anti-thrombosis is the focus of therapy. As one common antiplatelet drug after PCI, APC can substantially reduce stent thrombosis and adverse vascular events [34]. However, APC resistance gives rise to a huge risk for adverse prognosis. Therefore, it is of value to identify the risk of APC resistance early to realize targeted medication guidance after PCI. Our study has revealed a notable increase in the frequency of ApoE ε4 allele in patients with APC resistance and the related risk value of 1.25, which implied that carriers of ApoE ε4 might face a higher risk of APC resistance. At the current stage, although no direct evidence has been found to verify the association of ApoE gene polymorphism with APC resistance, some studies believe that a high plasma LDL-C level is one risk factor for APC resistance after PCI. This is because blood of patients with hyperlipidemia is in a hypercoagulable state, and vascular endothelial function and the fibrinolytic system are easily damaged, which can affect the platelet membrane structure and reduce the anti-platelet effect [35]. ApoE ε4 carriers often have a significantly higher plasma LDL-C than non-carriers, so perhaps its mechanism of action is just as described in the above. However, this study revealed no difference in the incidence of adverse vascular events and bleeding events in patients with AMI in ApoE ε2/3/4 types after PCI within 3 months of follow-up. This result suggests that the ApoE gene polymorphism is not enough to directly increase this risk of adverse vascular events after PCI, but the result might also be accidental because our limited sample size. In a follow-up study, we can expand the sample size for analysis to further provide the basis for the prevention and control of patients' later adverse cardiovascular events.

Limitations

The shortcomings of this study lie in the limited sample size, the lack of large-scale and multi-regional sampling and detection, and our inability to fully monitor the transportation and detection process of all blood samples, which may lead to non-human errors. In future clinical studies, we will aim to expand the sample size, further explore the role of ApoE2 in atrial arrhythmia, and improve and refine multi-area population studies and long-term follow-up of patients.

Conclusions

The mechanism of AMI caused by ApoE gene polymorphisms is still under exploration, but

according to prior research and our research results, AMI is under the influence of the of ApoE gene polymorphism, among which ApoE ε4 allele is the primary risk allele for AMI. In addition, ApoE ε4 carriers are more likely to have APC resistance after PCI, which is of profound value for early clinical evaluation.

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This study was approved by the institutional review board ethical committee (The Second People's Hospital of Lianyungang Ethics Committee No. L1719). All participants provided written informed consent.

Disclosure of conflict of interest

None.

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