The Effect of Apolipoprotein E Gene Polymorphism and Lp (a) Levels on Coronary Artery Disease with Atrial Fibrillation

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Research Article

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Abstract

Background This study is the first to explore the influence of the apolipoprotein E gene (APOE) and blood lipid metabolism on coronary artery disease (CAD) with atrial fibrillation.

Methods In this study, there were a total of 2048 participants, including 400 patients in the control group (CAD- AF-), 126 AF patients without CAD (CAD- AF+), 1294 CAD patients without AF (CAD+ AF-) and 228 CAD patients with AF (CAD+ AF+). Blood lipid levels and APOE genotypes were determined by collecting blood samples from the patients.

Results Compared with CAD patients without AF, the age and Lp (a) levels of CAD patients with AF were significantly higher. Among CAD patients, the frequencies of E3/E3 and ε3 genotypes in patients with AF were significantly lower than those in patients without AF, and the frequencies of E4/E4 and ε4 genotypes were significantly increased. Spearman correlation analysis showed that in CAD patients, Lp(a) levels in the ε4 group were significantly higher than those in the group of patients without ε4, and there was a significant correlation between ε4 and Lp (a) levels ($p<0.001$, $r=0.106$). Multivariate logistic regression analysis found that the increase in Lp (a) levels ($p=0.023$) and age ($p=0.01$) were independent risk factors for CAD patients who develop AF.

Conclusion Patients with AF had increased age, ε4 frequencies and Lp (a) levels among CAD patients, age and Lp (a) levels may be independent risk factors for CAD patients to develop AF.

Background

Coronary heart disease is currently the most common cardiovascular disease, its incidence is gradually increasing, and it has become the main cause of death in developed and developing countries [1–3]. Atrial fibrillation is the most common arrhythmia[4]. In addition to increasing the incidence of cardiogenic stroke, atrial fibrillation can also significantly increase the risk of heart failure and death in patients with coronary heart disease[5, 6], which brings a heavy burden to human health[7, 8]. There is no doubt that atrial fibrillation and coronary heart disease have become the two cardiovascular diseases that are most worthy of attention. While atrial fibrillation is an electrical atrial disease, coronary artery disease is a vascular structure disease [9]. However, many studies have shown that atrial fibrillation and coronary heart disease are closely related [10–12], which may be related to the common occurrence and development mechanism and risk factors for the two, such as dyslipidemia, fibrosis, inflammation, hypertension, and age. [13–15]. In recent years, the correlation between dyslipidemia and the occurrence and development of atrial fibrillation has received increasing attention, and there are many controversies [16–20], which have attracted our attention.

The apolipoprotein gene (ApoE) involved in lipoprotein synthesis and metabolism has three main subtypes, E2, E3 and E4, that are encoded by the corresponding alleles ε2, ε3 and ε4, and has 6 genotypes, E2/2, E2/3, E2/4, E3/3, E3/4 and E4/4 [21]. Previous studies have shown that both atrial fibrillation and coronary heart disease are related to genetic factors, and there is a strong genetic

component for the diseases [22–24]. A large number of studies have confirmed that the ε4 allele of apolipoprotein E is related to the increased incidence of atherosclerosis and coronary heart disease [25, 26]. However, there are still few studies on the relationship between APOE and atrial fibrillation, particularly in Alzheimer's disease patients [27, 28]. There is currently no literature that reports on whether there is a difference in APOE expression in patients with coronary heart disease and atrial fibrillation. This study attempted to explain the relationship between coronary heart disease and atrial fibrillation by exploring the expression of APOE and the distribution of blood lipids in patients with coronary heart disease and atrial fibrillation.

Methods

Study population

The included subjects were from the Affiliated Hospital of Xuzhou Medical University. The study was approved by the Ethics Committee of Xuzhou Medical University (No.XYFY2020-KL131-07). Written informed consent was obtained from each patient and relevant information was collected from the patients' clinical records. We consecutively enrolled 2048 patients admitted to the hospital for suspected coronary heart disease (from June 2020 to July 2021), and all selected patients underwent coronary angiography or coronary CTA examination. The diagnostic criteria for coronary heart disease were a coronary vascular examination showed that the diameter of the subepicardial coronary artery was more than 50% and the patient had typical angina symptoms, or a noninvasive examination showed that the patient had evidence of myocardial ischemia [29]. Atrial fibrillation was defined as the disappearance of P waves on electrocardiogram, and F waves of different sizes, shapes, and amplitudes were found. The frequency of F waves was 350 to 600 beats per minute, and the R-R interval was absolutely different [30]. The exclusion criteria were as follows: (1) patients with incomplete clinical data, including the lack of basic clinical data, and coronary angiography or coronary CTA was not successfully completed; (2) patients with prehospital use of lipid-lowering drugs, such as statins; (3) patients with severe liver and kidney dysfunction; and (4) patients with thyroid disease and multiple organ dysfunction.

Determination of blood lipids and APOE genotype

Peripheral venous blood was drawn on patients with an empty stomach; total cholesterol and triglycerides were measured by the enzymatic method; HDL cholesterol was determined by the phosphotungstic precipitation method; LDL cholesterol was obtained by formula calculation; and measured using the ELISA double antibody sandwich method Lipoprotein (a). The kit was used to detect the single nucleotide polymorphism of the APOE gene; 2 ml of the patient's blood sample was used for EDTA anticoagulation and DNA extraction, and the polymerase chain reaction (PCR) was performed according to the following protocol: after 2 minutes at 50°C–95°C the DNA was predenatured for 15 minutes, denatured 45 times at 94°C for 30 seconds, and annealed at 65°C for 45 seconds. A gene chip reader was used to read the fluorescence curve of the amplified product sample.

Statistical analysis

SPSS 22.0 software was used for statistical analysis. Continuous data are expressed as the mean ± standard deviation (SD), and Student's t test was used to compare the groups. Categorical variables are expressed as frequencies and were compared using the chi-square ($\chi 2$) test or Fisher's exact test. Spearman correlation analysis was used to compare the correlation between ε4 and Lp (a). Then, the potential risk factors were incorporated into multiple logistic regression analysis to evaluate the independent factors that determine if patients with CAD develop AF. $P < 0.05$ was considered significant.

Results

1. Characteristics of the study population

The basic clinical information of patients was summarized in Table 1. The study included 2048 subjects who were divided into four groups: the control group (CAD- AF-, n=400), the CAD- AF+ group (n=126), the CAD+ AF- group (n=1294) and the CAD+ AF+ group (n=228). Compared with the control group, the age was significantly higher in AF or CAD patients, and the proportion of male, hypertension, diabetes, smoking, and BMI were significantly higher in CAD patients. Compared with the CAD without AF group, the age of the CVD patients with AF were significantly higher (Table 1).

Table 1
Clinical data of the study population

Variables	CAD-		CAD+	
	AF- (n=400)	AF+ (n=126)	AF- (n=1294)	AF+ (n=228)
Age (Years)	60.69±11.8	63.6±10.31*	64.89±10.69**	66.86±10.78**#
Male(n, %)	191(47.8%)	59(46.8%)	816(63.1%)**	143(62.7%)**
Hypertension (n, %)	200(50%)	69(54.8%)	745(57.6%)*	140(61.4%)*
Dyslipidemia (n, %)	58(14.5%)	20(15.9%)	332(25.7%)**	63(27.6%)**
Smoking (n, %)	88(22%)	26(20.6%)	482(37.2%)**	85(37.3%)**
BMI(kg/m^2)	21.61±3.67	22.53±3.91	24.95±3.72*	25.05±3.5*
BMI Body mass index, CAD coronary artery disease, AF Atrial fibrillation				
*p-value<0.05: Comparison with CAD-AF-. **p-value<0.001: Comparison with CAD-AF-. #p-value<0.05: Comparison with CAD+AF-.				

2. Comparison of blood lipids in the study population

Among the enrolled population, compared with the control group, the TC, LDL-C, and Lp (a) levels of the CAD patients were significantly increased, and HDL-C was significantly decreased. Although the TG tended to increase, it was not statistically significant. Compared with the CAD without AF group, the Lp (a) levels of the CAD patients with AF was significantly higher (Table 2).

Table 2
Blood lipids of the study population

Variables	CAD-		CAD+	
	AF- (n=400)	AF+ (n=126)	AF- (n=1294)	AF+ (n=228)
TC (mmol/L)	4.73±1.36	4.81±1.51	4.92±1.45*	5.07±1.32*
TG (mmol/L)	1.66±1.35	1.52±1.16	1.71±1.22	1.68±1.14
LDL-C (mmol/L)	2.68±1.04	2.74±1.14	2.85±1.18*	2.98±1.17*
HDL-C (mmol/L)	1.35±0.43	1.36±0.38	1.29±0.41*	1.27±0.38*
Lp(a) (mg/L)	231.87±195	263.84±263.43	254.92±222.81*	280.29±165.08*#
CAD coronary artery disease, AF Atrial fibrillation				
*p-value<0.05: Comparison with CAD-AF-. #p-value<0.05: Comparison with CAD+AF-.				

3. Distribution of APOE genotypes of the subjects

Compared with the control group, the frequencies of E3/E4, E4/E4 and ε4 genotypes in CAD patients were increased significantly, and the frequencies of E3/E3 and ε3 genotypes were decreased significantly. In addition, among CAD patients, the frequencies of E3/E3 and ε3 genotypes in patients with AF were significantly lower than those in patients without AF, and the frequencies of E4/E4 and ε4 genotypes were significantly increased (Table 3).

Table 3
APOE polymorphism of the study population

Genotype	CAD-		CAD+	
	AF- (n=400)	AF+ (n=126)	AF- (n=1294)	AF+ (n=228)
E2/E2	3(0.8%)	0(0%)	6(0.5%)	1(0.4%)
E2/E3	42(10.5%)	14(11.1%)	153(11.8%)	25(11%)
E3/E3	268(67%)	84(66.7%)	742(57.3%)*	111(48.7%)**#
E2/E4	11(2.8%)	1(0.8%)	22(1.7%)	4(1.8%)
E3/E4	56(14%)	20(15.9%)	250(19.3%)*	53(23.2%)*
E4/E4	20(5%)	7(5.6%)	121(9.4%)*	34(14.9%)**#
ε2	60(7.5%)	15(6%)	187(7.2%)	31(6.8%)
ε3	633(79.1%)	202(80.2%)	1886(72.9%)**	300(65.8%)**#
ε4	107(13.4%)	35(13.9%)	515(19.9%)**	125(27.4%)**##

CAD coronary artery disease, AF Atrial fibrillation

*p-value<0.05: Comparison with CAD-AF-. **p-value<0.001: Comparison with CAD-AF-. #p-value<0.05: Comparison with CAD+AF-. ##p-value<0.05: Comparison with CAD+AF-.

4. Correlation between ε4 and Lp (a) levels in patients with CAD with or without AF

Through Spearman's correlation analysis and comparison, it was found that in CAD patients, ε4 and Lp (a) levels had a significant correlation, but the correlation coefficient (r=0.106) was low (Table 4). In CAD patients, Lp (a) levels in the ε4 group were significantly higher than those in the without ε4 group (Figure 1).

Table 4
Correlation between ε4 and Lp(a) in CAD patients.

Variable	Lp(a)	
	r	*P*-value
With ε4	0.106	<0.001

5. Multiple logistic regression analysis of CAD patients with or without AF

All risk factors were included in the logistics regression analysis, and it was found that the increase in Lp (a) levels (p=0.023) and age (p=0.01) were independent risk factors for CAD patients to develop AF (Table 5).

Table 5
Multiple logistics regression analysis of CAD with or without AF

Variables	B	SE	Wald χ2	P-value	OR
Constant	-2.6307	0.728	13.037	0.000	0.072
Male	0.014	0.174	0.006	0.938	1.014
Age	0.018	0.007	6.684	0.010	1.019
Hypertension	-0.112	0.150	0.558	0.455	0.894
Dyslipidemia	-0.074	0.163	0.207	0.649	0.928
Lp(a)	-0.001	0.000	5.188	0.023	0.999
Smoking	-0.060	0.174	0.119	0.730	0.942
BMI	0.006	0.020	0.090	0.764	1.006
With ε4	-0.191	0.154	1.542	0.214	0.826
BMI Body mass index					

Discussion

Coronary heart disease (CAD) and atrial fibrillation, the most common cardiovascular diseases and arrhythmia, respectively, have become significant threats to human health. The correlation between the two has been confirmed by a large number of studies [31–33]. The main risk factors for atrial fibrillation include age, race, blood lipid levels, obesity, hypertension, and certain lifestyle factors, which are also risk factors for coronary heart disease [34–36]. Among them, blood lipid levels are an established risk factor for coronary heart disease. In recent years, the relationship between blood lipid levels and atrial fibrillation has also become a research hotspot [16, 17]. Both coronary heart disease and atrial fibrillation show strong genetic correlations. This study attempted to explore the internal connection between coronary

heart disease and atrial fibrillation through the differences in the expression of blood lipids and the regulatory gene APOE in patients with coronary heart disease and atrial fibrillation.

In the comparison of clinical data, it was found that, compared with the control group, the age of patients with AF or CAD was significantly higher, and the proportion of male, hypertension, diabetes, smoking, and BMI were significantly higher in CAD patients. In CAD patients, the age of patients with AF was significantly higher compared with patients without AF. This is in line with the epidemiological manifestations of coronary heart disease and atrial fibrillation [29, 30]. Our study found that compared with the control group, the TC, LDL-C, and Lp (a) levels of patients with CAD were significantly increased, and HDL-C was significantly reduced. Since TG has been controversial in recent years, it is worth nothing that although the number of patients with coronary heart disease were found to have an increasing trend in this study, no statistical significance was found. Recently, a report from Navar AM [37] has attracted much attention. This study pointed out that hypertriglyceridemia should not be regarded as a single entity but should be regarded according to the multiple conditions of total particle number and composition, which seems to explain the ongoing controversy over TG in the research of coronary heart disease. Research data on the relationship between blood lipid levels and atrial fibrillation have been inconclusive and controversial. Among the studies, the study of Jiang Q, et al. [38] seems more convincing. They used Mendelian random methods to assess the risk of blood lipid levels and atrial fibrillation. Regarding causality, large-scale MVMR studies have shown that there is a positive causal relationship between high Lp (a) levels and an increased risk of atrial fibrillation. Similar to results of this study. Among CAD patients, the Lp (a) levels of patients with AF was significantly higher compared with the patients without AF. However, in patients without CAD, the Lp (a) levels of patients with AF did not show significant differences. This may be caused by the relatively low sample size of patients or different comorbid diseases, which requires more data from large samples for further discussion.

Next, we compared the expression of APOE genotypes in each group. Compared with the control group, the frequency of E3/E4, E4/E4 and ε4 genotypes in CAD patients increased significantly, and the frequency of E3/E3 and ε3 genotypes decreased significantly. This is similar to the results of previous studies [25, 26] that indicated that the APOE genotype is closely related to the occurrence and development of CAD. It is worth noting that among CAD patients, the frequency of ε4 in patients with AF was significantly higher than that in patients without AF. Previous studies on AF and APOE are lacking, and currently, studies mainly focus on cerebrovascular diseases, especially studies on Alzheimer's disease [27, 28, 39, 40]. Falsetti L, et al. [39] has shown that in Alzheimer's disease, the ε4 genotypes of AF was associated with a higher risk of rapid cognitive deterioration. Another population-based CAIDE study from Finland [40] showed that AF was an independent risk factor for dementia and Alzheimer's disease, and this association was related to the ε4 genotype. Similar to these results, it seems that ε4 plays an important role in patients with CAD and AF.

APOE is an apolipoprotein gene, and ε4 carriers have been shown to have higher TC and Lp (a) levels [41, 42]. This study found that in CAD patients, Lp (a) levels in the with ε4 group were significantly higher than that in the group without ε4. Although the subsequent Spearman correlation analysis showed that

there was a significant correlation between ε4 carriers and Lp (a) levels, the correlation coefficient was low. Therefore, we included Lp (a) levels, the ε4 genotype and other possible risk factors in the multiple logistics regression analysis. The results indicate that age and Lp (a) levels may be independent risk factors for CAD patients to develop AF, which is a brand new idea that provides information for coronary heart disease with atrial fibrillation.

There are some shortcomings in this study. First, this was a single-center study, and the ethnicity of the patients was Han, which leads to a lack of universal representativeness of the research results. In addition, we did not observe similar results when comparing AF in patients with CAD to patients without CAD. At present, we could not provide a satisfactory explanation. Future multicenter or larger sample studies are needed to further clarify this hypothesis.

Conclusion

Patients with AF had increased age, ε4 frequencies and Lp (a) levels among CAD patients, age and Lp (a) levels may be independent risk factors for CAD patients to develop AF.

Abbreviations

AF: Atrial fibrillation, BMI: Body mass index, CAD: Coronary Artery Disease, TC: Total Cholesterol, TG: Triglycerides, LDL-C: Low Density Lipoprotein Cholesterol, HDL-C: High Density Lipoprotein Cholesterol, Lp(a): Lipoprotein a.

Declarations

Acknowledgments

Not applicable.

Consent for publication

Not applicable.

Funding

Not applicable.

Ethics approval and consent to participate

This study has been approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Xuzhou, china), and the ethics number is: XYFY2020-KL131-07. All methods have been implemented in accordance with relevant guidelines and regulations, and all enrolled patients have signed the informed consent.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YL, LC and MZ performed the experiments and analyzed the data. LC and WC designed the study and wrote the manuscript. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

The authors declare that they have no competing interests.

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Figures

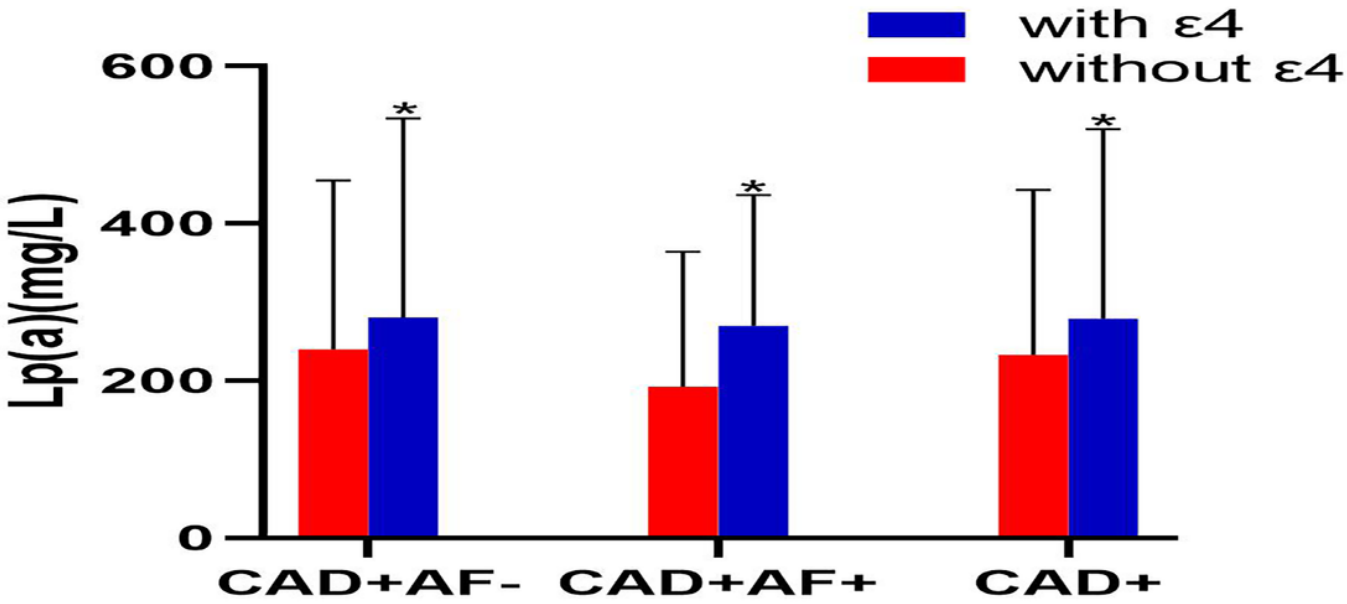

Figure 1

Comparison of Lp(a) between with ε4 and without ε4 in CAD patients. *p-value<0.05: Comparison with without ε4.