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Original Article

Apolipoprotein B and Low-Density Lipoprotein Cholesterol are Associated with Left Atrial Enlargement in Patients with Nonvalvular Atrial Fibrillation

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SUMMARY

Background: Patients who had left atrial enlargement (LAE) with atrial fibrillation (AF) had an increased risk of LA dysfunction. However, there were few reports about the relationship between apolipoprotein B (apo B) and LAE or the association between low-density lipoprotein cholesterol (LDL-C) and LAE. We aimed to evaluated the above relationships in patients with non-valvular atrial fibrillation (NVAF).
Methods: A total of 170 subjects were consecutively enrolled from December 2012 to July 2015. 87 subjects were retrospectively enrolled as control group. 83 patients were retrospectively included in NVAF group. Heart color Doppler ultrasound examination of all the study subjects were diagnosed by medical specialists. Routine biochemical indicators of hematology were tested in clinical laboratory.
Results: There were significant differences between the control and the NVAF group in terms of α-Hydroxybutyrate dehydrogenase (α-HBDH), triglyceride (TG), total cholesterol (TC) and LDL-C. In total NVAF patients, both the $CHADS_2$ (r = 0.578, *P* = 0.000) and CHA_2DS_2-VASc (r = 0.632, *P* = 0.000) scores were positively correlated with age. The $CHADS_2$ score was negatively correlated with apo B (r = -0.217, *P* = 0.049), and the CHA_2DS_2-VASc score was negatively correlated with TG (r = -0.256, *P* = 0.019) and calcium ion (CA) (r = -0.285, *P* = 0.009). In Pearson correlation analysis, LA diameter was negatively correlated with LDL-C (r = -0.425, *P* = 0.001), apo B (r = -0.407, *P* = 0.001) and TC (r = -0.378, *P* = 0.002) in patients with total NVAF accompanied by LAE. Multiple stepwise regression analysis revealed that LDL-C was an important factor influencing LA size in patients with NVAF.
Conclusion: In conclusion, apo B and LDL-C was associated with LAE in patients with NVAF, and LDL-C was an important factor influencing LA size in patients with NVAF.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, which affectsing 6% of men and 5% of women older than 65 years and increases the risk of stroke.[1] AF is not only associated with hypercoagulability and an inflammatory state but also increases the risk of dementia and cognitive impairment. The presence of diastolic dysfunction has been proven to increase the risk of AF.[2] It has been reported that increased LA size,[3] left ventricular (LV) hypertrophy,[4] and left ventricular systolic dysfunction are independent risk factors for thromboembolism in AF. CHA_2DS_2-VASc and $CHADS_2$ scores have been recommended as guides for antiplatelet or anticoagulation therapies in patients with NVAF. However, in clinical use, the CHA_2DS_2-VASc score is a more detailed assessment tool to evaluate the risk of thromboembolism in patients with AF.[5]

LAE has been defined as LA diameter (LAD) more than 39 mm in women and more than 41 mm in men.[3] LA size is a predictor of thromboembolism in patients with AF. LAE has been shown to predict systemic embolism and stroke in patients with NVAF.[6] α-Hydroxybutyrate dehydrogenase (α-HBDH), glutamic-oxaloacetic transaminase, creatine kinase, and lactate dehydrogenase (LDH) are myocardial enzymes and markers of cardiomyocyte damage, released from injured cardiomyocytes. Data from patients undergoing noncardiac surgery in Sichuan University West China Hospital demonstrated that the preoperative serum alpha-hydroxybutyrate dehydrogenase level is associated with in-hospital mortality and myocardial injury after noncardiac surgery.[7] α-HBDH levels may increase due to myocardial injury. Increased levels of myocardial damage markers, such as troponin I and troponin T, are often associated with heart enlargement.

Dyslipidemia is not only a risk factor for atherosclerosis and coronary heart disease but also is closely related to atrial fibrillation. Previous studies have revealed that low high-density lipoprotein is associated with diastolic function and modifies LV structure in patients with essential hypertension.[8] However, no studies have shown that apo B and LDL-C are associated with LAE in patients with AF. This study aimed to explore the relationships between apo B, LDL-C, and LAE in patients with AF.

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2. Methods

2.1. Patients

In this retrospective study, 170 subjects were consecutively enrolled. Eighty-seven subjects were randomly enrolled in the control group. These participants were healthy people from the outpatient department, and repeated ECG was used to exclude cardiac arrhythmias. Eighty-three patients were admitted to the cardiology department with the diagnosis of AF, including paroxysmal AF, persistent AF, and permanent atrial fibrillation. The participants in the two groups did not have hypertension, diabetes, hyperlipidemia, or other cardiovascular diseases, such as structural mitral regurgitation. All study subjects were enrolled from the first affiliated hospital of Jinan University from December 2012 to July 2015.

Heart color Doppler ultrasound can visualize the structure and function of the heart and its valves. In this study, color Doppler ultrasound was done by physicians from the cardiovascular department. The diameter of each heart chamber, thickness of the ventricular compartment, area of each heart valve, heart ejection fraction, E/A ratio, etc., were assessed. LAE was defined as an LA diameter (LAD) of more than 39 mm in women and more than 41 mm in men.[3] Routine hematologic indicators were measured in the clinical laboratory. AF was diagnosed by continuous electrocardiogram (ECG) monitoring, 12-lead ECG, or 24-hour Holter ECG. Exclusion criteria were age < 18 years, chronic obstructive pulmonary disease, serious renal diseases, and so on. All patients provided written informed consent to participate in this study. The protocol of this study was approved by the Ethics Committee of The First Affiliated Hospital of Jinan University, The First People's Hospital of Chenzhou, and Xiangya Hospital.

2.2. Baseline characteristics

In this study, baseline characteristics included age, sex, laboratory test results, echocardiography parameters, CHA_2DS_2-VASc score [congestive heart failure (1 point), hypertension (1 point), diabetes (1 point), age 65–74 years (1 point), female (1 point), peripheral vascular disease (1 point), age ≥ 75 years (2 points), and prior ischemic stroke (2 points)], and $CHADS_2$ score [age ≥ 75 years (2 points), hypertension (1 point), congestive heart failure (1 point), diabetes (1 point), and stroke (2 points)]. Data on clinical variables were collected (Table 1).

Blood samples were collected to measure apo B by immune turbidimetry.[9] First, 50 μL of sample and standard liquid were added to the standard well and the sample well, respectively. Then, 100 μL of horseradish peroxide (HRP)-conjugated detection antibody was added to each of the two wells. The wells were sealed with sealing plate film, and the test samples and standards were incubated in a 37 °C water bath pot or constant temperature box for 60 min. Next, we reversed the sample from the wells and absorbed the 96-well cell culture board with water-absorbent paper. The washing solution was added to each well. Thereafter, the substrate was added and incubated in a thermostatic box at 37 for 15 °C minutes. Finally, 50 μL of the termination solution was added to each well, and the OD value of each well was measured at 450 nm wavelength.

Blood samples were collected to measure LDL-C via the chemical precipitation method. First, a microcentrifuge tub was used to mix 100 μL of the 2x Precipitation Buffer with 100 μL of the serum sample. Then, the mixture was incubated at room temperature for 10 minutes and centrifuged at 2,000x g for 10 minutes. After centrifugation, the sediment in the lower layer was removed and placed in a new centrifugation tube. The centrifugation step was repeated. Next, the samples were resuspended with 200 μL of PBS. For colorimetric assays, the absorbance was measured at 570 nm (A570).

2.3. Statistical analyses

Continuous and discrete variables were shown as mean ± SD, respectively. Differences in continuous data were compared using two-tailed student's t-test. Categorical variables were compared using Chi-square test. All correlations were analyzed using Pearson correlation method. Multiple stepwise regression analysis was used to analyze the main influencing factors. All statistical analyses were conducted using SPSS version 20.0. Two-side p values of < 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

The clinical characteristics of all patients are shown in Table 1.

Compared with the control group, patients in the NVAF group showed higher age, LDH, α-HBDH, ADA, DBIL, and TG. Compared with the control group, patients in the NVAF group had lower TC, LDL-C, K, and CA. There were no significant differences between the two groups in terms of P, Mg, apo AI/B, and apo B.

3.2. Correlations of CHA_2DS_2-VASc score and $CHADS_2$ score with biochemistry index and clinical parameters in patients with NVAF

As shown in Table 2, among patients with NVAF, the $CHADS_2$ score was positively correlated with age (r = 0.578, p = 0.000), and negatively correlated with TC (r = -0.286, p = 0.009) and apo B (r = -0.217, p = 0.049). However, the CHA_2DS_2-VASc score was positively associated with age (r = 0.632, p = 0.000). On the other hand, it was negatively correlated with TG (r = -0.256, p = 0.019) and CA (r = -0.285, p = 0.009).

Table 1
Baseline characteristics.

	Control (N = 87)	Total AF (N = 83)	*P*
Age (years)	36.55 ± 11.05	70.95 ± 10.34	0.000
Female (n/N, %)	(33/83, 39.76%)	(1/87, 1.15%)	-
LDH (U/L)	157.09 ± 20.16	202.86 ± 56.22	0.000
α-HBDH (U/L)	114.38 ± 16.22	153.23 ± 49.49	0.000
ADA (g/L)	7.43 ± 2.00	13.86 ± 7.19	0.000
DBIL (umol/L)	3.69 ± 1.33	6.29 ± 4.14	0.000
TC (mmol/L)	4.72 ± 0.62	4.19 ± 1.06	0.000
LDL-C (mmol/L)	2.66 ± 0.50	2.34 ± 0.86	0.003
P (mmol/L)	1.17 ± 0.17	1.15 ± 0.27	0.507
Mg (mmol/L)	0.98 ± 0.09	1.00 ± 0.10	0.264
K (mmol/L)	4.12 ± 0.32	3.93 ± 0.44	0.002
Apo AI/B ratio	1.75 ± 0.53	1.85 ± 0.69	0.295
Apo B (g/L)	0.85 ± 0.17	0.85 ± 0.25	0.870
CA (mmol/L)	2.33 ± 0.13	2.24 ± 0.13	0.000
TG (mmol/L)	1.12 ± 0.76	1.41 ± 0.88	0.024
CHA_2DS_2-VASc score			
0 score, n (%)	0 (0%)	7 (8.43%)	-
1–2 score, n (%)	0 (0%)	4 (4.82%)	-
≥ 3 score, n (%)	0 (0%)	72 (86.75%)	-

Compared to control group, P < 0.05 were considered statistically significant.
Apo: apolipoprotein, ADA: adenosine deaminase, CA: calcium ion, DBIL: direct bilirubin, α-HBDH: α-hydroxybutyrate dehydrogenase, LAE: left atrial enlargement, LDH: lactate dehydrogenase, LDL-C: low density lipoprotein cholesterol, TC: total cholesterol, TG: triglyceride.

3.3. Correlations of left atrial diameter with biochemistry index in patients with NVAF

In patients with NVAF, left atrial diameter was positively correlated with DBIL (r = 0.218, *p* = 0.048), and negatively correlated with TC (r = -0.240, *p* = 0.029), LDL-C (r = -0.287, *p* = 0.009), and apo B (r = -0.281, *p* = 0.010) (Table 3).

3.4. Correlations of left atrial diameter with biochemistry index in patients with NVAF and concomitant LAE

Left atrial diameter was negatively correlated with LDL-C, apo B and TC in patients with NVAF and concomitant LAE. However, it is positively associated with DBIL (r = 0.253, *p* = 0.047) and apo AI/B (r = 0.269, *p* = 0.035) (Table 4).

The diagrams for the correlation between left atrial diameter and apo B or LDL-C, are shown in Figure 1.

3.5. Multiple stepwise regression analysis

In this study, the following items were included in multiple stepwise regression analyses: age, sex, LDH, a-HBDH, ADA, DBIL, TC, LDL-C, P, Mg, K, apo AI/B, apo B, CA, and TG. Multiple stepwise regression analysis revealed that LDL-C was an important factor influencing left atrium size in patients with NVAF (Table 5).

Table 2
Correlations of $CHADS_2$ score or CHA_2DS_2-VASc score with biochemistry index and clinical parameters in patients with non-valvular atrial fibrillation.

	r	*P*
$CHADS_2$ score		
Age (years)	0.578	0.000
TC (mmol/L)	-0.286	0.009
Apo B (g/L)	-0.217	0.049
CHA_2DS_2-VAS_C score		
CA (mmol/L)	-0.285	0.009
TG (mmol/L)	-0.256	0.019
Age (years)	0.632	0.000

Apo: apolipoprotein, CA: calcium ion, TC: total cholesterol, TG: triglyceride.

Table 3
Correlations of left atrial diameter with biochemistry index in patients with non-valvular atrial fibrillation.

	r	*P*
TC (mmol/L)	-0.240	0.029
DBIL (umol/L)	0.218	0.048
LDL-C (mmol/L)	-0.287	0.009
Apo B (g/L)	-0.281	0.010

Apo: apolipoprotein, DBIL: direct bilirubin, LDL-C: low density lipoprotein cholesterol, TC: total cholesterol.

Table 4
Correlations of left atrial diameter with biochemistry index in patients with non-valvular atrial fibrillation and concomitant left atrial enlargement.

	r	*P*
LDL-C (mmol/L)	-0.425	0.001
Apo B (g/L)	-0.407	0.001
DBIL (umol/L)	0.253	0.047
TC (mmol/L)	-0.378	0.002
Apo AI/B	0.269	0.035

Apo: apolipoprotein, DBIL: direct bilirubin, LDL-C: low density lipoprotein cholesterol, TC: total cholesterol.

4. Discussion

The major findings of the present study were that in patients with NVAF: (1) there were no significant differences between the control group and the NVAF group in terms of apo B; (2) there were significant differences between the control group and the NVAF group in terms of LDL-C; (3) $CHADS_2$ score was negatively correlated with TC and apo B; (4) CHA_2DS_2-VASc score was negatively correlated with TG; (5) left atrial diameter was negatively correlated with TC, LDL-C, and apo B in patients with NVAF; (6) in patients with NVAF and LAE, left atrial diameter was negatively correlated with LDL-C, apo B, and TC; (7) multiple stepwise regression analysis revealed that LDL-C is an important factor affecting left atrium size in patients with NVAF.

LAE occurs in patients with AF because (1) L-type Ca^{2+} channels

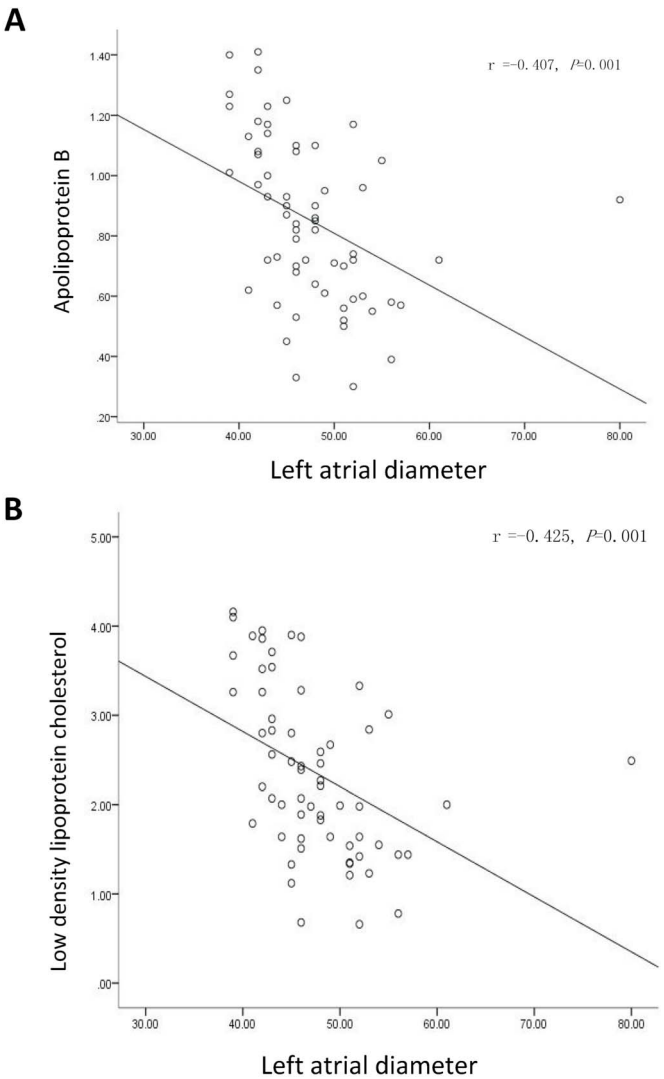

Figure 1. Correlation between left atrial diameter and apolipoprotein B (A) or low-density lipoprotein cholesterol (B) in patients with atrial fibrillation and concomitant left atrial enlargement.

Table 5
The results of multiple stepwise regression analysis in patients with total non-valvular atrial fibrillation and concomitant left atrial enlargement.

Model	β	Standard error	t	*P*	95% CI	
					Down	Up
Constant	50.556	2.355	21.464	0.000	45.870	55.243
LDL-C (mmol/L)	-2.547	0.946	-2.693	0.009	-4.428	-0.665

CI: confidence interval, LDL-C: low density lipoprotein cholesterol.

play an important role in the development of atrial electrical and structural remodeling leading to LAE.[10] However, there was no association between serum calcium level and LAE in this study. This may be due to the limited number of included participants. (2) Elevated systolic pressure of the pulmonary artery can increase LA pressure, leading to diastolic impairment. (3) AF increases LA size. LAE is a key risk factor for the development of AF.[11] In a multicenter study, Dittrich et al.[12] found that among patients with chronic NVAF, the mean LAD was 6 mm smaller in those with sinus rhythm (42 mm) than in those with AF (46 mm). (4) Mitral insufficiency causes mitral regurgitation. (5) Increased left ventricular mass,[1] subsequent elevation in the left ventricular filling pressure, and impaired LVEF lead to LAE.[14] (6) The total duration of the arrhythmia. (7) Structural remodeling,[15] such as fibrosis and apoptosis. (8) Intensified neurohormonal activation.

It has been proven that carotid plaque, increased carotid intima-media thickness, and higher levels of lipoprotein(a),[16] very low-density lipoprotein, and low-density lipoprotein cholesterol, apo B or apo AI are risk factors for coronary artery disease, ischemic stroke, atherosclerosis, and AF. LDL-C, a risk factor for atherosclerosis, dose-dependently increases the risk of ischemic stroke in patients with AF. To the best of our knowledge, plasma LDL-C levels > 2.48 mmol/L is a cut-off value and an independent risk factor for ischemic stroke.[17] We found that TC, LDL-C, and apo B are associated with AF. Pearson correlation analysis has indicated that in patients with NVAF, both apo B and LDL-C are negatively associated with left atrial diameter.

Recently, $CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2, and CHA_2DS_2-VASc-HS scores have been recognized as clinical predictors of stroke in patients with AF. In many studies, $CHADS_2$ and CHA_2DS_2-VASc scores have been recommended as guides to determine whether anticoagulation or antiplatelet therapy is required.[18] However, the $CHADS_2$ score has been replaced by the CHA_2DS_2-VASc score for identifying low-risk patients with AF.[5,19] In the present study, Pearson correlation analysis revealed that $CHADS_2$ score is not only positively associated with age but also negatively connected with apo B and LDL-C. We identified factors associated with CHA_2DS_2-VAS_C score or $CHADS_2$ score. Not all the diagnostic criteria were fixed. Future studies may add new factors to the CHA_2DS_2-VAS_C score or $CHADS_2$ score.

Females more frequently experience stroke or TIA,[20] heart failure, hypertension, hypercholesterolemia, and valvular disease than males. The prevalence of AF differs between females and males in Western countries,[21,22] and China,[23] particularly after 75 years of age. Previous studies found that female patients with AF are at a higher risk of thromboembolism than males.[24] Increased myocardial enzymes, such as lactic dehydrogenase, isoenzymes of CK, CK, α-HBDH, cardiac troponin T or I and myoglobin are reliable diagnostic markers for myocardial injury or myocardial infarction. Recently, it has been shown that four lipid-related differentially expressed genes (ACSL1, CH25H, GPCPD1, and PLA2G12A) can be diagnostic markers and therapeutic targets for AMI.[25] CK-MB, α-HBDH and LDH reach the maximal value of about 24, 24, and 36 hours after myocardial infarction, respectively. Preprocedural peak CK-MB (CK-MB point > 4.7) is a predictor of contrast-induced acute kidney injury among myocardial infarction patients.[26] Compared with α-HBDH activity in liver disease, α-HBDH activity is more increased in myocardial infarction. Elevated α-HBDH level (> 182 U/L) predicts a longer hospital stay and is significantly related to in-hospital mortality in elderly patients (age ≥ 60 years) with non-ischemic dilated cardiomyopathy (NIDCM).[27] Furthermore, previous studies have reported that serum α-HBDH activity increases in patients with severe and progressive muscular dystrophy, paroxysmal nocturnal hemoglobinuria, early-stage breast cancer,[28] and pregnancy.[29] Researchers have found that the serum level of α-HBDH is increased in the third trimester of pregnancy complicated by intrahepatic cholestasis of pregnancy. In addition, a-HBDH, another biochemical parameter, is used to assess the intrahepatic cholestasis of pregnancy severity.[29] It has been found that serum α-HBDH is an independent risk factor for in-hospital mortality and disease severity among COVID-19 patients. α-HBDH assessment may help clinicians identify high-risk individuals with COVID-19.[30] In an animal experiment, researchers have discovered that considerable changes in goat serum α-HBDH are accompanied by alterations in LDH and CK activity.[31] The present study found that α-HBDH has no relationship with LAE in patients with NVAF and demonstrated that apo B and LDL-C are associated with LAE in NVAF.

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Competing interests

The authors have no conflicts of interest.

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