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Original Article

The prospective effect of lipoprotein(a) on new-onset atrial fibrillation in patients with chronic heart failure

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Abstract: Background: Atrial fibrillation (AF) may persist due to atrial remodeling that is accelerated by inflammation and lipoprotein a (Lp(a)) is known to be involved in inflammatory reactions. But few studies have tried to confirm the association between them, even to prospect new-onset AF via Lp(a) levels especially in patients with chronic heart failure (CHF). The aim of our study was to explore Lp(a) as a predictor for future new-onset AF with univariate and multivariate analyses in patients with CHF. Methods: In this single-centre registry, Lp(a) measurement and cardiovascular assessment were performed in 679 subjects with CHF who underwent AF or not at enrollment. Patients were followed up for a mean of 25.3±0.6 (median 27.5) months. AF was identified by self-reported history or ECGs at baseline and by ECGs or hospital discharge diagnoses at follow-up. Results: Among 679 patients at enrollment, 145 (16.1%) of them had AF. Compared with the 534 patients without AF, AF patients had a higher concentration of Lp(a) (mean ± SD 0.4±0.2, P<0.05). Of 534 patients without AF at enrollment, approximately 6.7% developed new AF during the mean of 25.3±0.6 months follow-up with a higher Lp(a) levels (mean ± SD 0.5±0.3, P<0.05). In the Cox proportional hazards model, we confirmed that adjusted Lp(a) had a significant predictability of new-onset AF (adjusted hazard ratio for 1-SD increase, 2.693; 95% CI 1.005-7.22; P<0.05). Conclusions: In CHF patients with AF, LP(a) levels were higher compared with those without AF, and it had significantly predictive impact on future AF.

Keywords: Lipoprotein(a), Atrial fibrillation, Chronic heart failure, inflammation

Introduction

Atrial fibrillation (AF) is an abnormality of the heart's rhythm that is characterized by rapid and irregular activation of the atria. There are growing evidences tending that inflammatory processes may contribute to atrial injury by modifying the electrical activity of cardiac myocyte and therefore, precipitating AF [1]. AF increases in prevalence with age, and is particularly common in hypertensives and patients with heart failure [2]. Chronic heart failure (CHF) and AF often coexist and share risk factors. In a Framingham Heart Study, the combination of AF and heart failure carried a worse prognosis than either condition in isolation [men: HR, 1.6; 95% CI, 1.2-2.1; women: HR, 2.7; 95% CI, 2.0-3.6] [3].

Lipoprotein a (Lp(a)) which was discovered in 1963 by Kaare Berg in Norway is a plasma lipoprotein consisting of a cholesterol-rich LDL particle with one molecule of apo lipoprotein B100 and an additional protein, apo lipoprotein(a) attached via a disulfide bond [4]. Lp(a) is known to be involved in inflammatory reactions [5]. There are studies shown that its pathomechanism is mediated by pro-inflammatory and pro-atherogenic oxidated phospholipids (OxPL) associated with apo B 100-containing lipoproteins (OxPL/apo B) [6]. The correlation of elevated Lp(a) plasma levels with the increased cardiovascular risk is well-known since the 80 s [7]. Lots of studies revealed that elevated Lp(a) levels had a close relationship with cornory artery disease (CAD) and aortic valve stenosis (AVS) [8-11]. Pia R. Kamstrup' study has demonstrated that lowering Lp(a) levels might potentially not only decrease risk of myocardial infarction (MI) and AVS, but also decrease risk of heart failure [12]. However, it is unknown whether elevated Lp(a) levels contribute to

Table 1. Baseline HF patients' characteristics

	Atrial fibrillation at admission	No atrial fibrillation at admission	*P* value
Sex (men/women)	67/78	318/216	0.004
Age (year)	71.2±11.7	70.1±14.3	0.398
Cardiac function (NYHA grading) (III&IV), n (%)	125 (86.2)	459 (86.0)	0.938
I, n (%)	4 (2.8)	6 (1.1)	
II, n (%)	16 (11)	72 (13.5)	
III, n (%)	53 (36.6)	173 (32.4)	
IV, n (%)	72 (49.7)	283 (53.0)	
Diabetes, n (%)	67 (46.2)	190 (35.6)	0.019
Hypertension, n (%)	98 (67.6)	324 (60.7)	0.128
SBP (mmHg)	137.6±24.8	134.8±26.5	0.020
DBP (mmHg)	78.9±13.6	79.1±14.8	0.643
HR (bpm)	91.8 (28.6)	84.4 (20.1)	0.039
Coronary artery disease (CAD), n (%)	86 (59.3)	403 (75.5)	0.000
Valvular heart disease, n (%)	95 (65.5)	249 (46.6)	0.000
Cerebral vascular disease, n (%)	58 (40.0)	146 (27.3)	0.003
Peripheral vascular disease, n (%)	25 (17.2)	108 (20.2)	0.422
Autoimmunity disease, n (%)	16 (11.0)	55 (10.3)	0.798
Smoking, n (%)	30 (20.7)	201 (37.6)	0.000
Family history of CAD, n (%)	6 (4.1)	27 (5.1)	0.648
RAS inhibitor, n (%)	58 (40.0)	279 (52.2)	0.009
Statins, n (%)	55 (37.9)	276 (51.7)	0.003
LVEF (%)	32.9±16.2	38.7±16.7	0.000
HB (g/L)	124.8±26.9	118.6±30.5	0.014
TC (mmol/L)	3.9±1.5	4.2±1.7	0.212
LDL-C (mmol/L)	2.4±1.1	2.9±1.2	0.004
HDL-C (mmol/L)	2.3±0.8	1.1±0.5	0.439
TG (mmol/L)	1.2±0.7	1.2±0.8	0.534
LP(a) (g/L)	0.4±0.2	0.3±0.2	0.001
FBG (mmol/L)	7.3±2.8	6.8±2.9	0.054
FT3 (pmol/L)	4.1±1.8	4.2±1.7	0.214
FT4 (pmol/L)	19.2±3.4	13.9±6.7	0.000
TSH (μIU/ml)	2.1±1.6	2.4±4.4	0.180
Ptfv1 (mm•s)	-0.01±0.04	-0.001±0.08	0.000

Continuous variables are presented as mean ± SD; categorical variables are presented as percentages. NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RAS, renin-angiotensin system; LVEF, left ventricular ejection fraction; Ptfv1, P-wave terminal force in lead V1.

the presence of AF even more predicts new-onset AF, especially in patients with CHF.

Methods

Study population

679 patients with CHF who were admitted from January 2012 to December 2015 at Department of Cardiology of Shandong Provincial Hospital, in Jinan, China were included in the study. Before enrollment, they were collected a comprehensive inquiry at baseline, which included a thorough medical history especially present history and past medical history such as diabetes mellitus, hypertension, coronary artery disease with or without revascularization, valvular disease, cerebral vascular disease etc, physical examination, laboratory testing including total cholesterol, HDL, LDL triglycerides, fasting blood-glucose (FBG), LP(a) etc. 12-lead resting

Table 2. Baseline HF patients' characteristics after follow-up

	(+) New atrial fibrillation	(-) New atrial fibrillation	*P* value
Sex (men/women)	18/18	300/198	0.227
Age (year)	71.9±10.6	70.0±14.6	0.594
Cardiac function (NYHA grading) (III&IV), n (%)	33 (91.7)	426 (85.5)	0.307
I, n (%)	1 (2.8)	5 (1.0)	
II, n (%)	5 (13.9)	67 (13.5)	
III, n (%)	9 (25.0)	164 (32.9)	
IV, n (%)	21 (58.3)	262 (52.6)	
Diabetes, n (%)	20 (55.6)	170 (34.1)	0.010
Hypertension, n (%)	23 (63.9)	301 (60.4)	0.683
SBP (mmHg)	143.4±23.5	134.2±26.6	0.016
DBP (mmHg)	80.0±16.4	79.0±14.7	0.638
HR (bpm)	92.9±27.3	83.8±19.4	0.073
Coronary artery disease, n (%)	22 (61.1)	381 (76.5)	0.038
Valvular heart disease, n (%)	20 (55.6)	229 (46.0)	0.266
Cerebral vascular disease, n (%)	13 (36.1)	133 (26.7)	0.221
Peripheral vascular disease, n (%)	9 (25.0)	99 (19.9)	0.460
Autoimmunity disease, n (%)	6 (16.7)	49 (9.8)	0.193
Smoking, n (%)	14 (38.9)	187 (37.6)	0.873
Family history of CAD, n (%)	2 (5.6)	25 (5.0)	0.887
RAS inhibitor, n (%)	20 (55.6)	259 (52.0)	0.681
Statins, n (%)	17 (47.2)	259 (52.0)	0.579
LVEF (%)	33.0±12.8	39.1±16.9	0.002
HB (g/L)	100.7±33.8	120.0±29.8	0.000
TC (mmol/L)	4.2±1.4	4.2±1.7	0.754
LDL-C (mmol/L)	2.8±1.1	2.8±1.2	0.833
HDL-C (mmol/L)	1.2±0.7	1.3±0.9	0.756
TG (mmol/L)	1.2±0.7	1.3±0.8	0.628
LP(a) (g/L)	0.5±0.3	0.3±0.3	0.001
FBG (mmol/L)	8.9±3.5	6.7±2.8	0.000
FT3 (pmol/L)	3.9±1.1	4.2±1.7	0.742
FT4 (pmol/L)	14.4±3.8	13.8±6.9	0.013
TSH (μIU/ml)	1.8±1.3	2.8±4.7	0.134
Ptfv1 (mm•s)	-0.04±0.10	-0.01±0.08	0.003

electrocardiograms (ECGs) were collected and analysed at admission and AF was identified by self-reported history or ECGs at baseline. We also gathered echocardiography results including atrial ventricular size and evaluation of left ventricular ejection fraction (LVEF).

Lp(a) analysis

Baseline blood samples were obtained early in the day after an overnight fast at admission. Plasma and serum samples were all collected to the Central Laboratory, where they measured Lp(a) levels by an enzyme-linked immunoabsorbent assay (reagents of Pharmacia Diagnostic AB, Uppsala, Sweden).

Follow-up and study end points

New-onset AF was defined when paroxysmal AF (pAF) or persistent AF was firstly diagnosed attending physician(s) at hospital or community clinics according to ECG without a history of AF at enrollment. The patients without AF at enrollment were followed up clinically at one, three and six months and subsequently every six months for up to three years through telephone interviews. All baseline, clinical and in-hospital

Table 3. Multivariate Cox regression analysis for risk of new onset of AF

Risk factors	HR	95% CI	P
HR	1.017	1.002-1.031	0.024
LVEF	0.977	0.958-0.998	0.030
Hb	0.991	0.984-0.999	0.026
FBG	1.142	1.051-1.241	0.002
Lp(a)	2.693	1.005-7.221	0.049
FT4	1.086	1.043-1.130	0.000
ptfv1	0.025	0.001-0.535	0.018

Variables considered in the multivariate analyses included HR, heart rate at admission; LVEF, left ventricular ejection fraction; Hb; FBG; Lp(a); FT4 and Ptfv1, P-wave terminal force in lead V1.

datas were obtained and analyzed prospectively among positive results and negative events.

Statistical analysis

Distributions were tested for normality by Shapiro-Wilk W test. Continuous variables were presented as mean ± SD and categorical variables were presented as frequency (%). Continuous variables were compared by T test or Nonparametric test depending on normal distribution or not. The chi-square statistic was used to compare proportions. The association between Lp(a) and development of new-onset AF was estimated with multivariate Cox proportional-hazards regression models and the Kaplan-Meier method. Models were developed by a directed, forward stepwise selection technique and confirmed with bootstrap random resampling. All comparisons were carried on in SPSS 20.0 (SAS Institute, Cary, NC, USA) and results were considered statistically significant at a level of $P<0.05$.

Results

Of 679 subjects enrolled in our study, 145 (21.4%) patients had AF at baseline. Mean age was 70.4 years; 394 (58.0%) patients were men. Baseline clinical characteristics are presented in (**Table 1**). Among Patients with AF, prevalence of CAD, DM, hypertension, valvular heart disease and smoking habit is 59.3%, 46.2%, 67.6%, 65.5% and 20.7% respectively. Compared with those without AF, The AF group patients were older and were characterized by higher prevalence of DM, valvular heart disease, higher FT4 and lower LVEF and hemoglobin (Hb). We also observed patients with AF had higher levels of Lp(a) in contrast to those without AF.

For all 534 subjects without AF at enrollment were followed up for a mean of 25.3±0.6 months, 47 patients lost follow-up due to death or out of control and among the rest 36 individuals had new-onset AF. (**Table 2**) lists the baseline characteristics of patients in the 2 groups defined as (-) new AF, (+) new AF. the patients with new AF had higher FBG, Lp(a), FT4, lower LVEF, Hb, P-wave terminal force in lead V1 (PTFV-1) (negative deflections record to negative values) and higher prevalence of diabetes with a significant *P* value (<0.05).

Furthermore, a multivariable Cox proportional hazard model was performed to evaluate the prospective impact of Lp(a) on future AF. After adjustment for age, FBG, LVEF, heart rate (HR) at admission, FT4, Hb and ptfv-1, there were no interactions between Lp(a) and these variables and Lp(a) was found to be an independent predictor of new-onset AF (**Table 3**). **Figure 1** shows Kaplan-Meier AF-free survival curves comparing patients between the median of Lp(a) levels. The curve separated the entire follow-up period and confirmed the association of Lp(a) with new AF.

Discussion

The major findings of the present study were that (1) patients with AF at enrollment had higher Lp(a) levels compared with those without AF; (2) among the patients without history of AF at enrollment, approximately 6.7% developed new AF with a higher Lp(a) level than those without new-onset AF; (3) given that AF patients were characterized by clinical profiles such as age, sex, 2-DM etc, adjusted Lp(a) had a significant predictability of new-onset AF in the cox proportional hazards models.

AF is reported to be found in >5% of patients over 75 years old and the incidence of AF increases with age [13]. Because of the aging population, Atrial fibrillation (AF), the most common sustained arrhythmia in clinical practice, is becoming an increasing cause for morbidity and hospitalization including stroke, congestive heart failure, and cardiomyopathy. Rapid atrial rates leads to an impaired venatricular function by increased atrial size, increased fibrosis, and decreased cardiomyocyte contractility [2]. So

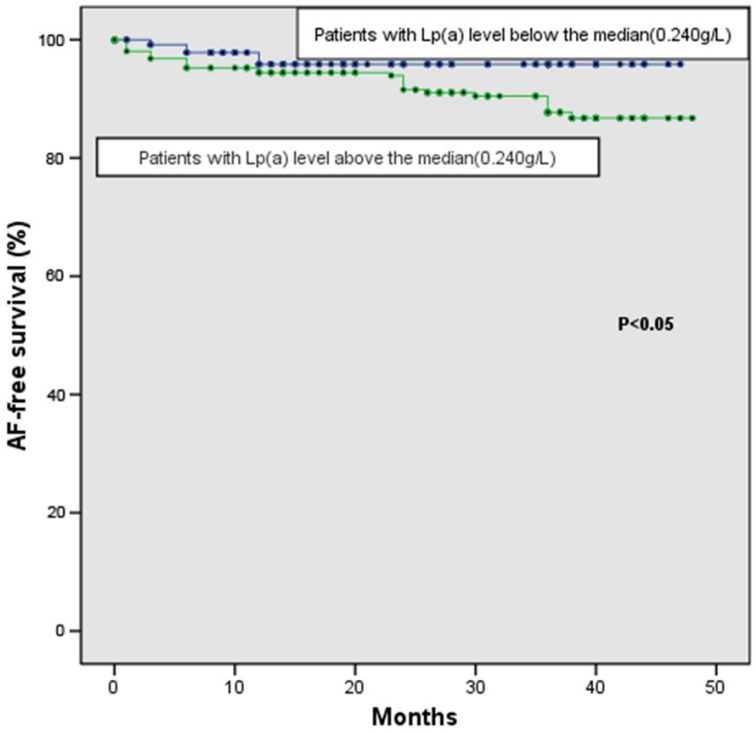

Figure 1. Kaplan-Meier curves for survival rate for subjects below and above median Lp(a) levels (0.240 g/L). Subjects above median Lp(a) value of 0.240 g/L had lower AF-free survival (log rank, P<0.05).

finding a predictive way of AF seems to be an urgent problem to be addressed.

Other predictors of new-onset AF in CHF patients

The development of AF in CHF patients appears to be a multifactorial process, involving structural and neurohormonal processes and electrical remodeling. Inflammation, stretch and ischemia were thought to be the pathophysiologic basis of AF. In our study, we found PTFV-1 was associated with new-onset AF. PTFV-1 has been reported to be an ECG marker of left atrial abnormality years ago [14]. LA dilation or LA abnormality can be single trigger of AF, but it can also be a result of long-term LV compliance/relaxation abnormality, especially in patients with low LVEF [15]. But no matter left cardiac insufficiency or dysfunction of right atrium, can evaluate the atrial internal pressure, leading to electrical remodeling of atrial muscles and finally inducing atrial fibrillation. Whether heart rate facilitates incidence of AF still remained controversial now. Some researches showed an increase in AF incidence at higher HR [16] and some had an opposite conclusion eapecially in patients with lower HR during exercise [17]. In our research, we have the same conclusion with the prior one. It could be thought that higher HR shorten the diastolic period, which would aggravate ischemia especially under the background of coronary stenosis. A meta analysis with Seven prospective cohort studies and 4 case-control studies has described the association between Diabetes mellitus (DM) and AF [18], which was identical to our conclusion for their positive correlation. In pathophysiology aspects, DM elicits AF via both structural remodeling, mediated by advanced glycosylation end products and autonomic nervous system remodeling [19, 20]. And a recent study revealed that activation of protein kinase C system could promote inflammation and atrial fibrosis, which could also be a potential trigger of new AF [21]. Dong-Zhu Xu's study demonstrated anemia was independently associated with increased risk for new-onset AF [22]. As reported, Anemia would lead to cardiac overload by decreasing oxygen-carrying capacity and increase neurohormonal activity, all of which can cause arrhythmogenic remodeling susceptible to AF. Early studies have concluded that hypertension is a well-established and highly prevalent risk factor for new-onset atrial fibrillation (AF) by electrical and structural remodeling changes via ventricular hypertrophy, impaired relaxation, and subsequent left atrial pressure overload and fibrosis [23]. Correspondingly, the proinflammatory molecules: Angiotensin II and aldosterone maybe other triggers of AF and more researches are now in progress. Over the past few years, free thyroxine (FT4) levels were found as a predictor of AF, as thyroid hormones would promote shortening of the action potential duration and refractory period, enhance automaticity and trigger activity in the pulmonary veins [24, 25] and we have got the same conclusion.

Prognostic impacts of Lp(a) in new AF with CHF

To pre-existing CHF patients, new-onset AF were considered to be associated with poor prognosis. Wang et al examined 1,470 individuals in a Framingham Heart Study and demonstrated that new on-set AF increased mortality in CHF subjects [3]. In a new recent CHART-2 study, Takeshi Yamauchi et al discovered 106 of 2,953 patients (3.6%) without a history of AF developed new onset AF during the median 3.2-years follow-up [26]. Overall, the proportion of new-onset AF patients is high in pre-existing heart failure patients. Franjo Naji's previous study discovered no association between Lp(a) levels and AF recurrencen patients after successful electrical cardioversion of persistent AF [27]. But in the present study we have found significant difference between them. In our study we followed 534 CHF patients without a history of AF from their admission until the new AF occurrence and observed that patients with elevated Lp(a) levels had a higher occurrence of new-onset AF. In the cox model, we found adjusted Lp(a) had a significant predictability of new-onset AF after ruling out clinical profiles such as age, sex, 2-DM etc. In CHF patients, there are AF susceptibility. For elevated lipoprotein(a) levels, risk estimates were even more attenuated since Lp(a) deteriorates the inflammation, disorders electrophysiological activity and then increases cardiac insufficiency. The difference with Franjo Naji's study could in part be explained as the characteristic of the enrolled patients such as worse cardiac function, higher lipid levels or more coronary heart disease background patients. Further studies are needed to elucidate the role of Lp(a) in this clinical setting.

As mentioned earlier, Lp(a) levels have a role in the pathogenesis of atherosclerosis, by affecting coronary artery disease, valvular heart disease etc. The relationship between Lp(a) with AF could partly be explained by the connection between Lp(a) and inflammation and its similarity with plasminogen interferes with fybrinolitic system [28, 29]. It is possible that in patients with higher levels of inflammation there would be stronger association between AF and levels of Lp(a). The modulation of platelet function by Lp(a) as a part of the prothombotic action has also been proposed, postulating an interaction between the apo(a) subunit and a specific receptor at the platelet surface [30]. Yutaka study shows the Lp(a) elevation and reduced left atrial appendage flow velocities are independently associated with thromboembolism in chronic nonvalvular atrial fibrillation [31].

These findings are clinically important because relying on Lp(a) would partly predict new-onset AF and help to adopt relevant measures in advance and correspondingly crucial for better management of CHF patients in the current aging society.

For the first time, we demonstrated a clear stepwise association of elevated lipoprotein(a) levels with increased risk of new-onset AF currency in the CHF population ($P<0.05$, 95% CI (1.005-7.22)). In addition, we found statistically significant conclusions between new-onset AF and ptfv-1, FBG, HR and FT4. The implications of our findings were that Lp(a) was an independent risk factor for AF currency, so lowering of lipoprotein(a) levels might potentially decrease risk of AF morbidity, then correspondingly decrease risk of CHF. Our results emphasize the need for randomized clinical trials on the effect of lowering lipoprotein(a) levels to prevent AF. Maybe feasible drug studies with marked lipoprotein(a) lowering effects will be increasingly carried out in the near future.

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Disclosure of conflict of interest

None.

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