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RESEARCH ARTICLE

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Association of serum adropin with the presence of atrial fibrillation and atrial remodeling

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Objective: Adropin, a newly identified regulatory protein encoded by Enho gene, suppressed tumor necrosis factor α-induced THP1 monocyte adhesion to human umbilical vein endothelial cells. In addition, inflammation is demonstrated to be involved in the mechanism of atrial fibrillation (AF). Atrial remodeling is correlated with the persistence and progression of AF. Adropin is hypothesized to correlated with AF and atrial remodeling. This study aims to determine the correlation of serum adropin and the presence of AF and remodeling.

Methods: This study consisted of 344 AF patients and 210 healthy controls. AF patients were then divided into three subgroups of paroxysmal AF, persistent AF, and permanent AF. Serum adropin concentrations were examined using enzyme-linked immunosorbent assay method. Left atrial diameter (LAD) was measured to evaluate atrial remodeling.

Results: Decreased serum adropin concentrations were found in AF patients compared with healthy controls. Logistic regression analysis confirmed that serum adropin was inversely associated with the presence of AF (OR 0.218, 95% CI 0.15-0.316; $P < 0.001$). Permanent AF patients had significantly reduced serum adropin concentrations compared with persistent and paroxysmal AF patients. There were decreased serum adropin concentrations in persistent AF group than those in paroxysmal AF group. Simple linear regression analyses showed that serum adropin in AF patients were negatively correlated with BMI, SBP, and LAD. Multiple stepwise regression analysis showed that LAD remained to be inversely associated with serum adropin ($\beta = 0.2$, $P = 0.010$).

Conclusion: Serum adropin concentrations are inversely correlated with the presence of AF and atrial remodeling.

KEYWORDS

adropin, atrial fibrillation, atrial remodeling, inflammation, left atrial diameter

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1 | INTRODUCTION

Atrial fibrillation (AF) is the most common type of clinical arrhythmia. The incidence of AF is increasing with the prolonged life of the general population.[1] AF results in a great public health cost due to its effect of hemodynamic impairment and increased risk of congestive heart failure, stroke, morbidity, and mortality.[2] The underlying mechanism of AF is still understood. Recent studies focus on the substantial link between inflammation and AF.[3] A variety of inflammatory factors were found to be elevated in AF patients.

Adropin, a newly found regulatory protein, is encoded by Enho gene (energy homeostasis associated) in the brain and liver of mice.[4] Adropin plays an important role in adiposity, insulin resistance, glucose, and lipid metabolism.[5] Sato et al reported that adropin suppressed tumor necrosis factor α-induced THP1 monocyte adhesion to human umbilical vein endothelial cells.[6] This indicates the anti-inflammatory role of adropin. As we know, inflammation is a clear mechanism of AF. Therefore, we speculate that adropin may be correlated with AF. However, no previous studies focused on the association of serum adropin and the presence of AF.

The aim of this study was to determine the correlation between serum adropin concentrations and the presence of AF and atrial remodeling.

2 | MATERIALS AND METHODS

2.1 | Patients

This study consisted of a population of 344 AF patients. AF patients were diagnosed according to the guidelines established by the European Society of Cardiology in 2010. Patients were enrolled consecutively from the consecutive outpatients who came to the outpatient clinic of our department in Tangdu Hospital from January 2017 to October 2017. Patients were excluded if they had congenital heart disease, valvular heart diseases, acute coronary syndrome, and systemic disease including diabetes, cancer, hypertension, as well as those had a history of infectious, and inflammatory diseases, or anti-inflammatory drugs during the past 3 months. These patients were excluded based on the disease history, blood pressure measurements, and laboratory testing results. AF patients were then divided into paroxysmal AF group (n = 122), persistent AF group (n = 130), and permanent AF group (n = 92). The control group included 210 consecutive healthy volunteers who had routine medical checkup in the medical examination center of our hospital from January 2017 to August 2017. The study protocol was approved by the Human Ethics Review Committee of our hospital and a signed consent form was obtained from each subject.

2.2 | Measurements

Serum was obtained from blood samples by centrifugation and stored at −80°C until analysis. Serum adropin concentrations were measured using an enzyme-linked immunosorbent assay (Phoenix Pharmaceuticals, Inc., Belmont, CA, USA). Two-dimensional and Doppler echocardiography was performed by an experienced sonographer by using a Vivid4 System (GE Healthcare Systems, Piscataway, NJ, USA). Left atrial diameter (LAD) was evaluated by an experienced sonographer who was blinded to the clinical status of the participants in parasternal long axis view at end systole.

2.3 | Statistical analysis

The parameters differences between case and control groups were compared by unpaired *t* test, Chi-square tests, or Mann-Whitney *U* test. Logistic regression analysis was performed to determine the correlation of serum adropin concentrations with the presence of AF. Chi-square tests, one-way ANOVA, or Kruskal-Wallis test were utilized to determine the parameter differences between different AF subgroups. Spearman correlation analysis was used to analyze the correlation of serum adropin with the subtype of AF. The correlation between serum adropin and other parameters was analyzed using simple linear regression analysis. Then, a multiple stepwise linear regression analysis was used to determine the contribution of various factors to serum adropin. *P* less than 0.05 was statistically significant.

3 | RESULTS

3.1 | Baseline clinical characteristics

Atrial fibrillation patients showed higher systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), LAD, and C-reactive protein (CRP), and as well as reduced high-density lipoprotein cholesterol (HDL-C) compared with healthy controls (Table 1). There were no significant differences in other characteristics between the two groups.

3.2 | Serum adropin concentrations in AF patients

Atrial fibrillation patients showed significantly reduced serum adropin concentrations compared with healthy controls (Table 1). Simple logistic regression analysis indicated that SBP, DBP, TG, HDL, and serum adropin showed a trend toward an association with the presence of AF (Table 2). All these parameters were then entered into a multivariate logistic regression model. Serum adropin concentrations remained to be adversely associated with the presence of AF (OR 0.218, 95% CI 0.15-0.316; $P < 0.001$) (Table 2).

3.3 | Serum adropin concentrations with the subtype of AF

Table 3 presented the characteristics of the subgroups of AF patients. There were no significant differences in the prevalence of hypertension, diabetes, and coronary artery disease, as well as medications targeting hypertension, diabetes, and coronary artery disease between

TABLE 1 Clinical and biochemical characteristics of the case and control groups

	The controls	AF patients	*P* value
N	210	344	
Age (y)	59.34 ± 10.11	60.65 ± 9.32	0.123
Gender (M/F)	122/88	196/148	0.796
BMI (kg/m^2)	24.31 ± 2.2	24.57 ± 2.89	0.253
SBP (mm Hg)	124.28 ± 14.11	138.95 ± 14.46	**<0.001**
DBP (mm Hg)	82.1 ± 8.96	85.58 ± 11.13	**0.007**
TG (mmol/L)	1.1 ± 0.46	1.64 ± 0.86	**<0.001**
TC (mmol/L)	4.95 ± 0.92	5.05 ± 1.06	0.249
HDL-C (mmol/L)	1.31 ± 0.2	1.1 ± 0.23	**<0.001**
LDL-C (mmol/L)	3.17 ± 0.44	3.23 ± 0.73	0.28
LAD (mm)	29.2 ± 3.26	41.28 ± 4.23	**<0.001**
CRP (mg/L)	2.1 (1.2-3.2)	3.3 (2.3-5.2)	**<0.001**
Adropin (ng/mL)	3.86 (2.95-4.74)	2.69 (2.32-3.33)	**<0.001**

P values with bold font mean statistically significant.

the three subgroups. In AF subgroups, permanent AF patients had reduced serum adropin concentrations than paroxysmal and persistent AF groups (Figure 1). Furthermore, decreased serum adropin concentrations were found in persistent AF patients than in paroxysmal AF subjects (Figure 1). Spearman correlation analysis indicated that serum adropin concentrations were inversely correlated with the subtype of AF ($r = -0.57$, $P < 0.001$).

3.4 | Serum adropin concentrations with other clinical characteristics

Simple linear regression analyses showed that serum adropin in AF patients were negatively correlated with body mass index (BMI) ($r = -0.159$, $P = 0.003$), SBP ($r = -0.187$, $P < 0.001$), LAD ($r = -0.195$, $P < 0.001$), and CRP ($r = -0.169$, $P < 0.001$) (Table 4). Multiple stepwise regression analysis showed that LAD ($\beta = -0.178$, $P = 0.001$) remained to be inversely associated with serum adropin (Table 4).

4 | DISCUSSION

The present study indicated that serum adropin concentrations were decreased in AF patients. Serum adropin was inversely associated with AF subtype. In addition, serum adropin concentrations were negatively correlated with LAD which is a parameter of atrial remodeling. This indicates that adropin is associated with the presence of AF and atrial remodeling.

Inflammation is involved in the pathogenesis of AF. Circulating inflammatory biomarkers were elevated in AF patients. And those inflammatory markers could predict the AF development and AF recurrence after cardioversion or catheter ablation.[3] The atrial interleukin (IL)-17A levels were elevated and correlated with AF. And treatment with anti-IL-17A monoclonal antibody decreased atrial IL-17A levels and significantly suppressed AF development in rats.[7] Adropin suppressed tumor necrosis factor α (TNFα)-induced THP1 monocyte adhesion to human umbilical vein endothelial cells.[6] Adropin also shifted the phenotype to anti-inflammatory M2 rather than pro-inflammatory M1 via peroxisome proliferator-activated receptor γ upregulation during monocyte differentiation into macrophages.[6] Intraperitoneal administration of adropin could decrease mRNA expressions of pro-inflammatory cytokines TNF-α and IL-6 via regulating the expressions of iNOS in hyperlipidemic rats.[8] All these findings point to the role of adropin in inhibiting inflammation. Our study showed that serum adropin concentrations are inversely correlated with the presence of AF. In addition, CRP is a inflammatory parameter which is demonstrated to be correlated with AF.[9] The current study demonstrated that serum adropin was negatively correlated with CRP. This indicates the possible anti-inflammatory role of adropin. Therefore, it is assumed that adropin may protect against the development of AF by suppressing inflammation. However, this hypothesis should be verified in the future studies.

TABLE 2 Logistic regression Analysis for the presence of AF

	Simple regression		Multiple regression	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (y)	1.014 (0.996-1.033)	0.123		
Gender (M/F)	1.047 (0.74-1.482)	0.796		
BMI (kg/m^2)	1.039 (0.973-1.109)	0.253		
SBP (mm Hg)	1.086 (1.067-1.105)	**<0.001**	1.103 (1.07-1.138)	**<0.001**
DBP (mm Hg)	1.034 (1.016-1.053)	**<0.001**	0.947 (0.91-1.008)	0.148
TG (mmol/L)	3.958 (2.744-5.71)	**<0.001**	3.319 (2.054-5.364)	**<0.001**
TC (mmol/L)	1.107 (0.931-1.316)	0.249		
HDL-C (mmol/L)	0.016 (0.006-0.039)	**<0.001**	0.022 (0.007-0.07)	**<0.001**
LDL-C (mmol/L)	1.162 (0.885-1.526)	0.279		
CRP (mg/L)	1.595 (1.41-1.803)	**<0.001**	1.384 (1.173-1.632)	**<0.001**
Adropin (ng/mL)	0.236 (0.182-0.308)	**<0.001**	0.299 (0.215-0.415)	**<0.001**

P values with bold font mean statistically significant.

TABLE 3 Clinical and biochemical characteristics of AF subgroups

	Paroxysmal AF	Persistent AF	Permanent AF	*P* value
N	122	130	92	
Age (y)	59.87 ± 8.68	60.98 ± 9.55	61.2 ± 9.82	0.513
Gender (M/F)	74/48	68/62	54/38	0.379
BMI (kg/m^2)	24.29 ± 2.87	25.02 ± 2.8a	24.31 ± 3	0.08
SBP (mm Hg)	137.79 ± 12.65	136.08 ± 13.57	144.57 ± 16.4ab	<0.001
DBP (mm Hg)	85.38 ± 10.97	82.39 ± 10.88a	88.2 ± 10.91a	0.001
TG (mmol/L)	1.78 ± 0.87	1.52 ± 0.71a	1.63 ± 1.01	0.057
TC (mmol/L)	5.06 ± 1.22	5.09 ± 0.86	4.99 ± 1.08	0.8
HDL-C (mmol/L)	1.12 ± 0.27	1.12 ± 0.2	1.04 ± 0.21ab	0.015
LDL-C (mmol/L)	3.14 ± 0.7	3.31 ± 0.72	3.24 ± 0.77	0.188
LAD (mm)	38.69 ± 4.5	41.7 ± 2.9a	44.12 ± 3.33ab	<0.001
CRP (mg/L)	2.85 (1.9-4.4)	3.25 (2.38-5.23)*	4.4 (2.9-5.88)*,**	<0.001
Adropin (ng/mL)	3.32 (2.64-3.86)	2.72 (2.16-3.23)[a]	2.36 (2.06-2.66)*,**	<0.001
Hypertension (%)	24 (19.7%)	35 (26.9%)*	28 (30.4%)*	0.173
Diabetes (%)	14 (11.5%)	18 (13.8%)	13 (14.1%)	0.805
CAD (%)	15 (12.3%)	22 (16.9%)	18 (16%)	0.333
Medication				
ACEI/ARB	21 (17.2%)	28 (21.5%)	26 (28.3%)	0.152
CCB	20 (16.4%)	29 (22.3%)	24 (26.1%)	0.213
OAD	14 (11.5%)	18 (%)	11 (12%)	0.836
Insulin	8 (6.6%)	9 (6.9%)	7 (7.6%)	0.956
Statins	27 (22.1%)	40 (30.8%)	31 (33.7%)	0.137

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CAD, coronary artery disease; OAD, oral antidiabetic drug.
*P < 0.05 vs paroxysmal AF patients.
**P < 0.05 vs persistent AF patients.
P values with bold font mean statistically significant.

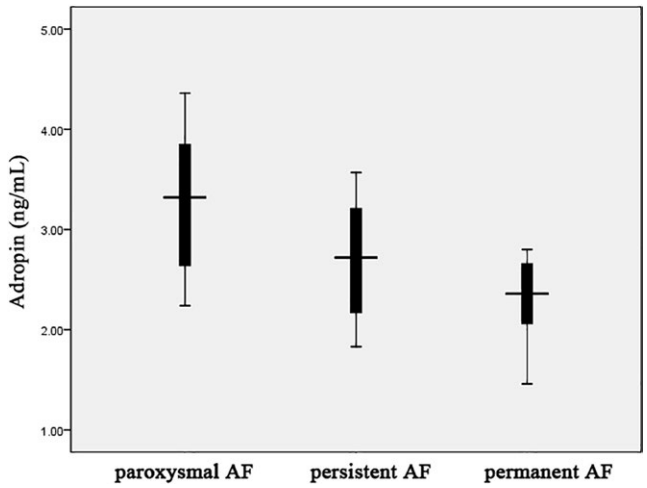

FIGURE 1 Serum adropin concentrations in paroxysmal AF, persistent AF, and permanent AF groups. Permanent AF patients had reduced serum adropin concentrations than paroxysmal and persistent AF groups. Furthermore, decreased serum adropin concentrations were found in persistent AF patients than in paroxysmal AF subjects

TABLE 4 The correlation of serum adropin concentrations with other clinical characteristics in AF patients

	Simple linear correlation		Multiple linear regression	
	r	*P*	β	*P*
Age (y)	−0.067	0.214		
Gender (M/F)	0.024	0.662		
BMI (kg/m^2)	−0.159	**0.003**	−0.173	**0.001**
SBP (mm Hg)	−0.187	**<0.001**	−0.167	**0.001**
DBP (mm Hg)	−0.007	0.899		
TG (mmol/L)	0.05	0.354		
TC (mmol/L)	0.066	0.222		
HDL-C (mmol/L)	0.011	0.832		
LDL-C (mmol/L)	−0.097	0.072		
LAD (mm)	−0.195	**<0.001**	−0.178	**0.001**
CRP (mg/L)	−0.169	0.002	−0.125	**0.018**

P values with bold font mean statistically significant.

Obesity is considered as a traditional risk factor for AF development. Framingham Heart Study results showed that greater pericardial fat was associated with an increased risk of incident AF.[10] Severe obesity with a BMI of 35 kg/m^2 or higher was demonstrated as a risk factor for postoperative AF after isolated coronary artery bypass grafting.[11] Overweight and obesity were associated with an increased AF risk, whereas weight reduction was independently associated with a reduced risk in a study performed in a population of 18, 290 subjects.[12] Adropin is correlated with obesity mechanism. Adropin is encoded by a gene called Energy Homeostasis Associated (Enho) gene. Liver Enho expression decreased with diet-induced obesity associated with 3 months of fed high-fat diet or with genetically induced obesity, suggesting an association with obesity.[4] Adropin regulated expression of hepatic lipogenic genes and adipose tissue peroxisome proliferator-activated receptor gamma, a major regulator of lipogenesis.[4] In addition, adropin levels were correlated negatively with BMI. Lower adropin levels were observed in overweighted and obese subjects compared with normal subjects.[13] Adropin concentrations increased after 3 months after Roux-en-Y gastric bypass surgery.[13] All these results suggest that adropin is closely correlated with obesity. Then, adropin is assumed to be involved in the mechanism of AF development and progression through the cross talk with obesity.

Left atrial diameter is utilized as a parameter of assessing atrial remodeling. In patients with sinus rhythm, LAD was shown to predict a future occurrence of AF.[14] A meta-analysis of 22 studies with 3750 patients also showed that increased LAD was associated with an increased risk of the recurrence of AF after radiofrequency ablation.[15] In addition, various results have reported that LAD was a risk factor of cardiovascular events in patients with atrial fibrillation.[16] The current study indicates that serum adropin was correlated with LAD.

This study has several limitations. First, this is a cross-sectional study. The causative relation must be confirmed by future longitudinal studies. Secondly, the control subjects were recruited from subjects undergoing routine medical checkups in hospital. They are not entirely healthy controls, which may lead to potential bias. Last, Subjects with hypertension, diabetes, and coronary artery disease were excluded from the control group, while some AF patients were companied with hypertension, diabetes, and coronary artery disease. This may also have some confounding effects on the results.

In conclusion, Serum adropin concentrations are inversely correlated with AF and atrial remodeling.

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