



## Serum fibroblast growth factor 21 levels are increased in atrial fibrillation patients



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### ABSTRACT

**Background:** Fibroblast growth factor 21 (FGF-21), a newly discovered adipokine, plays an important role in glucose and lipid metabolism and is associated with the development of metabolic disorders, such as obesity, and cardiovascular diseases. This study aimed to investigate the association of serum FGF-21 levels with the presence of atrial fibrillation (AF).

**Methods:** Total 113 patients with AF and 60 healthy control subjects were enrolled. All AF cases were categorized into paroxysmal, persistent and permanent AF. Serum levels of FGF-21, high-sensitivity C-reactive protein (hs-CRP) and other routine biochemical parameters were measured.

**Results:** Serum FGF-21 levels were significantly higher in AF patients than in controls ( $250.12 \pm 78.48$  vs.  $144.15 \pm 56.31$  pg/mL,  $P < 0.001$ ), and hs-CRP levels were significantly higher in AF patients than in controls ( $2.36 \pm 1.10$  vs.  $1.24 \pm 0.82$ ,  $P < 0.05$ ). In subgroup studies, patients with permanent AF had higher serum FGF-21 levels than those with persistent and paroxysmal AF. After the adjustment of the age, gender and body mass index, serum FGF-21 levels were positively correlated with left atrial diameter (LAD) ( $P < 0.01$ ). A multivariate logistic regression analysis showed that FGF-21, LAD and hs-CRP were correlated with AF ( $P < 0.05$ ).

**Conclusions:** Our data demonstrate that serum FGF-21 levels are elevated in AF patients and associated with atrial remodeling, independent of established risk factors such as C-reactive protein.

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### 1. Introduction

Atrial fibrillation (AF) is one of the most common clinical arrhythmia and is associated with substantially increased risk of death, stroke, and heart failure [1]. Previous studies have shown that the age, diabetes, hypertension, and cardiovascular diseases could increase the risk of AF development [2]. In addition, obesity emerges as an independent risk factor that contributes significantly to the onset of AF [3]. For example, each unit increase in body mass index (BMI) was associated with 3–8% higher incidence of AF [4]. Moreover, several studies suggest that pericardial fat is associated with the presence and the severity of AF [5–7].

Fibroblast growth factor (FGF) 21 is a member of the FGFs family which has been identified to play important roles in

regulating glucose and lipid metabolism. FGF-21 is produced by the liver, adipose tissue and the pancreas. In animal studies, FGF-21 has been demonstrated to stimulate glucose incorporation and lower blood glucose and triglyceride levels [8,9]. In human studies, serum FGF-21 levels were elevated in patients with obesity, metabolic syndrome, type 2 diabetes mellitus (DM) [10–12].

Furthermore, recent studies have demonstrated that FGF-21 was closely associated with cardiovascular diseases, such as coronary heart diseases (CHD), carotid atherosclerosis and hypertension [13–15]. More recently, serum FGF-21 concentration was reported to be associated with regional adipose deposits, including pericardial fat accumulation [16]. However, the relationship between FGF-21 and AF remains unclear. Therefore, in this study we examined serum concentrations of FGF-21 in 113 Chinese AF patients and analyzed the association of serum FGF-21 levels with AF. We also measured established cardiovascular risk factors and high sensitive C-reactive protein (hs-CRP) level to determine whether FGF-21 was an independent risk factor for AF.

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## 2. Materials and methods

### 2.1. Study subjects

We enrolled 113 consecutive patients with AF from Shaanxi Provincial People's Hospital, from 2013 April to 2014 March. AF was diagnosed by personal interview and reviewing the medical history and ECG data of all patients.

AF patients were divided into three groups according to American Heart Association guideline [17]. Paroxysmal AF was defined as recurrent AF that terminates spontaneously or with intervention within 7 days of onset. Persistent AF was defined as continuous AF that is sustained more than 7 days or that lasts <7 days but necessitates pharmacological or electrical cardioversion. Patients with AF of  $\geq 6$  months in duration and  $\geq 1$  attempt of unsuccessful cardioversion to restore normal sinus rhythm were considered to have permanent AF.

Exclusion criteria for patients with AF were valvular heart disease, diabetes, hyperthyroidism, acute coronary syndrome, previous cardiac surgery, severe pulmonary or renal disease, severe heart failure (NYHA III and IV), known ongoing systemic inflammation (cancer, infection, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, and liver fibrosis).

Sixty healthy individuals were selected as control group who matched with AF patients for the gender and body mass index (BMI). The study conformed to the principles outlined in the Declaration of Helsinki and the research protocol was approved by the Ethics Committee of Shaanxi Provincial People's Hospital.

### 2.2. Clinical data

The clinical data were recorded for all subjects, including the name, age, gender, height, weight, BMI, waist and hip circumference, blood pressure of all subjects during their admission. A detailed physical examination, routine laboratory testing, electrocardiographic and additional clinical data were available for all patients. The presence or the absence of AF at the time of sampling and symptomatic AF within the previous 24 h was determined for all AF patients. The echocardiographic data including the left ventricular ejection fraction (LVEF) and left atrial diameter (LAD) were measured by an experienced echocardiography specialist using a Vivid 3 System device (GE Healthcare Systems, Piscataway, NJ, USA).

All biochemical measurements were performed by the central clinical laboratory of our hospital, including total cholesterol (TC), total triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and high-sensitivity C reactive protein (hs-CRP).

### 2.3. Measurement of serum FGF-21

All blood samples were obtained after an overnight fast and stored in tubes. Serum was immediately separated by centrifugation at 3000 g for 10 min at 4 °C and kept at –80 °C until analysis. Serum levels of FGF-21 were determined in duplicates with a commercial Human FGF-21 enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. The intra-assay coefficient was 2.9–3.9% and determined by three samples of known concentration tested twenty times on one plate. The inter-assay coefficient was 5.2–10.9% and determined by three samples of known concentration tested in forty separate assays. The assay's sensitivity was 4.67 pg/mL, and the ELISA was specific for human FGF-21 with no cross-reactivity with human FGF-19 and human FGF-23.

### 2.4. Statistical analysis

Statistical analyses were performed using the SPSS software version 17.0. Normally distributed values were expressed as mean  $\pm$  SD, and categorical variables expressed as the percentage. Comparisons of clinical values between AF and the control group were determined using the Student's *t*-test (normally distributed data) or the Mann–Whitney *U* test (skewed data). Differences between AF subgroups were evaluated using the Kolmogorov–Smirnov test or ANOVA with the Tukey's post hoc test as appropriate. Inter-group comparisons of categorical variables were tested using the Chi-square test. Pearson or Spearman correlation tests were performed to explore the relationship between FGF-21 and clinical parameters. The multivariate logistic regression models were performed to identify the independent predictors of AF. All *P*-values were two-tailed and a *P*-value < 0.05 was considered statistically significant.

## 3. Results

### 3.1. Characteristics of subjects

113 patients with AF (paroxysmal AF 40 cases; persistent AF 38 cases; permanent AF 35 cases) and 60 controls were included in this study. Characteristics of the study sample are summarized in Table 1. The gender, BMI, and waist/hip ratio, blood pressure and smoking status were similar between the two groups. However, the AF group was older (66.56  $\pm$  11.0 years old vs. 57.78  $\pm$  5.52 years old, *P* < 0.001) and had a larger LAD than the control group (38  $\pm$  6.6 vs. 31  $\pm$  3.5 mm, *P* < 0.001). In addition, hs-CRP level was higher in the AF group than in the control group (1.24  $\pm$  0.82 mg/l vs. 2.36  $\pm$  1.10 mg/l, *P* = 0.005).

In subgroup analysis, permanent AF patients were older compared to paroxysmal and persistent AF subgroups (*P* < 0.05). Patients with permanent AF presented with higher hs-CRP levels, larger LAD and lower LVEF than those with paroxysmal and persistent AF subgroups, but these differences were not statistically significant (Table 2).

### 3.2. Serum FGF-21 levels in AF patients

Serum FGF-21 levels were significantly higher in patients with AF compared to the controls (250.12  $\pm$  78.48 vs. 144.15  $\pm$  56.31 pg/mL, *P* < 0.0001; Table 1, Fig. 1a). As shown in Table 2 and Fig. 1b, serum FGF-21 levels were significantly higher in permanent AF patients (353.88  $\pm$  95.77 pg/mL) than in paroxysmal (187.21  $\pm$  66.13 pg/mL, *P* < 0.0001) and persistent AF patients (193.45  $\pm$  83.81 pg/mL, *P* < 0.0001). On other hand, serum FGF-21 levels in AF patients with hypertension (313.73  $\pm$  102.38 pg/mL, *n* = 69) were not statistically higher than AF patients without hypertension (213.78  $\pm$  85.90 pg/mL, *n* = 44), but there was an elevated trend of serum FGF-21 levels in AF patients with hypertension (*P* = 0.069, Fig. 1c).

### 3.3. Association of serum FGF-21 levels with clinical parameters

In the AF group, serum FGF-21 level was positively associated with BMI (*r* = 0.43; *P* = 0.004) and waist circumference (*r* = 0.43; *P* = 0.005). After adjusting for the age, gender and BMI, serum FGF-21 level was significantly correlated with LAD (*r* = 0.482; *P* = 0.009, Table 3).

### 3.4. Association between serum FGF-21 levels and AF

Multivariate logistic regression analysis was structured with independent variables of age, gender, BMI, waist circumference

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