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Elevated soluble ST2 concentration may involve in the progression of atrial fibrillation

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ABSTRACT

Background: The aim of this study is to investigate the value of soluble suppression of tumorigenicity 2 (sST2) in Atrial fibrillation (AF) patients' risk prediction.
Methods: Healthy people (n = 60) and AF patients (n = 194) were consecutively enrolled into this project.
Results: In the health group, the mean age was 54 y (55% males). Serum median concentration of sST2 in healthy individuals was 17.04 ng/ml. In the AF patients group, the mean age was 61 years, and 64% were males. Median sST2 value was 21.69 ng/ml. According to subgroup analysis, median sST2 value of paroxysmal and persistent AF patients was 19.82 ng/ml and 24.15 ng/ml, respectively. Emergency AF patients showed much higher median sST2 concentration than AF outpatients (41.59 ng/ml *vs.* 20.53 ng/ml, $p < 0.01$). By multiple linear regression analysis adjusted for age and sex, heart failure (HF) and BNP strongly associated with sST2 concentration. After healthy people and AF patients with HF excluded, whether emergency visit or not become a patent predictor of sST2 concentration (n = 172).
Conclusion: sST2 is probably an objective biomarker that can predict AF patients' risk of emergency admission or HF. Elevated sST2 concentration may involve in the progression of AF.

1. Introduction

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia very common in medical practice, often associated with heart failure (HF) [1]. The association between AF and HF is bidirectional. Congestive heart failure (CHF) was associated with an increased risk of AF, and AF was associated with an increased risk of CHF [2]. Incident HF precipitated by AF is associated with a more benign prognosis, but new-onset AF in a patient with established HF is associated with a worse outcome [3]. Despite this, we should not ignore HF caused by AF. For women AF patients, they are prone to develop HF with preserved ventricular ejection fraction (HFpEF) [4].

Suppression of tumorigenicity 2 (ST2) is a member of the IL-1 receptor (IL-1R) family that plays a major role in immune and inflammatory responses. Alternative promoter activation and splicing produce 2 isoforms of ST2 [5]. The membrane-bound isoform (ST2L) induces an immune response when bound to its ligand, IL-33. The other isoform is a soluble protein (sST2) that is thought to be a decoy receptor for IL-33 signaling [6]. As a biomarker, sST2 is a strong independent risk predictor in HF patients and can provide additional prognostic value to NT-proBNP in risk prediction [7]. Rienstra et al. speculated, sST2 may be a useful marker of elevated risk after AF onset, rather than a marker of incident AF prediction [8].

As stated above, AF is a syndrome with a high prevalence of co-morbidities which increase the risk of recurrent AF and AF-associated complications.

2. Methods

2.1. Study population

The study was approved by the human subjects committee at Beijing An Zhen Hospital, China. An informed consent was obtained from all the participants. We randomly enrolled patients with a diagnosis of AF from December 2014 to January 2015. The patients' diagnosis was carried out by 2 specialists according to all clinical examination and ACCF/AHA/HRS guidelines [9]. AF was diagnosed if either atrial flutter (AFl) or AF was present on an electrocardiogram. Echocardiographic examination was done in certain AF patients enrolled in the study. AF patients with a diagnosis of cancer, acute infection, and immunological diseases were excluded from this study. Whether AF patients were HF patients, especially asymptomatic HF patients with preserved

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ventricular ejection fraction, were carefully evaluated according to HF guidelines [10,11]. The symptoms and signs of AF patients were evaluated first, then left ventricular ejection fraction (LVEF), B-type natriuretic peptide (BNP) and other 2 additional conditions were evaluated further [11].

The information from medical records was abstracted by 1 trained lab clinicians and was entered into a predefined electronic form. Clinical data including demographic characteristics, coexisting comorbidities, LVEF and several laboratory markers including BNP, high-sensitivity C reactive protein (hsCRP), glucose, creatinine and sodium were obtained in the medical records.

2.2. Laboratory analyses

Venous blood samples were drew for emergency patients immediately, or drew in the second day morning for outpatients and hospitalized patients, then centrifuged after 30 min at room temperature, and serum was frozen at −80 °C. Biomarkers were measured on samples that were not thawed previously. Soluble ST2 was measured by a high-sensitivity, second-generation enzyme-linked immunosorbent assay (Presage ST2; Critical Diagnostics) with a detection limit of 2 ng/ml. The inter-assay CV was 8.4% at low (22 ng/ml, low concentration control) and 1.8% at high sST2 concentrations (62 ng/ml, high concentration control). Serum hsCRP concentration was measured with turbidimetric inhibition immunoassay. Plasma BNP was measured by the Alere Triage immunoassay using the DxI800 platforms (Beckman Coulter Diagnostics) [12].

2.3. Statistical analysis

The demographic and clinical characteristics of the patient population were described by percentages, and means and standard deviations as appropriate. Comparison of ≥2 groups was performed by the Student's *t*-test, ANOVA or nonparametric tests. Because sST2, BNP and hsCRP measurements were right skewed, values were natural logarithmically transformed ($\log_e$) for analysis. The associations between serum sST2 and common cardiovascular comorbidities (AF, hypertension, diabetes mellitus, coronary artery disease (CAD) and HF), as well as biomarkers, were analyzed using univariant and multivariant linear regression models in all participants. Results were presented as either the relative or absolute change in the marker (depending on whether the marker was log transformed prior to modeling or not) associated with a one standard deviation increase in log-transformed sST2, with a 95% CI and *p*-value. Univariant and multivariant linear regression analyses were then used to examine whether sST2 is a correlative marker of AF clinical parameters adjusted for age and sex only in AF patients without HF. A $p < 0.05$ was considered statistically significant. The SPSS 24.0 statistical package was used for statistical analyses.

3. Results

3.1. Baseline characteristics

A total of 60 healthy people were enrolled as controls with 55% males. The mean age was 54 ± 8 y. The median value of sST2 concentrations in serum was 17.04 ng/ml (13.98–21.93 ng/ml). The median value of sST2 concentrations in men was 19.39 ng/ml (14.74–23.22 ng/ml), and the median value of sST2 concentrations in women was 16.40 ng/ml (13.47–20.31 ng/ml). Characteristics of the AF participants are reported in Table 1. Except serum sodium and hsCRP, there were significant differences of clinical variables between healthy group and AF group including glucose, sST2, creatinine and BNP ($p < 0.05$). Median sST2 in AF was 21.69 ng/ml (16.54–29.97 ng/ml). Other laboratory markers were measured in a part of AF patients (see Table 1).

Table 1
Baseline characteristics of the AF study cohort ($n = 194$).

Clinical variables	Observation[a]
Age (years)	61 ± 11
Males, n (%)	124 (64%)
Hypertension, n (%)	77 (40%)
Diabetes mellitus, n (%)	21 (11%)
CAD, n (%)	29 (15%)
Heart failure[b], n (%)	22 (11%)

Laboratory markers (n)[c]	Observation[a]
Glucose (mmol/l) (104)	5.83 ± 0.87
Creatinine (μmol/l) (182)	81.61 ± 20.64
Sodium (mmol/l) (169)	140.53 ± 2.25
hsCRP (mg/l) (155)	0.90 (0.45, 1.88)
BNP (ng/l) (99)	106 (41, 271)
sST2 (ng/ml) (194)	21.69 (16.54, 29.97)

AF subgroups	Observation[a]
Paroxysmal AF, n (%)	82 (42%)
Persistent AF, n (%)	51 (26%)
Unclassified AF, n (%)	61 (31%)
Preablation AF, n (%)	105 (54%)
Postablation AF, n (%)	13 (7%)
Outpatient AF, n (%)	53 (27%)
Emergency AF, n (%)	23 (12%)

[a] Data are expressed as mean (standard deviation), median [percentiles 25th–75th] or absolute number (percentage).
[b] 8 patients were of New York Heart Association (NYHA) Class II-III, and the rest 14 patients were of NYHA class I.
[c] n in brackets indicated the case number certain laboratory marker was measured.

In patient groups, emergency group presented the highest serum sST2 concentration. The median value of sST2 was 41.43 ng/ml (23.38–50.59 ng/ml). The second high group was preablation group, median sST2 value being 21.88 ng/ml (15.97–29.98 ng/ml). After sST2 being natural logarithmically transformed, *t*-test showed sST2 concentrations of emergency AF group and preablation AF group elevated significantly ($p < 0.01$; $p < 0.05$), compared with healthy group. Eight patients were excluded in below statistical analysis because their cardiac function was NYHA Class II or III (except for the first multiple linear regression analyse).

3.2. sST2 concentrations of different AF types

A total of 194 AF patients were enrolled between December 2014 and January 2015 (mean age of 61 ± 11 years, 64% males). A large percentage of patients had paroxysmal AF at 42%, followed by unclassified AF at 31%, then persistent AF at 26%. Median sST2 value in patients presenting with persistent AF was higher than that in patients presenting with paroxysmal AF (24.15 ng/ml (17.66–33.33 ng/ml) *vs.* 19.82 ng/ml (15.84–27.70 ng/ml), $p < 0.05$). The median sST2 in unclassified AF patients was 22.40 ng/ml (18.36–34.12 ng/ml), which fell between sST2 concentration of paroxysmal AF and persistent AF (Fig. 1). The group of unclassified AF was composed mainly of AF outpatients.

3.3. sST2 concentrations before and after catheter ablation

One hundred and one of AF patients who would receive catheter ablation within one week were recruited as preablation group, among which, 61% patients suffered from paroxysmal AF, and 39% patients suffered from persistent AF. Thirteen AF patients 4 to 6 months after catheter ablation were enrolled as postablation group. Ten (77%)