



Does an imbalance in circulating vascular endothelial growth factors (VEGFs) cause atrial fibrillation in patients with valvular heart disease?

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Background: The pathogenesis of atrial fibrillation (AF) remains unclear. Vascular endothelial growth factors (VEGFs) can stimulate fibrosis within the atrium and ventricle. We hypothesized that there is a relationship between the serum VEGFs/soluble vascular endothelial growth factor receptor (sVEGFRs) levels and AF in patients with valvular heart disease (VHD). This provides a new paradigm for studying AF.

Methods: The plasma levels of VEGF-A, VEGF-C, sVEGFR-1 and sVEGFR-2 were detected by enzyme-linked immunosorbent assay (ELISA). A total of 100 people, consisting of AF patients (long-standing, persistent AF; n=49), sinus rhythm (SR) patients (n=31) and healthy controls (n=20), were included in this study.

Results: The plasma levels of VEGF-A were significantly higher in AF patients compared to healthy control ($P<0.05$). The plasma levels of sVEGFR-1 were significantly higher in AF compared to SR ($P<0.05$). The plasma levels of sVEGFR-2 were significantly lower in AF patients compared to SR patients and healthy controls (both $P<0.05$). There was a significant and negative correlation between AF and the sVEGFR-2 levels in the groups ($r=-0.432$, $P=0.000$).

Conclusions: An imbalance in VEGFs and sVEGFRs may contribute to AF by breaking the balance of angiogenesis and lymphangiogenesis. Additionally, sVEGFR-2 may be an important biomarker of AF.

Keywords: Atrial fibrillation (AF); vascular endothelial growth factor-A (VEGF-A); vascular endothelial growth factor-C (VEGF-C); soluble vascular endothelial growth factor receptor-1 (sVEGFR-1); soluble vascular endothelial growth factor receptor-2 (sVEGFR-2)

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Introduction

Atrial fibrillation (AF), one of the most prevalent cardiac arrhythmias, affects 2.5–3.5% of the population worldwide, and increases the overall and cardiovascular mortality of patients (1,2). Furthermore, AF is commonly associated with valvular heart disease (VHD), with VHD also present

in 63.5% of AF patients in Europe (3). The outcomes of AF are not satisfactory, with neither medication nor ablation leading to sufficient resolution (4,5).

The pathophysiology of AF is highly complex, and the mechanisms underlying the initiation and maintenance of AF remain elusive (6,7). It is well known that AF occurs in

the setting of hypertension, VHD, coronary artery disease, congenital heart disease, alcohol intake, and various other conditions. It is possible that different causes of AF may share common features, or that distinct mechanisms may lead to the same symptoms. It was found that the level of vascular endothelial growth factor (VEGF) is higher in the left atrium of paroxysmal AF patients versus healthy subjects, suggesting that the heart itself is the most likely source of VEGF (8). There is evidence that VEGF and VEGF receptor (VEGFR) mRNA are both expressed in heart tissue (9,10). Many pathological conditions, such as inflammation, oxygen deficiency, and pulsatile mechanical stretch, induce VEGF secretion (11). It was previously noted that elevated VEGF was often associated with angiotensin-2 (Ang-2) and von Willebrand factor (vWF), suggesting a possible link between abnormal endothelial damage/dysfunction and angiogenesis, which would contribute to the prothrombinase state in AF (12). It was also shown that VEGF could stimulate fibrosis within the atrial tissue (13). Evaluating the expression and balance between VEGFs and their receptors may represent a new paradigm in the study of AF.

The VEGF-VEGFR system is crucial in angiogenesis and lymphangiogenesis (14). VEGFs activate VEGFR tyrosine kinases in endothelial cells to stimulate angiogenesis and lymphangiogenesis (15). There are five VEGF family members: VEGF-A through D and placenta growth factor (PlGF). Their regulation of angiogenesis mainly depends on binding to VEGFR-1 and VEGFR-2 (16). There are also two soluble VEGFRs, sVEGFR-1 and sVEGFR-2, which can act as negative regulators of the VEGF system by trapping VEGF family ligands such as VEGF-A, VEGF-C and VEGF-D (17).

We hypothesized that the VEGFs/sVEGFRs play an important role in the progression and maintenance of AF. In order to explore this hypothesis, we measured the plasma levels of VEGF-A, VEGF-C, sVEGFR-1 and sVEGFR-2 in VHD patients with persistent AF.

Methods

Clinical information of participants

We recruited 80 patients with VHD who were admitted to the Department of Cardiac Surgery of The First Affiliated Hospital of Sun Yat-sen University in China between March 2015 and March 2017. Forty-nine VHD patients had persistent AF. Persistent AF was defined as AF that

had persisted without interruption for 7 days or longer in patients receiving pharmacological intervention, or for whom electrical cardioversion was required to terminate the arrhythmia. Although there was some variation among patients, the disease severity was generally similar as assessed by their history of AF (all longer than 1 year) and the ultrasound findings. A total of 31 patients had sinus rhythm (SR). All of the patients had VHD, underwent a valve replacement procedure, and recovered well. We also recruited 20 subjects without VHD or any history of AF as a healthy control group. Each patient's heart rhythm was determined by an electrocardiogram taken at the time of admission. VHD was diagnosis by ultrasonic cardiogram and a post-operation pathological examination.

The exclusion criteria included recent-onset acute cardiovascular or cerebrovascular events, trauma or surgery, coronary artery heart disease, malignancy, connective tissue disease, acute or chronic infection, and pulmonary, hepatic, or renal dysfunction. Patients who were receiving treatment with anti-inflammatory or steroid drugs were also excluded. A formal medical and drug history-taking was done for each enrolled patient. All patients received a physical examination and routine laboratory tests. This study was approved by the Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University, and all patients enrolled in this study gave written informed consent.

Blood samples and biomarker analysis

Blood samples from both VHD patients and controls were obtained from the forearm veins using 6.0 mL vacutainer tubes (BD, Plymouth, UK) containing EDTA. The blood samples were immediately placed on ice before being centrifuged at 3,000 rpm for 10 minutes at 4 °C. Plasma samples were then stored at -80 °C until analysis. The plasma levels of sVEGFR-1, sVEGFR-2, VEGF-A, and VEGF-C were determined by enzyme-linked immunosorbent assays (Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan).

Statistical analysis

Values are expressed as the mean [\pm standard deviation (SD)] numbers and percentages. Categorical data were compared using a chi-squared test, and two-sample *t*-tests and Mann-Whitney tests were used as appropriate for parametric and non-parametric continuous variables. A receiver-operating characteristic (ROC) curve analysis was used to calculate the area under the curve (AUC) for the ability of the variables

Table 1 Clinical characteristics of the study groups

Parameters	Control (n=20)	VHD with SR (n=31)	VHD with AF (n=49)
Age (years)	32 (±9)	56 (±11)	55 (±10)
Men, n (%)	9 (45.0)	26 (83.9)	14 (28.6)
BMI (kg/m ²)	21.6 (±3.6)	23.0 (±2.5)	22.9 (±3.7)
Hypertension, n (%)	0 (0.0)	10 (32.3)	3 (6.1)
Diabetes mellitus, n (%)	0 (0.0)	3 (9.7)	1 (2.0)
Smokers, n (%)	0 (0.0)	7 (22.6)	8 (16.3)
β-blocker treatment, n (%)	0 (0.0)	9 (29.0)	10 (20.4)
Statin treatment, n (%)	0 (0.0)	4 (12.9)	5 (10.2)
Left ventricular EF, n (%)	68 (±7)	67 (±8)	60 (±8)**
Creatinine	82.1 (±24.3)	83.1 (±25.7)	83.7 (±23.3)
ALT	21.4 (±14.6)	22.4 (±13.3)	28.6 (±8.5)
NT-proBNP	435.1 (±876.4)	899.1 (±1,396.7)	1,319.9 (±1,002.2)

The results are expressed as numbers (percentages) or means (±standard deviation). Chi-squared values were used for categorical data, and two-sample *t*-tests and Mann-Whitney tests were used (as appropriate) for parametric and non-parametric continuous variables. **, $P < 0.001$, SR vs. AF. VHD, valvular heart disease; SR, sinus rhythm; AF, atrial fibrillation; BMI, body mass index; EF, ejection fraction; ALT, alanine aminotransferase; NT-proBNP, N-terminal pro-brain natriuretic peptide.

to predict AF in VHD patients. Multiple logistic regression models were also performed to assess the ability to predict AF in VHD patients. Comparisons between groups were made using a one-way analysis of variance (one-way ANOVA). Correlations were determined using Pearson's correlation or Spearman's rank correlation method, as appropriate. A two-tailed P value < 0.05 was considered statistically significant. Statistical analyses were performed with IBM SPSS 25.0 for Windows (IBM SPSS, Armonk, NY, USA).

Results

Baseline characteristics

The demographic and clinical characteristics of the study population, together with the laboratory findings, are presented in *Table 1*. The mean age, number of smokers, number of subjects with a history of hypertension or diabetes, and number of subjects receiving treatment with β-blockers or statins were significantly higher in the two groups of VHD patients than in the controls. The percentage of males and mean body mass index were not significantly different between the VHD patients and controls.

There were no significant differences between the SR

and AF groups in terms of the sex ratio, mean body mass index, smoking status, history of hypertension or diabetes, treatment with β-blockers or statins, or in the creatinine and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. The left ventricular ejection fraction (EF) (%) was significantly higher in the SR patients than in the AF patients, which was expected given that AF can influence the ventricular systolic function. The alanine aminotransferase (ALT) level was significantly higher in the AF patients than in the SR patients. This may have been due to the decreased cardiac function and increased pulmonary circulatory pressure, which might have resulted in hepatic congestion.

The concentrations of VEGFs among the AF, SR and healthy control subjects

The differences in the serum VEGF-A and VEGF-C levels among patients with AF and SR and controls are shown in *Table 2*. The plasma levels of VEGF-A were significantly higher in AF patients than in healthy controls [mean 188.81 (95% CI: 121.99–255.63) versus 88.90 (95% CI: 65.52–112.28) pg/mL, $P = 0.02$ by one-way ANOVA]. The plasma levels of VEGF-A were also higher in SR patients than in healthy controls [mean 149.37 (95% CI: 96.10–202.63) versus 88.90 (95% CI: 65.52–112.28) pg/mL, $P = 0.23$ by

Table 2 The VEGF-sVEGFR levels in the three study groups

Parameter	Control (n=20)	VHD with SR (n=31)	P value ^a	VHD with AF (n=49)	P value ^b
VEGF-A (pg/mL)	88.90 (±45.48)	149.37 (±99.95)	0.37	188.81 (±185.34)	0.02
VEGF-C (pg/mL)	1,040.20 (±308.61)	956.56 (±510.92)	0.40	1,051.91 (±543.35)	0.93
sVEGFR-1 (pg/mL)	92.91 (±26.64)	82.77 (±41.85)	0.03	138.87 (±149.48)	0.11
sVEGFR-2 (pg/mL)	6,239.05 (±1,030.40)	5,351.81 (±1,150.83)	0.00	4,627.65 (±1,076.69)	0.00

The results are expressed as the means (±standard deviation). Two-sample *t*-tests and Mann-Whitney tests were used as appropriate for parametric and non-parametric continuous variables. Comparisons between groups were made using a one-way Analysis of Variance (one-way ANOVA). P value^a: atrial fibrillation vs. sinus rhythm; P value^b: atrial fibrillation vs. control. VEGF, vascular endothelial growth factor; sVEGFR, soluble vascular endothelial growth factor receptor; VHD, valvular heart disease; SR, sinus rhythm; AF, atrial fibrillation.

one-way ANOVA]. The plasma levels of VEGF-A were not significantly different between the AF and SR patients. The area under the ROC curve for VEGF-A was 0.57 (95% CI: 0.42–0.71). There were no significant differences among the AF, SR and healthy control groups in terms of the plasma levels of VEGF-C. The area under the ROC curve for VEGF-C was 0.50 (95% CI: 0.39–0.62).

The concentrations of soluble VEGFRs among the subjects

The plasma levels of sVEGFR-1 were significantly higher in AF patients than SR patients [mean 138.87 (95% CI: 92.87–184.88) versus 82.77 (95% CI: 66.85–98.69) pg/mL, $P=0.03$ by one-way ANOVA]. The plasma levels of sVEGFR-1 were also higher in AF patients than healthy control [mean 138.87 (95% CI: 92.87–184.88) versus 92.91 (95% CI: 80.44–105.38) pg/mL, $P=0.11$ by one-way ANOVA]. However, there was no statistically significant difference between the SR group and healthy controls. The area under the ROC curve for sVEGFR-1 was 0.65 (95% CI: 0.53–0.76).

The plasma levels of sVEGFR-2 were highest in the healthy controls, followed by the SR group, then the AF group. The plasma levels of sVEGFR-2 were significantly lower in the AF group than in the SR group [mean 4,627.65 (95% CI: 4,318.39–4,936.91) versus 5,351.81 (95% CI: 4,929.68–5,773.94) pg/mL, $P=0.00$ by one-way ANOVA]. The plasma levels of sVEGFR-2 were also significantly lower in SR patients than in healthy controls [mean 5,351.81 (95% CI: 4,929.68–5,773.94) versus 6,239.05 (95% CI: 5,756.81–6,721.29) pg/mL, $P=0.01$ by one-way ANOVA]. The area under the ROC curve for sVEGFR-2 was 0.77 (95% CI: 0.67–0.86).

A multiple logistic regression analysis including VEGF-A, sVEGFR-1 and sVEGFR-2 was performed, and

the area under the ROC curve was 0.80 (95% CI: 0.69–0.91]. The Chi-squared test gave a value of $P=0.00$.

Correlation of the VEGF-A, sVEGFR-1 and sVEGFR-2 levels with other clinical features

Correlations between and among the levels of VEGF-A, sVEGFR-1, and sVEGFR-2, the presence of AF, the left ventricular EF (%), and the creatinine, ALT, and NT-proBNP levels were examined (listed in Table 3). There was a significant positive correlation between sVEGFR-2 and the left ventricular EF ($r=0.311$, $P=0.005$). There was also a significant and negative correlation between AF and the sVEGFR-2 level ($r=-0.432$, $P=0.000$). In addition, there was a negative correlation between the NT-proBNP and sVEGFR-2 levels ($r=-0.256$, $P=0.024$).

Discussion

The main findings of the present study are that the plasma levels of VEGF-A and sVEGFR-1 were significantly higher in AF patients than controls and SR patients. The plasma levels of sVEGFR-2 were significantly lower in the AF group than in the control and SR groups. The plasma levels of sVEGFR-2 were also significantly lower in the SR group than in the control group. The left ventricular EF (%) was significantly higher in the SR patients than in the AF patients, which is in agreement with the fact that AF can influence the ventricular systolic function. There was a significant negative correlation between AF and the sVEGFR-2 level.

Why are the plasma levels of VEGF-A and sVEGFR-1 significantly elevated in AF patients?

This is the first study to demonstrate that there are

Table 3 Correlation of the VEGF-A, sVEGFR-1 and sVEGFR-2 levels with clinical variables

Features	VEGF-A		sVEGFR-1		sVEGFR-2	
	r	P value	r	P value	r	P value
VEGF-A	1.000	–	0.153	0.128	0.091	0.368
sVEGFR-1	0.153	0.128	1.000	–	–0.071	0.483
sVEGFR-2	0.091	0.368	–0.071	0.483	1.000	–
Atrial fibrillation	0.168	0.095	0.167	0.096	–0.432	0.000
Left ventricular EF (%)	–0.051	0.655	–0.077	0.497	0.311	0.005
Creatinine	0.005	0.966	0.004	0.970	–0.007	0.954
ALT	0.021	0.865	0.049	0.669	–0.064	0.570
NT-proBNP	–0.029	0.805	0.002	0.985	–0.256	0.024

Correlations were ascertained with Pearson's correlation or Spearman's rank correlation method, as appropriate. VEGF, vascular endothelial growth factor; sVEGFR, soluble vascular endothelial growth factor receptor; EF, ejection fraction; ALT, alanine aminotransferase; NT-proBNP, N-terminal pro-brain natriuretic peptide.

differences in the plasma VEGF-A and sVEGFR-1 levels in VHD patients with and without AF. It is known that AF can cause endothelial dysfunction (18). Our results showing that the plasma levels of VEGF-A and sVEGFR-1 were significantly higher in AF patients suggests that endothelial dysfunction may be the cause of AF. The level of vWF, an indicator of endothelial damage or dysfunction, was previously found to be increased in AF patients, supporting the role of endothelial dysfunction in AF (19,20). Further, the proliferation of circulating endothelial progenitor cells (EPCs), which contribute to endothelium repair by replacing damaged endothelial cells, was significantly reduced in patients with permanent AF (21). Electrical remodeling, structural remodeling caused by aging, coronary artery disease, hypertensive heart disease, diabetes mellitus and inflammation have all been suggested to play important roles in the progression and maintenance of AF (22,23). The remodeling can be seen as atrial fibrosis (24). Further, many studies showed significantly increased secretion of VEGF, possibly originating from cardiac myocytes (8,12,25,26).

Hypoxia is known to upregulate VEGF via HIF-1 α (27). AF can cause tissue hypoxia, and VEGF may ameliorate myocardial ischemia (28,29). Using left atrial appendage (LAA) samples obtained from 59 AF patients, Abe *et al.* (30) found that overexpression of HIF-1 α may be involved in atrial myocardial fibrosis. Scridon *et al.* suggested that the secretion of VEGF in the left atrium is a transient event in the natural history of AF, where the spreading cardiac

fibrosis would reduce the degree of pulsatile stretch and subsequently diminish the VEGF levels (8).

Although VEGF does not appear to play a direct role in angiogenesis or the vascular permeability in AF, some studies had shown that VEGF could stimulate the fibrosis process within the atrium and ventricle (31-34). It is known that soluble VEGFR-1 (sFlt-1) is an endogenous VEGF inhibitor. For example, sVEGFR-1 neutralizes VEGF-A, and is critical for maintaining the corneas devoid of blood vessels in the eyes (35). According to the literature, the sVEGFR-1 level is correlated with morbidity and mortality, and is a potent marker of disease severity in patients with sepsis or who are critically-ill (36). Our findings show that the plasma levels of VEGF-A and sVEGFR-1 are both increased in AF patients. While VEGF-A promotes angiogenesis, sVEGFR-1 can downregulate VEGFR signaling, mainly by trapping VEGF-A. This system may explain why AF is associated with endothelial dysfunction and fibrosis. However, more research is needed to explain why the expression levels of sVEGFR-1 are increased in patients with persistent AF.

The two most important complications of AF are thromboembolism and heart failure. In our study, we found that the plasma levels of VEGF-A and sVEGFR-1 were significantly elevated in AF patients, while the left ventricular EF (%) was significantly higher in the SR patients than the AF patients. Heart failure and AF often coexist and form a vicious cycle. Risk factors such as hypertension, diabetes and valvular disease may lead

to AF, while AF can cause heart failure. However, heart failure is also a risk factor for AF, and the incidence of AF is directly related to the New York Heart Association (NYHA) classification. The incidence of AF in NYHA class I heart failure patients was less than 10%, while in NYHA IV patients, AF was present in more than 55% of cases. Moreover, severe heart failure can also increase the rate of AF (37-39). Our study shows that targeting VEGF-A and soluble VEGFR-1 may provide a new way to study the causes of AF, and may represent targets for treatment.

Why are the plasma levels of sVEGFR-2 decreased in AF patients?

The VEGF family plays a crucial role in the formation of blood vessels and in lymphangiogenesis (40). Atrial tissue fibrosis is promoted by lymphangiogenesis. Although VEGF-C is one of the most important factors involved in lymphangiogenesis, our results showed that the plasma levels of VEGF-C were not significantly different among the groups. sVEGFR-2 plays a key role in maintaining the status of the cornea as a lymphatic-free tissue, and it selectively inhibits lymphangiogenesis, but not angiogenesis (41). By inhibiting lymphangiogenesis, sVEGFR-2 can also influence tumor progression by regulating lymphatic formation and metastasis *in vivo* (42-44). However, it is unknown whether sVEGFR-2 can inhibit lymphangiogenesis in atrial tissues during fibrosis. In the present study, the plasma level of sVEGFR-2 was decreased in AF patients. This may suggest that the suppression of lymphangiogenesis was weakened in these patients. This is consistent with the finding by Berntsson *et al.* that increased VEGF-D is associated with AF (45). Further studies will be needed to determine whether this is the case, and to identify the detailed mechanism(s) underlying this phenomenon.

Limitations

This study is limited by its cross-sectional design. Thus, as an observational study, cause-effect relationships could not be established. Further prospective studies are necessary to confirm our present findings. The sample size of our study was also small, and did not include patients with isolated AF who didn't have VHD. As a result, we were unable to rule out the effects of VHD on the findings. We also did not evaluate the changes in the plasma levels of sVEGFR-1, sVEGFR-2, VEGF-A and VEGF-C after valve

replacement surgery. Future studies might examine whether the expression of these proteins is changed after surgery, and how the levels correlate with the response to valve replacement.

Conclusions

The present findings indicate that an imbalance in the VEGFs/sVEGFRs may contribute to AF, possibly by breaking the balance between angiogenesis and lymphangiogenesis. Although further studies are needed due to the small sample size and cross-sectional design of the present study, our findings suggest that these proteins may be involved in AF, and sVEGFR-2 may represent an important biomarker of AF.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University [No. [2017]157], and all patients enrolled in this study gave written informed consent.

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