BMC Cardiovascular Disorders

RESEARCH

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Vascular Cell Adhesion Molecule 1 in atrial fibrillation

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Abstract

Objective Assessing whether serum Vascular Cell Adhesion Molecule 1(VCAM-1) concentration in the left atrial appendage(LAA) and the expression of VCAM-1 in LAA tissues are associated with the risk of atrial fibrillation-related stroke.

Method Blood samples were collected from atrial fibrillation(AF) patients scheduled for catheter ablation of AF, both from within the LAA and peripheral veins(PV). The serum concentration of VCAM-1 was quantitatively analyzed using ELISA. Additionally, LAA tissues were obtained from AF patients undergoing cardiac surgery, and immunohistochemical quantification was conducted to assess VCAM-1 expression in these tissues. Univariate analysis and multivariate logistic regression were performed to examine the association between VCAM-1 levels and the risk of atrial fibrillation-related stroke.

Results A total of 146 patients scheduled for AF ablation and 34 patients scheduled for cardiac surgery were enrolled in this study. Among these two groups, there were 67 cases (45.9%) and 13 cases (38.2%) of AF patients who experienced strokes, respectively. Serum analysis revealed that in the AF group with strokes, the LAA serum VCAM-1 concentration was higher compared to the AF group without strokes (631.64 ± 143.48 pg/ml vs. 336.71 ± 201.66 pg/ml, $P < 0.001$). Similarly, the PV serum VCAM-1 concentration was higher in the AF group with strokes compared to the group without strokes (591.65 ± 128.23 pg/ml vs. 257.71 ± 157.92 pg/ml, $P < 0.001$). Additionally, both the AF group with strokes and the group without strokes exhibited higher LAA serum VCAM-1 concentrations compared to PV serum concentrations (631.64 ± 143.48 pg/ml vs. 591.65 ± 128.23 pg/ml, $P = 0.041$) and (336.71 ± 201.66 pg/ml vs. 257.71 ± 157.92 pg/ml, $P = 0.004$).Regarding left atrial tissue analysis, the AF group with strokes had a higher average optical density value (AOD) of VCAM-1 compared to the group without strokes (1.257 ± 0.147 vs. 1.093 ± 0.161, $P < 0.001$), indicating a higher expression level of VCAM-1 in the LAA in the AF group with strokes. In univariate analysis, LAA serum VCAM-1 concentration (OR = 1.15, $P < 0.001$), PV VCAM-1 concentration (OR = 1.11, $P < 0.001$), and LAA VCAM-1 AOD value (OR = 3.04, $P = 0.021$) were all associated with the risk of atrial fibrillation-related stroke. In the multivariate logistic regression analysis, LAA serum VCAM-1 concentration (OR = 1.17, $P = 0.002$) and PV VCAM-1 concentration (OR = 1.30, $P = 0.034$) were predictive of atrial fibrillation-related stroke. Specifically, left atrial appendage serum VCAM-1 concentration greater than 387.93 pg/ml and peripheral vein VCAM-1 concentration greater than 344.04 pg/ml were predictive of atrial fibrillation-related strokes.

Conclusions The risk of stroke in AF is associated with VCAM-1, and elevated serum VCAM-1 concentrations in AF patients who experience strokes may be attributed not only to systemic inflammatory responses but also to increased

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VCAM-1 expression in LAA tissues. Serum VCAM-1 concentrations in AF patients can serve as predictive factors for atrial fibrillation-related stroke, with LAA serum VCAM-1 concentrations exceeding 387.93 pg/ml and peripheral vein VCAM-1 concentrations exceeding 344.04 pg/ml being predictive of atrial fibrillation-related strokes.

Keywords Vascular Cell Adhesion Molecule 1, Atrial fibrillation, Left atrial appendage, Stroke

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and a major contributor to thromboembolic strokes, with an associated increase in mortality rates [1]. The primary site for thrombus formation in AF is the left atrial appendage. The mechanism of embolization in AF is linked to the rapid atrial rhythm disrupting hemodynamics and triggering systemic oxidative stress and inflammatory responses. Some studies suggest that during episodes of sustained atrial rhythm irregularities in AF, oxidative stress and inflammatory responses are not limited to systemic effects but also involve increased local inflammation within the atria. Simultaneously, pro-inflammatory and pro-thrombotic gene expression within the atria may also alter [2–4]. Vascular Cell Adhesion Molecule 1(VCAM-1) is a cell surface protein primarily expressed by endothelial cells and has been confirmed to be associated with the persistence of AF in various epidemiological studies, with the highest serum concentrations observed in patients with left atrial appendage thrombi [5, 6]. In a 2017 Bruneck study, Karin Willett demonstrated a significant association between serum VCAM-1 concentrations and new-onset AF in the general community, as well as an association with AF-related ischemic strokes [1]. In this study, we aim to explore the relationship between VCAM-1 and the risk of AF-related strokes, as well as whether VCAM-1 levels are linked to local inflammatory responses within the left atrial appendage, by analyzing the concentrations of VCAM-1 in the left atrial appendage and peripheral vein sera, as well as the expression levels of VCAM-1 in left atrial appendage tissues.

Methods

Study population

The study included patients who were candidates for atrial fibrillation catheter ablation and those scheduled for cardiac surgery with cardiopulmonary bypass, encompassing individuals with and without a history of stroke within the past year among AF patients. All patients took oral rivaroxaban anticoagulation (dosage determined by creatinine clearance rate, 20 mg qd or 15 mg qd).They were categorized into two groups based on stroke occurrence: the stroke-AF group and the non-stroke AF group. Blood samples were collected from patients undergoing AF catheter ablation, including samples from within the left atrial appendage(LAA) and peripheral veins(PV). LAA tissues were collected from AF patients scheduled for cardiac surgery with cardiopulmonary bypass. Relevant clinical data of the study participants were obtained, including age, height, gender, BMI, NYHA classification, complete blood count, liver and kidney function tests, D-Dimer, fibrinogen levels, echocardiography, cardiac CT, 12-lead ECG, as well as their medical history of prior cardiac surgeries, concurrent medical conditions, and medications. The research protocol was reviewed and approved by the ethics committee, and all participants with concurrent malignancies or autoimmune diseases, and patients with hyperthyroidism. The definition of ischemic atrial fibrillation-related provided written informed consent before entering the study.

Ascertainment of AF and ischemic AF-related stroke

The diagnosis of AF is established through a 12-lead electrocardiogram (ECG) and 24-h ambulatory ECG monitoring, encompassing both valvular and non-valvular atrial fibrillation. Exclusion criteria comprise patients with the following conditions: those requiring pacemaker therapy due to concomitant bradyarrhythmias, patients stroke is as follows: 1) a confirmed diagnosis of atrial fibrillation, 2) the occurrence of a stroke or transient ischemic attack (TIA) within one year (the diagnoses of stroke and TIA were established through outpatient interviews and CT/MRI imaging), 3) the absence of vascular-related stroke etiologies, such as intracranial or extracranial arterial stenosis (determined by cerebral vascular CTA).

Sample acquisition

For patients scheduled for AF catheter ablation, with blood samples collected from within the LAA and PV: 2% lidocaine local anesthetic was administered for right femoral vein puncture in the groin area. Subsequently, a Super Stiff Guidewire (Abbott Medical, 180 cm) and a Transseptal Guiding Introducer (Fast-Cath, Abbott Medical, 8.5F, 63 cm) were advanced through the femoral vein into the right atrium. Using the Fast-Cath, a Transseptal Needle (St. Jude Medical, 71 cm) was employed to puncture the interatrial septum. A PIG (Cordis, 6F, 110 cm) was then positioned deep within the LAA to collect 5 ml

of blood from within the LAA, simultaneously with the collection of 5 ml of blood through the femoral vein. Subsequently, 10 ml of Iodixanol (32 mg/100 ml) was injected through the PIG, and fluoroscopy was employed to confirm the placement of the catheter tip deep within the LAA (Fig. 1).

For patients scheduled for surgical atrial fibrillation ablation under cardiopulmonary bypass,with left atrial appendage tissue collected: General anesthesia was administered during surgery, and cardiopulmonary bypass was established. The pericardium was opened using thoracoscopy, and a portion of the LAA tissue was isolated and excised after ligation. The harvested left atrial appendage tissue was rinsed with sterile injection water and fixed in 10% formaldehyde for subsequent analysis (Fig. 2).

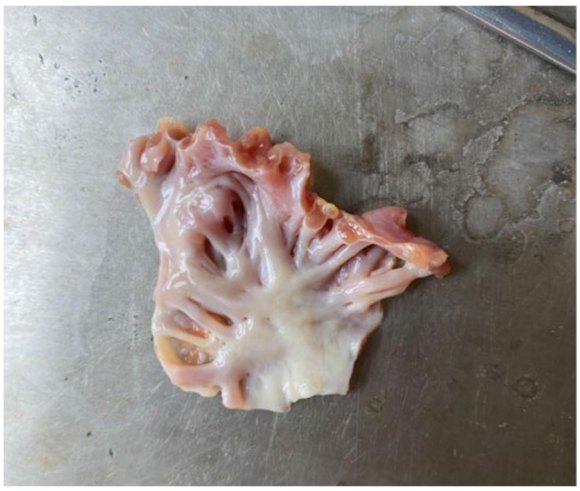


Fig. 2 Left atrial appendage tissue

Laboratory methods

The serum VCAM-1 concentration (pg/ml) was quantitatively analyzed using ELISA. Following blood sample collection, centrifugation was performed at 3000 rpm for 20 min, and the upper serum layer was collected and stored at -80 degrees Celsius. Serum VCAM-1 concentrations were determined for all samples using an enzyme-linked immunosorbent assay (ELISA) kit from Animal union Biotechnology, with intra-assay and inter-assay coefficients of variation of 4.5% and 8.9%, respectively.

Immunohistochemical assessment of VCAM-1 average optical density values (AOD) in LAA tissue was conducted. Left atrial appendage tissues fixed in 10% formaldehyde were prepared as paraffin sections. All tissue sections were stained with hematoxylin and eosin after being labeled with recombinant antibodies, where positive expression was indicated by brownish-yellow coloration. Images were acquired by scanning the slides using Omnipath Slide Center software, and subsequent analysis of AOD was performed using Image J software. (AOD was calculated as the optical density value (OD) divided by the area (Area)).

Statistical analysis

Statistical analysis was performed using SPSS 23.0 software (SPSS, Chicago, Illinois, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test, and these variables were presented as mean ± standard deviation (Mean ± SD). The analysis of continuous variables was conducted using the t-test. Risk factors for atrial fibrillation-related strokes were assessed through univariate analysis and multivariate logistic regression analysis. Receiver Operating Characteristic

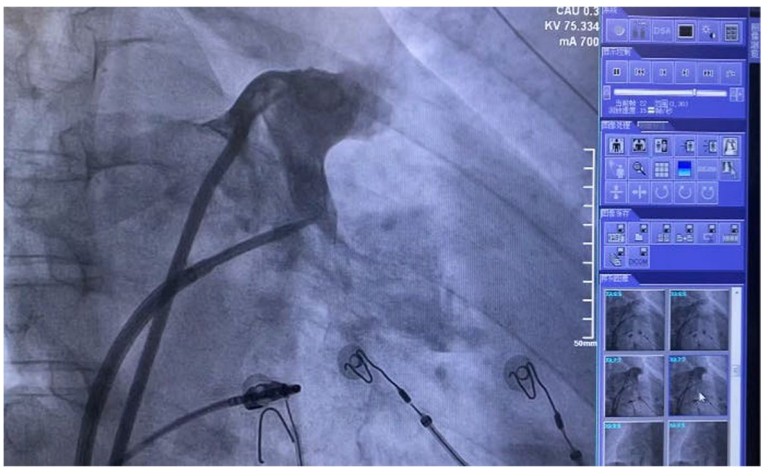


Fig. 1 Left atrial appendage angiography confirms PIG in LAA

(ROC) curves were constructed, and the optimal cutoff values were selected using the Youden Index.

Results

Baseline comparison

A total of 146 patients scheduled for atrial fibrillation catheter ablation and 34 patients scheduled for cardiac surgery were enrolled in the study, constituting the serum group ($n=146$) and the LAA tissue group ($n=34$). Within these groups, patients were further categorized into stroke-AF and non-stroke AF groups based on whether they had experienced a stroke, with 67 cases (45.9%) in the former and 13 cases (38.2%) in the latter. Table 1 presents a comparison of baseline characteristics among the patient groups, revealing no statistically significant differences in the proportions of hypertension, diabetes, atherosclerosis, gender, age (years), BMI (kg/m2), left atrial diameter (cm), LVEF (%), D-Dimer (ug/ml), fibrinogen (ug/ml), NT-proBNP (pg/ml), or NYHA classification (≥2, %) between the groups.

Table 1 Baseline characteristics

	Serum ($n=146$)		*P* Value	LAA Tissue ($n=34$)		*P* value
	Stroke AF ($n=67$)	Non-stroke AF ($n=79$)		Stroke AF ($n=13$)	Non-stroke AF ($n=21$)	
Age (y)	65.8 ± 7.7	65.0 ± 7.9	.766	60.4 ± 9.8	54.0 ± 5.1	.182
Sex (Female, n, %)	21 (31.3)	29 (36.7)	.836	3 (23.0)	6 (28.5)	.089
BMI (kg/m^2)	25.5 ± 3.4	23.9 ± 3.0	.157	23.7 ± 4.1	19.9 ± 11.5	.328
Paroxysmal AF (n, %)	29 (43.3)	56 (70.8)	.010	6 (47.2)	11 (52.3)	.316
LAD(cm)	4.43 ± 0.80	3.95 ± 0.69	.090	5.75 ± 1.29	4.71 ± 0.42	.106
LVEF (%)	59.5 ± 3.3	60.5 ± 3.0	.377	52.6 ± 7.1	57.4 ± 8.3	.258
Hypertension (n, %)	37 (55.3)	44 (55.6)	.957	8 (61.5)	6 (28.3)	.021
Diabetes (n, %)	7 (10.4)	17 (21.5)	.233	2 (15.3)	2 (9.5)	.486
Arteriosclerosis (n, %)	36 (53.7)	51 (65.2)	.582	8 (61.5)	8 (38.0)	.035
Fibrinogen(ug/mL)	1.9 ± 0.6	1.8 ± 0.7	.069	1.7 ± 0.5	1.6 ± 0.6	.071
D-Dimer(ug/mL)	0.23 ± 0.21	0.18 ± 0.15	.081	0.19 ± 0.20	0.14 ± 0.23	.092
NT-proBNP(pg/mL)	445 ± 169	387 ± 210	.580	505 ± 113	441 ± 107	.312
NYHA class ≥ 2 (n, %)	30(44.8)	43 (54.4)	.063	7(53.8)	9(42.8)	.059

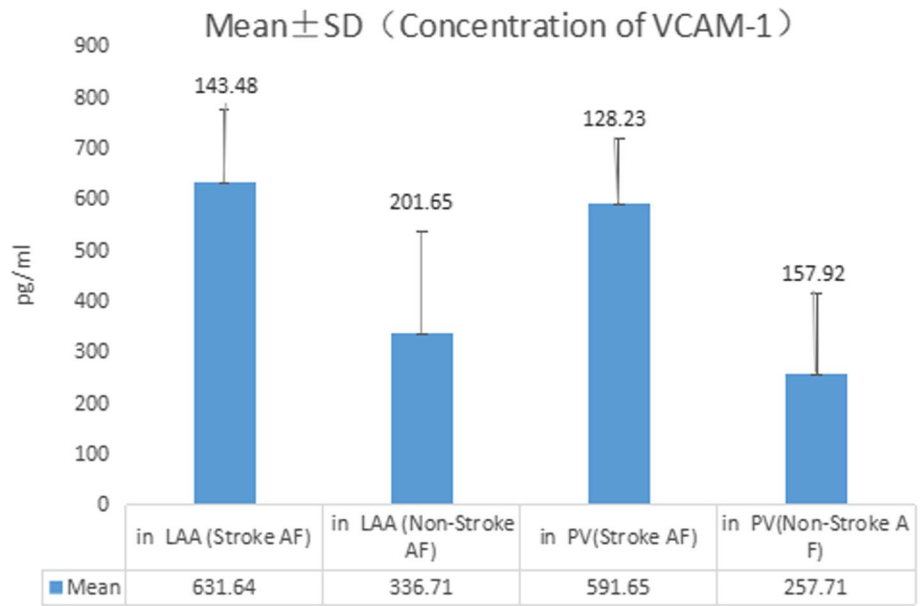


Fig. 3 Comparison of serum VCAM-1 concentrations at different locations

Table 2 Comparison of VCAM-1 concentrations in serum

VCAM-1 concentration (pg/ml)	Stroke AF ($n=67$)	Non-Stroke AF ($n=79$)	*P*- value
serum of LAA	631.64 ± 143.48	336.71 ± 201.66	<.001
serum of PV (pg/ml)	591.65 ± 128.23	257.71 ± 157.92	<.001
***P* -value**	.041	.004	–

Comparison of VCAM-1 concentrations in serum (Fig. 3, Table 2)

The serum VCAM-1 concentration within the left atrial appendage was significantly higher in the stroke-AF group compared to the non-stroke AF group (631.64 ± 143.48 pg/ml vs. 336.71 ± 201.66 pg/ml, $P<0.001$). Additionally, the stroke-AF group exhibited higher serum VCAM-1 concentrations in peripheral veins compared to the non-stroke AF group (591.65 ± 128.23 pg/ml vs. 257.71 ± 157.92 pg/ml, $P<0.001$). When comparing intra-group measurements in the stroke-AF and non-stroke AF groups, it was observed that both groups had higher left atrial appendage serum VCAM-1 concentrations compared to peripheral vein serum concentrations (631.64 ± 143.48 pg/ml vs. 591.65 ± 128.23 pg/ml, $P=0.041$) and (336.71 ± 201.66 pg/ml vs. 257.71 ± 157.92 pg/ml, $P=0.004$).

Comparison of VCAM-1 expression in LAA tissue

VCAM-1 expression in LAA tissue was assessed through immunohistochemical (IHC) staining and the measurement of average optical density values (AOD). Figures 4 and 5 depict the results of VCAM-1 immunohistochemical staining for the stroke-AF and non-stroke AF groups, respectively. In both images, abundant brownish-yellow granules were observed, indicating positive VCAM-1 expression. Quantitative comparison of the AOD between the stroke-AF and non-stroke AF groups revealed that the AOD value in the stroke-AF group was higher than that in the non-stroke AF group (1.257 ± 0.147 vs. 1.093 ± 0.161, $P<0.001$) (Table 3). This demonstrates the expression of VCAM-1 in LAA tissue of AF patients, with a higher level of expression in the LAA of patients who had experienced a stroke compared to those who had not.

Univariate analysis and multivariate logistic regression of VCAM-1 and stroke risk in AF

Univariate analysis was conducted on left atrial appendage serum VCAM-1 concentration, peripheral vein VCAM-1 concentration, and left atrial appendage VCAM-1 AOD values. Left atrial appendage serum VCAM-1 concentration (OR = 1.15, $P<0.001$), peripheral vein VCAM-1 concentration (OR = 1.11, $P<0.001$), and left atrial appendage VCAM-1 AOD value (OR = 3.04, $P=0.021$) were all found to be associated with the risk of AF-related stroke. When LAA serum VCAM-1 concentration and PV regression model, both LAA serum VCAM-1 concentration (OR = 1.17, $P=0.002$) and PV VCAM-1 concentration (OR = 1.30, $P=0.034$) were identified as predictive factors for atrial fibrillation-related stroke (Table 4). Figure 6 displays the ROC curves for left atrial appendage serum VCAM-1 concentration and peripheral vein VCAM-1 concentration in relation to the risk of AF-related stroke. The areas under the curves were 0.863 ($P<0.01$) and 0.925 ($P<0.01$), respectively, indicating a high predictive value for atrial fibrillation-related

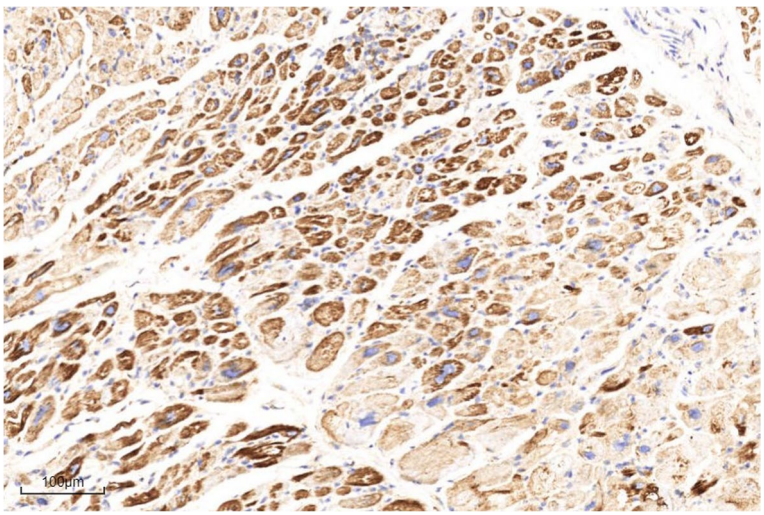


Fig. 4 Immunohistochemical of stroke AF (5x)

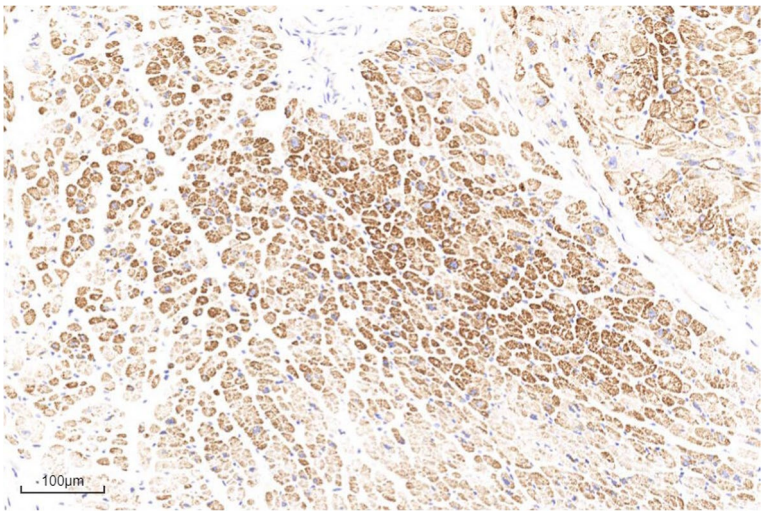


Fig. 5 Immunohistochemical of non-stroke AF (5x)

Table 3 Comparison of AOD values in LAA tissue

	Stroke AF (*n* = 13)	Non-Stroke AF (*n* = 21)	*P* value
Average Density of LAA (AOD)	1.257 ± 0.147	1.093 ± 0.161	<.001

stroke. By using the Youden index, it was determined that left atrial appendage serum VCAM-1 concentration greater than 387.93 pg/ml and peripheral vein VCAM-1 concentration greater than 344.04 pg/ml could predict the occurrence of atrial fibrillation-related stroke.

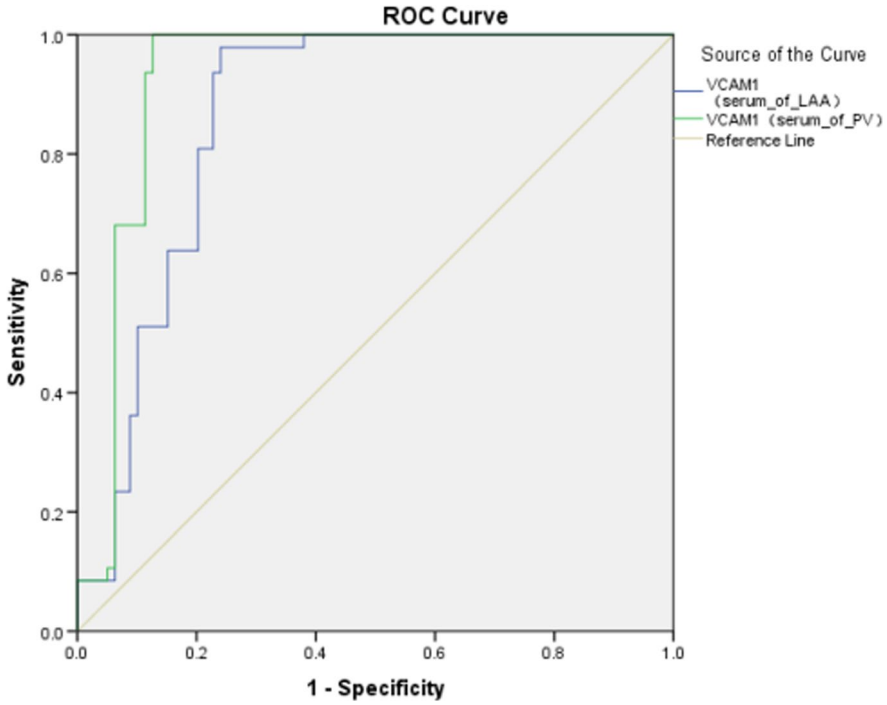
Discussion

VCAM-1 is a member of the immunoglobulin superfamily associated with the inflammatory process, responsible for cell adhesion and transendothelial migration of macrophage-like and dendritic cells [7]. VCAM-1 is constitutively expressed and its expression can be induced by various stressors such as inflammation and hemodynamic changes, with higher expression observed in patients with left atrial thrombus [8]. Current research tends to support a more meaningful connection between localized endocardial inflammation, oxidative activation, tissue remodeling, and AF, while the epidemiological evidence linking systemic inflammation to AF is weaker. In a large-scale, multicenter epidemiological study published in JAMA by Karin Willeit and colleagues in 2017, thirteen cytokines, including matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1, monocyte chemotactic protein-1, P-selectin, fibrinogen, receptor activator of nuclear factor-κB ligand, high-sensitivity C-reactive protein, adiponectin, leptin, soluble intercellular adhesion molecule-1, E-selectin, soluble vascular cell adhesion molecule-1 (VCAM-1), and osteoprotegerin, were selected for their correlation with AF and AF-related stroke events. It was found that VCAM-1 levels were significantly associated with incident AF (HR: 1.49; 95% CI, 1.26–1.78; and HR: 1.46; 95% CI, 1.25–1.69; $P < 0.001$), and VCAM-1 was also associated with AF-related stroke events. However, after adjusting for age and gender, osteoprotegerin lost significance (HR = 1.05; 95% CI 0.87–1.27; $P > 0.99$). These findings suggest a correlation between soluble VCAM-1 levels and incident AF and AF-related stroke events in the community [1].

Our study, based on previous epidemiological research findings, compared the LAA serum VCAM-1

Table 4 Univariate analysis and multivariate logistic regression of VCAM-1 and stroke risk

	Univariate Analysis			Multivariate Logistic Regression				
	OR	95%CI	*P*-vaule	OR	95%CI	*P*-vaule	*B*	*Constant*
VCAM-1 concentration in serum of LAA	1.15	1.01 ~ 1.21	< .001	1.170	1.013 ~ 1.317	0.002	0.170	-8.547
VCAM-1 concentration in serum of PV	1.11	1.05 ~ 1.16	< .001	1.030	1.017 ~ 1.125	0.034	0.030	
AOD value of LAA	3.04	1.92 ~ 7.65	.021	–				



Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
VCAM1（serum_of_LAA）	.863	.033	.000	.798	.927
VCAM1（serum_of_PV）	.925	.026	.010	.874	.977

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Fig. 6 ROC curve of serum concentration of VCAM-1 in LAA and PV

concentration, peripheral venous VCAM-1 concentration, and immunohistochemical quantification (AOD value) of VCAM-1 expression in LAA tissues between AF patients with and without stroke. The results revealed that irrespective of the occurrence of stroke, AF patients had higher LAA serum VCAM-1 concentrations compared to peripheral venous serum VCAM-1 concentrations. Immunohistochemical analysis of VCAM-1 expression in LAA tissues showed positive expression in AF patients, and those who experienced a stroke had higher levels of VCAM-1 expression in LAA compared to those who did not have a stroke. In univariate analysis, the AOD value of VCAM-1 in LAA tissues was associated with the risk of AF-related stroke. These results suggest that the elevation of LAA serum VCAM-1 concentration may not only be a result of systemic inflammatory responses but may also be related to the increased expression of VCAM-1 in local LAA tissues. These findings support the current trend in research that emphasizes the meaningful connection between localized endocardial oxidative inflammation activation, tissue remodeling, and atrial fibrillation. In the comparison of LAA serum VCAM-1 concentrations and peripheral venous serum VCAM-1 concentrations between AF patients who experienced a stroke and those who did not, it was found that AF patients who had a stroke had higher LAA serum VCAM-1 concentrations than those who did not, and similarly, the peripheral venous serum VCAM-1 concentrations were also higher in AF patients who had a stroke compared to those who did not. In both univariate and multivariate logistic regression models, LAA serum VCAM-1 concentration and peripheral venous VCAM-1 concentration were associated with the risk of atrial fibrillation-related stroke. Furthermore, LAA serum VCAM-1 concentration and peripheral venous VCAM-1 concentration had predictive value for AF-related stroke,

with LAA serum VCAM-1 concentration greater than 387.93 pg/ml and peripheral venous VCAM-1 concentration greater than 344.04 pg/ml serving as predictors for the occurrence of AF-related stroke. In the current clinical prevention and treatment of AF-related stroke, we tend to use the CHA2DS2 score or the CHA2DS2-VASc score to assess patients' stroke risk and determine their anticoagulation regimens. However, both of these scoring systems do not include an evaluation of inflammatory factors or LAA-related factors. Our study confirms the association between VCAM-1 and the risk of AF-related stroke and establishes VCAM-1 as a predictive indicator for whether atrial fibrillation patients will experience a stroke. This may provide a new supplementary assessment for evaluating the risk of AF-related stroke and initiating anticoagulation treatment beyond the standard CHA2DS2 score and CHA2DS2-VASc score.

Limitation

Due to clinical diagnosis and treatment standards and practical situations, the sample size of this study is not large, especially the difficulty in obtaining left atrial appendage tissue, so the sample size is relatively small; However, there is currently limited research on the relationship between left atrial appendage tissue, serum, and atrial fibrillation ischemic stroke. More data and larger samples may be available in the future.

Conclusion

VCAM-1 is associated with an increased risk of stroke in AF patients. Elevated serum VCAM-1 concentrations in AF patients who experience a stroke may not solely result from systemic inflammatory responses but may also be linked to increased VCAM-1 expression within LAA tissues. Serum VCAM-1 concentration can serve as a predictive factor for AF-related strokes, with serum VCAM-1 concentrations exceeding 387.93 pg/ml in the LAA and 344.04 pg/ml in peripheral veins predicting the occurrence of AF-related strokes.

Acknowledgements
Not applicable.

Statement
All methods were performed in accordance with the relevant guidelines and regulations.

Authors' contributions
ZhiZhi Jiang collected and analyzed blood samples and data, and wrote a manuscript; YaZhou Lin was responsible for collecting blood samples, Hang Ding completed the collection of left atrial appendage samples, Liang Hua Lian, Jian Quan Chen, and Mei Qing Wu were responsible for collecting some blood samples, Xin Chen made left atrial appendage pathological sections, and Jian Cheng Zhang reviewed the manuscript and provided research funding.

Funding
National Natural Science Foundation of China (No.82070341).

Data availability
The datasets generated and analysed during the current study are not publicly available due case privacy but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was consented and approved by the Ethics Committee of Shengli Clinical Medical College, Fujian Medical University (NO.FJMU20220310).

Consent for publication
All patients provide written informed consent and allow publication before entering the study.

Competing interests
The authors declare no competing interests.

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Received: 13 June 2024 Accepted: 6 December 2024
Published online: 20 December 2024

References

1. Karin W, Raimund P, Peter W, et al. Association Between Vascular Cell Adhesion Molecule 1 and Atrial Fibrillation. JAMA Cardiol. 2017;2(5):516–23.
2. Renate B, Martin G, Jennifer F, et al. Relation of Multiple Inflammatory Biomarkers to Incident Atrial Fibrillation. Am J Cardiol. 2009;104(1):92–6.
3. Wijffels M, Kirchhof C, Dorland R, et al. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995;92:1954–68.
4. Neuman R, Bloom H, Shukrullah I, et al. Oxidative stress markers are associated with persistent atrial fibrillation. Clin Chem. 2007;53:1652–7.
5. Rahimi M, Faridi L, Nikniaz L, et al. Effect of Endothelial Adhesion Molecules on Atrial Fibrillation: A Systematic Review and Meta-analysis. Heart Int. 2022;16(2):75–84.
6. Breitenstein A, Glanzmann M, Falk V, et al. Increased prothrombotic profile in the left atrial appendage of atrial fibrillation patients. Int J Cardiol. 2015;15(185):250–5.
7. Pepinsky B, Hession C, Chen LL, et al. Structure/function studies on vascular cell adhesion molecule-1. J Biol Chem. 1992;267:17820–6.
8. Wara AK, Mitsumata M, Yamane T, et al. Gene expression in endothelial cells and intimal smooth muscle cells in atherosclerosis-prone or atherosclerosis-resistant regions of the human aorta. J Vasc Res. 2008;45:303–13.

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