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Original Article

Coronary Lesions in Patients with Atrial Fibrillation: A Retrospective Study

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Abstract

Background and objectives: This study was performed to determine whether atrial fibrillation (AF) is related to the precise location of a coronary artery lesion.

Methods: A single-center retrospective study was conducted to compare data from clinical, laboratory, and instrumental examinations of 89 patients with AF (main group) who were admitted to the department between October 2015 and October 2019. One-hundred-and-sixty patients (comparison group) were selected according to balanced matching.

Results: There were no statistically significant differences in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), troponin, or creatine kinase-myocardial band (CK-MB) between the two groups. However, the levels of homocysteine (17.0 ± 1.7 μmol/L vs. 13.7 ± 1.0 μmol/L, $p = 0.001$), uric acid (342.8 ± 16.7 μmol/L vs. 308.5 ± 15.1 μmol/L, $p = 0.003$) and creatinine (79.3 ± 4.7 μmol/L vs. 72.9 ± 3.1 μmol/L, $p = 0.017$) were higher in the AF group compared to the non-AF group. Moreover, the left atrium (LA) diameter (40.2 ± 1.4 mm vs. 33.5 ± 0.8 mm, $p = 0.001$) was larger in the AF group compared to the non-AF group. Patients with AF compared to those without AF had no significant differences in the degree or location of coronary artery lesions.

Conclusions: AF in patients was not associated with specific coronary artery lesions in the current study.

Introduction

Atrial fibrillation (AF), the most commonly encountered cardiac arrhythmia in clinical practice, is the most important risk factor for myocardial infarction, ischaemic stroke, heart failure, and cardiovascular (CV) mortality.[1] AF creates a very severe situation, which has caused a great burden on the social economy and medical resources.[2] It has been identified that patients with advanced age, of the male sex, and with the presence of CV diseases are more susceptible to develop AF.[3] Mechanisms leading to AF include remodelling of the atrial structure and ion channel function. Other factors such as hypertension, structural heart disease, possibly diabetes, and also AF itself induce a slow but progressive process of remodelling the atrial structure.[2] Some studies have shown that AF is related to certain definite locations, the extent of coronary artery lesions, or types of coronary circulation. Yaroslavskaya *et al.* reported that AF in patients with ischaemic heart disease (IHD) is associated with right coronary artery lesions and right dominant coronary circulation.[4] However, other studies have reported that the independent association of the absence of AF with the localization of significant coronary lesions indicates a mixed (coronary and non-coronary) AF origin in patients with coronary artery disease (CAD).[5] Therefore,

Keywords: Atrial fibrillation; Coronary heart disease; Coronary angiography; Homocysteine; Uric acid.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CCS, chronic coronary syndrome; CV, cardiovascular; DM, diabetes mellitus; ECG, electrocardiogram; Hcy, homocysteine; HDL-C, high density lipoprotein cholesterol; HL, hyperlipidemia; HT, hypertension; IHD, ischemic heart disease; IVS, interventricular septum; LA, left atrium; LAD, left anterior branch; LCX, the left circumflex branch; LDL-C, low density lipoprotein cholesterol; LM, left main branch; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; RCA, the right coronary artery; TC, total cholesterol; TGs, triglycerides; TTE, chest echocardiogram; UA, uric acid.

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Table 1. Baseline demographic and clinical features of the study population

Variables	AF patients (n = 89)	Non-AF patients (n = 106)	*p*-value
Age, years	68.5 ± 1.6	66.5 ± 1.3	0.054
Sex, M/F	58	52	0.361
BMI, kg/m^2	25 ± 0.7	24 ± 0.9	0.202
Smoking rate, %	25	26	0.787
Drinking rate, %	19	16	0.574
DM, %	17	29	0.042
HT, %	66	62	0.559

Mean values ± standard deviation and % (n) were reported for continuous and categorical variables, respectively. Abbreviations: AF, atrial fibrillation; BMI, body mass index; DM, diabetes mellitus; HT, hypertension.

whether atrial coronary circulation plays an important role in the formation of AF is unknown. Further investigation is crucial. In the current study, a retrospective study was conducted to investigate the association between AF and coronary artery lesions.

Methods

Patient selection

This single-center retrospective study was performed to investigate the association between AF and coronary artery lesions. The ethics committee of the Fourth Affiliated Hospital of Zhejiang University School of Medicine approved the use of clinical data, the informed consent was waived due to the retrospective nature of the analysis, and the protocols were confirmed to follow the ethical guidelines of the latest version of the Declaration of Helsinki.

The medical records were reviewed of 195 patients hospitalized in the Fourth Affiliated Hospital of Zhejiang University School of Medicine, between October 2015 and October 2019, who underwent a coronary angiogram procedure due to recurrent chest pain/chest tightness, a long history of angina, or other symptoms such as dyspnea. Exclusion criteria included patients with acute coronary syndrome (ACS), advanced heart failure, valvular heart disease, cardiomyopathy, chronic lung disease, severe liver and renal insufficiency, chronic severe anaemia, chronic hypertension (HT) with poorly controlled blood pressure, and patients with thyroid disease. All patients underwent an electrocardiogram (ECG) and a 24-hour Holter ECG on admission. AF was first divided into two categories: paroxysmal AF (sudden onset) or chronic AF (persistent and permanent). One-hundred-and-six patients (comparison group) were selected according to propensity score matching with balancing by age, sex, and body mass index (BMI) from a group that was mechanically sampled (every 20 patients) from a chronological cohort of non-AF patients. Finally, 89 patients with AF (main group) and 106 patients (comparison group) were elected for the study. Demographic data and laboratory results, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), homocysteine (Hcy), uric acid (UA), creatinine levels, troponin, and creatine kinase-myocardial band (CK-MB) were recorded.

Echocardiographic examination

Motion (M)-mode echocardiography and quantitative analysis were conducted using parasternal long-axis images. The left atrium (LA) diameter, left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD), interventricular septum (IVS) thickness, and left ventricular ejection fraction (LVEF) were calculated according to the biplane modified Simpson's method.[6]

Holter monitoring

All participants were monitored using the 24-hour Holter ECG system on admission. AF was defined as absolutely irregular RR intervals with fibrillatory waves and no defined P waves on surface ECG.[6]

Coronary angiography

All patients underwent coronary angiography in the catheter laboratory. Coronary angiograms were saved in digital format. The main coronary vessels for analysis included the left main branch (LM) as well as the proximal, middle, and distal sections of the left anterior branch (LAD), the left circumflex branch (LCX), and the right coronary artery (RCA). A total of 50% vascular stenosis was defined as a critical lesion of the coronary arteries.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as absolute numbers and percentages. The differences in continuous variables were assessed using the independent sample Student's *t*-test or one-way analysis of variance (ANOVA) and the chi-square test was used to test for differences among the subtypes of AF. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (version 25.0; IBM Corp.; Armonk, NY, USA).

Results

Patient characteristics

The baseline characteristics of the AF and non-AF groups are shown in Table 1. The two groups did not differ regarding sex, mean age, body mass index(BMI), smoking rates, drinking rates,

Table 2. Laboratory, electrocardiographic, and echocardiographic results of the study population

Variables	AF patients (n = 89)	Non-AF patients (n = 106)	*p*-value
TC, mmol/L	3.7 ± 0.2	3.7 ± 0.2	0.882
LDL-C, mmol/L	1.9 ± 0.2	1.8 ± 0.1	0.193
HDL-C, mmol/L	1.1 ± 0.1	1.1 ± 0.1	0.805
TGs, mmol/L	1.4 ± 0.2	1.5 ± 0.2	0.339
Hcy, μmol/L	17.0 ± 1.7	13.7 ± 1.0	0.001
UA, μmol/L	342.8 ± 16.7	308.5 ± 15.1	0.003
Creatinine, μmol/L	79.3 ± 4.7	72.9 ± 3.1	0.017
Average heart rate, bpm	73.6 ± 3.0	67.3 ± 1.4	0.001
LVEDD, mm	48.4 ± 1.0	46.7 ± 0.8	0.010
LVESD, mm	31.5 ± 1.4	29.6 ± 0.7	0.010
IVS thickness, mm	9.6 ± 0.3	9.4 ± 0.3	0.273
LA diameter, mm	40.2 ± 1.4	33.5 ± 0.8	0.001
LVEF, %	63.6 ± 1.7	66.6 ± 1.2	0.005

Abbreviations: AF, atrial fibrillation; bpm, beats per minute; Hcy, homocysteine; HDL-C, high density lipoprotein cholesterol; IVS, interventricular septum; LA, left atrium; LDL-C, low density lipoprotein cholesterol; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; TC, total cholesterol; TG, triglyceride; UA, uric acid.

or HT. However, patients with AF have a higher incidence of diabetes. Paroxysmal AF was the most frequent type observed (35%, 28/79) and the prevalence of permanent AF was marginally lower (30%, 24/79). The laboratory, electrocardiographic, and echocardiographic results of the study patients are shown in Table 2. Troponin and CK-MB were within the normal range, which further excluded ACS. There were no statistically significant differences in TC, LDL-C and HDL-C, TGs, and IVS between the two groups, while the levels of Hcy, UA, and creatinine in the AF group were higher than those in the non-AF group. The average heart rate and LVEF in the AF group were also higher compared to the non-AF group. Moreover, the LVEDD, LVESD, and LA diameter were larger in the AF group. However, there was no significant difference in IVS thickness between the two groups.

Coronary angiography

The analysis of coronary angiography data is shown in Table 3. Patients with AF compared with those without AF had no significant differences in the degree or location of coronary artery lesions.

Atrial fibrillation population

The mean HAS-BLED score (that considers hypertension, ab-

Table 3. Coronary angiography data of the study population

Variables	AF patients (n = 89)	Non-AF patients (n = 106)	*p*-value
LM, %	9.4	3.4	0.092
LAD, %			
Proximal	34.8	53.8	0.080
Middle	31.5	31.1	0.961
Distal	9.0	6.6	0.534
LCX, %			
Proximal	18.0	15.1	0.588
Middle	15.7	23.6	0.172
Distal	11.2	18.9	0.141
RCA, %			
Proximal	14.6	22.6	0.154
Middle	19.1	30.2	0.075
Distal	12.4	15.1	0.582

Abbreviations: AF, atrial fibrillation; LAD, left anterior branch; LCX, the left circumflex branch; LM, left main branch; RCA, the right coronary artery.

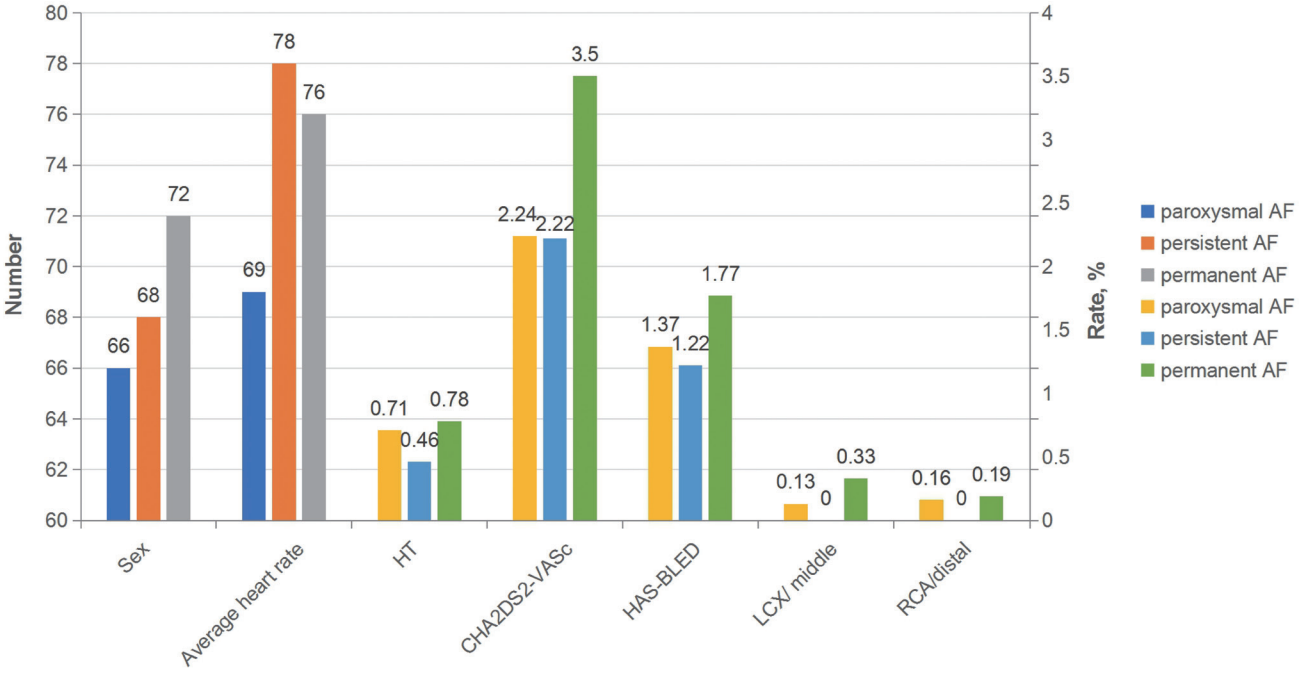

Fig. 1. Comparison between paroxysmal, persistent, and permanent AF. AF, atrial fibrillation; CHA2DS2-VASc score: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65-74 years, sex condition; HAS-BLED score: hypertension, abnormal renal and liver function; stroke, bleeding, labile INR, elderly, drugs or alcohol; HT, hypertension; LCX, the left circumflex branch; RCA, the right coronary artery.

normal renal and liver function; stroke, bleeding, labile INR, elderly, drugs or alcohol) was 1.45 in AF patients while the mean CHA2DS2-VASc score (that considers congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, sex condition) was 2.61. Results of the three groups of AF patients are shown in Figure 1. There was statistical significance in eight indicators including age, HT, heart rate, CHA2DS2-VASc score, HAS-BLED score, the middle sections of LCX, and the distal sections of RCA. Permanent AF patients were the oldest, had the highest prevalence of HT, had the highest CHA2DS2-VASc and HAS-BLED scores, and had more lesions in the middle sections of the LCX and the distal sections of the RCA.

Discussion

In this retrospective analysis, the levels of Hcy, creatinine, and UA were significantly associated with AF. The above indicators were higher in patients with AF compared with those without. Moreover, patients with AF had faster average heart rates, larger left ventricular and left atrial volumes, and reduced ejection fractions.

Hcy, a sulphur-containing amino acid, is an intermediate byproduct during the metabolism of dietary methionine[7] and is associated with a number of cardiovascular events, including stroke, CAD, venous thromboembolism, and HT.[8] Many studies have reported that plasma Hcy levels are elevated in AF patients and that they are affected by age and gender.[7] Yao *et al.* further reported that plasma Hcy levels may increase the early recurrence of atrial tachyarrhythmia after catheter ablation in persistent AF patients.[9] AF is the result of electrical and structural atrial remodelling.[10,11] Current studies have found that hyperhomocysteinaemia may cause structural atrial remodelling in AF patients by activating the extracellular signal regulated kinase–matrix metalloproteinase-9 signalling axis,[12] resulting in oxidative stress and inducing an inflammatory response.[13,14] It has also been reported that hyperhomocysteinaemia can inhibit potassium channels in atrial myocytes and cause atrial electrical remodelling.[15] It is now highly recognized that diet supplementation with folic acid and vitamin B can lower Hcy levels.[7] However, research on whether vitamin B supplementation can prevent cardiovascular disease in patients with AF is not uniform and needs further confirmation.

UA, produced in the liver, muscles, and intestines, is an end-product of purine metabolism in humans.[16] A number of previous studies have shown a positive association between serum uric acid (SUA) and the prevalence of AF[17] in both hypertensive[18] and chronic systolic heart failure patients.[19] It has been reported that SUA is clearly associated with inflammation and oxidative stress in certain pathological conditions.[17] As the final product of purine metabolism, SUA aggravates cellular damage through oxidative stress.[20,21] Moreover, SUA promotes inflammation by stimulating the release of pro-inflammatory cytokines,[22–24] resulting in atrial structural remodelling. Importantly, both electrical and structural remodelling contribute to the occurrence and development of AF.[25]

Several previous studies found that elevated creatinine levels may increase adverse events in patients with AF, including CV mortality and major bleeding in patients receiving oral anticoagulants.[26] Creatinine levels are also considered an auxiliary reference standard to assist in the CHA2DS2-VASc score, which is used to assess the risk of stroke in AF patients. Research concerning the impact of AF per se on creatinine levels is not sufficient. AF affects microvascular flow in different organs,[27] especially in the left ventricle, brain, and kidneys. However, patients with AF often have other coexisting diseases, such as diabetes mellitus and arterial hy-

pertension. These factors as well as ageing may affect creatinine levels.[28] Thus, whether the elevation of creatinine levels is solely an epiphenomenon induced by the presence of vascular risk factors or is directly associated with these many complications is unclear.

AF contributes to the progression of CHF,[29] and its main causes are hemodynamic disturbances caused by the absence of full atrial contractions, mismatch of atrioventricular interaction, and uneven ventricular filling.[4] In addition, remodelling of the atrial myocardium plays a special role that may precede the development of AF in many patients with accompanying myocyte hypertrophy, fibrosis, or impairment of the electrophysiological properties of the myocardium.[2] The intergroup differences that were detected (heart rate, LA, ventricle size, etc.) were due to the presence or absence of AF, which was consistent with the existing theory, and it was also found that the permanent AF patients had the highest CHA2DS2-VASc and HAS-BLED scores, and had more lesions in the middle section of the LCX and the distal section of the RCA. Statistically significant differences were not found in LVEFs between the two groups in the current study, which may be due to the fact that some advanced heart failure were excluded, and patients who were included in our cohort had not reached cardiac insufficiency yet. In addition, this study also investigated the relationship between AF and some definitive locations or the extent of the coronary artery lesions. However, a clear correlation was not found between the incidence of AF and coronary artery lesions. Based on this negative result, it was considered that patients with AF completed stress tests and computed tomography scans less frequently because of the rapid rhythm. Furthermore, coronary angioplasty was also less common compared to those with sinus rhythm. This raises the possibility that it may be difficult to discover patients with AF for invasive procedures.

The current study has several limitations. Firstly, the results were based on a small population and were obtained from a retrospective single-centre study. Secondly, some excluded patients may lead to a selection bias. Thirdly, fractional flow reserve measurements were not performed to accurately assess the significance of coronary stenosis. Therefore, only cases of stenosis with a reduction of 50% were defined as significant. Fourthly, medications (lipid-lowering, antidiabetic, antihypertensive or other drugs) were not considered within the study groups. Fifthly, retrospective databases have some limitations such as potential selection bias, which should be taken into consideration. Lastly, newly diagnosed AF was not considered.[5]

Future directions

Given that the findings were based on a small population and were obtained from a retrospective single-centre study, a multi-centre prospective study should be conducted to verify these results.[5] As mentioned above, coronary angioplasty was less common in patients with AF compared to those with sinus rhythm. This raises the possibility that it may be difficult to discover patients with AF for invasive procedures. Therefore, there may be a need for a more efficacious non-invasive diagnostic approach for patients with AF and suspected chronic coronary syndrome (CCS). Use accurate non-invasive method to assess the patient's coronary artery, and then compare whether there are statistical differences in coronary artery between patients with AF and non-AF.

Conclusions

Hcy, creatinine and UA levels were associated with AF, and they also were associated with a faster average heart rate, larger left ventricular and left atrial volumes, and a smaller ejection fraction. This study did not find a specific correlation between the occurrence of AF and specific coronary artery lesions. However, during the analysis of the three subtypes of AF, it was revealed that in the cases of permanent AF, thrombosis and bleeding events were more likely to occur, and there were more lesions in the middle section of the LCX and the distal section of the RCA.

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Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Study design (SDX), performance of experiments (YWC), analysis and interpretation of data (YWC), manuscript writing (YWC), critical revision (SDX).

Data sharing statement

The data that support the findings of this study are available from the corresponding author, SDX, upon reasonable request.

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