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Original Article

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Possible Risk Factors Contributing to Atrial Fibrillation Occurrence in Heart Failure With Mildly Reduced Ejection Fraction

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Abstract

Background: Heart failure (HF) is often accompanied by atrial fibrillation (AF), which significantly worsens the outcome of both diseases. Half of individuals with HF has AF, and HF occurs in more than one-third of individuals with AF. Thus, HF and AF are commonly encountered together and are closely interrelated with similar risk factors. The aim of this study was to investigate the impact of potential risk factors on the occurrence of paroxysmal/persistent AF in patients with heart failure with moderately reduced ejection fraction (HFmrEF).

Methods: The study included 193 patients with HFmrEF and non-valvular paroxysmal/persistent AF after successful cardioversion. As a control group the similar 76 patients without AF were examined. All patients underwent the examination, including electrocardiography (ECG), echocardiography, ambulatory blood pressure monitoring and Holter ECG monitoring. Levels of inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and the fibrotic marker transforming growth factor-β1 (TGF-β1) were measured using the enzyme-linked immunosorbent assay (ELISA) method. The obtained results were modeled using binary logistic regression using the odds ratio (OR).

Results: It was shown that frequent episodes of hypertensive crisis (HC) and increased body mass index (BMI) were possible risk factors for paroxysmal/persistent AF. An increased OR of diastolic and systolic parameters of the left ventricle was associated with significant atrial and ventricular remodeling. Statistically, higher OR of inflammatory markers levels, such as hs-CRP, IL-6 and TNF-α were associated with an increased risk of paroxysmal/persistent AF occurrence in HFmrEF patients compared to similar patients without AF. An increase of the fibrosis marker TGF-β1 OR was statistically significant in patients with persistent AF.

Conclusions: It could be considered that frequency of HC, BMI, atrial and ventricular remodeling, as well as an increase of inflammation markers were possible risk factors for the occurrence of paroxysmal/persistent AF in HFmrEF patients. Moreover, fibrosis factor level significantly increased the likelihood of persistent AF in these patients.

Keywords: Atrial fibrillation; Cardiac fibrosis; Inflammation markers; Mildly reduced ejection fraction; Risk factors

Introduction

Heart failure (HF) is a widespread clinical syndrome globally. The number of HF cases doubled from 33.5 million in 1990 to 64.3 million in 2018, and global prevalence remains high [1]. HF is associated with structural and functional abnormalities of the myocardium [2]. The main pathogenic mechanisms contributing to HF include increased hemodynamic overload, ischemia-related dysfunction, contractile protein mutations, ventricular remodeling and altered neurohumoral stimulation [3, 4]. Based on the huge variety of etiology and pathogenesis, HF has multiple causes, which makes precise classification and treatment difficult [5, 6]. Comparison of clinical characteristics, comorbidities, outcomes, and prognosis among patients with HF who have either preserved ejection fraction (EF) (> 50%, HFpEF), or moderately reduced ejection fraction (40-49%, HFmrEF), or reduced ejection fraction (< 40%, HFrEF) leads to consideration of HFmrEF as an intermediate HF phenotype [6, 7]. HFmrEF was first recognized as a new HF phenotype by the European Society of Cardiology in 2016 [8, 9]. Of the more than 6.5 million patients with HF in the United States, 13-24% had HFmrEF [8]. Recent research suggests that patients with HFmrEF benefit from therapies designed to improve outcomes for people with reduced EF [10, 11]. However, the characteristics of HFmrEF and its therapeutic potential remain poorly understood. Atrial fibrillation (AF) is the most common sustained and heterogeneous type of arrhythmia. There is plausible published evidence linking its onset and progression to inflammation and fibrosis [12, 13].

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Table 1. Baseline Demographics and Clinical Characteristics in all Observed HFmrEF Patient With and Without AF

Indices, units	HFmrEF/no AF (n = 76)	HFmrEF/paroxysmal AF (n = 103)	HFmrEF/persistent AF (n = 90)
Age (years)	56 (49 - 74)	54 (47 - 71)	56 (51 - 73)
Male (%)	53.2	50.8	52.4
BMI (kg/m^2)	29.8 (27 - 32)	30.1 (27 - 34)	31.1 (28 - 36)
History of smoking (%)	42.2	44.6	41.7
History of drinking (%)	11.9	14.7	12.6
IHD (%)	74.7	72.7	73.3
Hypertension (%)	87.4	88.7	89.1
Hypercholesterolemia (%)	47.9	48.9	46.8
Resting heart rate (bpm)	75.2 (68 - 89)	76.7 (72 - 91)	74.3 (65 - 90)
Peak heart rate (bpm)	116.8 (92 - 131)	121.7 (92 - 133)*	115.8 (96 - 123)
Resting SBP (mm Hg)	141.9 (125 - 155)	144.9 (131 - 160)	145.9 (131 - 150)
Peak SBP (mm Hg)	164.1 (145 - 180)	168.8 (140 - 185)	167.1 (40 - 180)
Resting DBP (mm Hg)	83.7 (75 - 95)	78.1 (70 - 90)	84.7 (75 - 95)
Peak DBP (mm Hg)	91.2 (80 - 110)	95.2 (80 - 105)*	92.1 (80 - 110)

Data represented as mean (range). *P < 0.05. AF: atrial fibrillation; BMI: body mass index; DBP: diastolic blood pressure; HR: heart rate; IHD: ischemic heart disease; HFmrEF: heart failure with mildly reduced ejection fraction; SBP: systolic blood pressure; bpm: beats per minute.

Although AF and HF are distinct diseases, they are increasingly found to overlap and are associated with high morbidity and mortality; in addition, patients with comorbid HF and AF suffer from even more severe symptoms and a worse prognosis [14]. Data from the Framingham Heart Study suggest that AF occurs in more than half of individuals with HF, and that HF occurs in more than one-third of individuals with AF. Thus, HF and AF are commonly encountered together and are closely interrelated with similar risk factors, and each predisposes to the other [15, 16]. However, while HFmrEF is well described, the determinants and outcomes of HFmrEF with concomitant AF remain unclear. In this study, we aimed to identify possible risk factors associated with the onset and progression of AF in patients with HFmrEF.

Materials and Methods

Ethical approval of study participants

Blood samples were collected from patients with heart failure (HF) and AF in the Department of Arrhythmia at the Research Institute of Cardiology named after L. Hovhannisyan (Yerevan, Armenia) under protocols approved by the Ethical Committee of the Institute of Cardiology and the Local Ethical Committee (Protocol no. 3 of 05.11.2021). Informed consent was obtained from all patients involved in the study.

Study patients

The study included 193 patients with non-valvular AF and HFrEF, who were admitted to the Research Institute of Cardiology over a period of 3 years and underwent successful cardioversion. Of these, 103 patients had paroxysmal AF, and 90 had persistent AF. Similar 76 patients with HFmrEF but without AF were examined as the control group. Moreover, the inclusion criteria were the following: HFmrEF 40-49%, N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 125 pg/mL and the presence of ischemic or hypertensive heart disease. Ischemic etiology was defined based on a documented history of myocardial infarction or coronary angiography. Arterial hypertension was diagnosed according to the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines for the management of arterial hypertension [17]. Furthermore, the exclusion criteria included the following: HF due to valvular heart disease, chronic obstructive pulmonary disease, systemic inflammatory diseases and diabetes. Patients were followed up according to the usual practice of the center. All participants underwent a detailed physical examination that included resting 12-lead electrocardiography (ECG) recording, 24-h blood pressure (BP) monitoring, echocardiography, and 24-h ambulatory Holter monitoring. BP in rest was calculated from the mean of the second and third readings and peak of BP by 24-h BP monitoring. The body mass index (BMI) was calculated as weight divided by height squared and expressed as kg/m^2. All examined patients were asked to complete a questionnaire about their lifestyle (e.g., smoking, drinking, and nutrition) and the presence of potential comorbidities. Table 1 presents the clinical characteristics of the patients.

All observed patients with HFmrEF received standard therapy. But patients with AF were prescribed also amiodarone and rivaroxaban in maintenance doses.

ECG

Since one of the main electrophysiological factors in the occurrence and maintenance of AF is the inhomogeneity of atrial

conduction velocity, the ECG display of this process is the dispersion of the P wave (Pdis), which is defined as the difference between the maximum (Pmax) and minimum (Pmin) duration of the P wave recorded in lead II of the ECG.

Echocardiography

To measure left ventricular ejection fraction (LVEF) according to standard criteria, traditional transthoracic echocardiography "Medison SonoAceX6" (Hungary) was used. Echocardiography measurements of chamber sizes, as well as systolic and especially early diastolic cardiac dysfunction were carried out in accordance with established recommendations.

Biochemical blood measurements

Quantifications were determined using standard laboratory procedures established at the Institute of Cardiology. Plasma levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), transforming growth factor-β1 (TGF-β1), and high-sensitivity C-reactive protein (hs-CRP) were measured by enzyme-linked immunosorbent assay (ELISA) kits according to manufacturer's instructions, using the Stat Fax 303 Plus analyzer (Awareness Technology, Palm City, FL, USA).

Statistical analysis

Statistically significant differences between parameters were identified using two-step cluster analysis. The findings were modeled using binary logistic regression using the odds ratio (OR). Binary logistic regression was performed for two groups, with the third group selected as a comparison. Using the binary logistic regression method, it is possible to study the dependence of dichotomous variables (binary, having only two possible values) on independent variables of any type of scale. As a rule, in the case of dichotomous variables, we are talking about some event that may or may not occur; binary logistic regression in this case calculates the probability of the event depending on the values of the independent variables. The probability of the event for a certain case is calculated using the formula:

$$P = \frac{1}{1 + e^{-z}}$$

where $z = b1 \cdot X1 + b2 \cdot X2 + \ldots + bn \cdot Xn + a$

X1 are the values of the independent variables, b1 are the coefficients, the calculation of which is the task of binary logistic regression, and a is some constant. If the value for P is less than 0.05, then it can be assumed that the event will not occur; otherwise, the occurrence of the event is assumed. The significance of the difference of the coefficients from 0 was tested using the Wald statistic, which uses the χ^2 distribution. This is calculated as the square of the ratio of the corresponding coefficient to its standard error.

OR is one of the most common approaches to describe how the absence or presence of a particular outcome is associated with the presence or absence of a particular factor in a particular statistical group. Thus, the results of using the OR include determining the statistical significance of the relationship between the factor and the result (outcome), as well as its quantitative assessment. It is very important to assess the statistical significance of the identified association between the outcome and the risk factor. If the OR is greater than 1, then the chances of detecting a risk factor in this group are greater, which means that the factor has a direct relationship with the probability of the outcome. Moreover, in each case, the statistical significance of the OR is necessarily assessed based on the values of the 95% confidence interval (CI) (P value < 0.05 was considered significant). This is due to the fact that even with low values of the OR, close to 1, the relationship may nevertheless be significant and should be taken into account in statistical conclusions. Conversely, with large values of the OR, the indicator turns out to be statistically insignificant, and therefore, the identified relationship can be neglected. The studies were conducted using simple randomized protocols using the universal statistical package SPSS 13.0.

Results

Clinical characteristics of the study participants

Table 1 presents the demographic and clinical characteristics of all studied patients. When analyzing the demographic characteristics of patients, all groups were comparable in terms of gender, age and BMI. The groups were also similar in the proportion of patients who smoked and drinking habits. There were no significant changes in heart rate at rest in the three examined groups. However, peak heart rate in patients with paroxysmal AF was significantly higher than that in patients with persistent AF and patients without AF. There were no significant differences in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at rest between the three groups of patients. However, peak DBP was significantly higher in patients with paroxysmal AF than in patients with persistent AF and the control group (P < 0.05).

Risk factors associated with paroxysmal AF

An OR method was used to assess the risk of developing paroxysmal AF compared with the control group without AF. Moreover, the indicators associated with an increased risk of developing paroxysmal AF in patients with HFmrEF included the following: age (OR = 1.8; CI = 1.08 - 1.28, P = 0.05), high DBP (OR = 1.09, CI = 1.01 - 1.17, P = 0.017), high frequency of hypertensive crises (HCs, OR = 1.17, CI = 1.07 - 1.43, P = 0.01), and high BMI (OR = 1.13, CI = 0.93 - 1.27, P = 0.031). According to electrocardiographic findings, P-wave maximum (Pmax) and P-wave dispersion (Pdis) were significantly prolonged and associated with increased risk for both paroxysmal AF (Pmax: OR = 3.92, CI = 3.88 - 3.96, P = 0.002; Pdis: OR = 3.91, CI = 3.87 - 3.95, P = 0.002) and persistent AF (Pmax: OR = 4.81, CI = 4.07 - 5.94, P < 0.001; Pdis: OR = 4.90, CI = 4.86 - 5.93, P <

0.001). In addition, based on echocardiographic measurements, it was found that with an increased left atrial volume (LAV), the risk of paroxysmal AF was significantly increased (LAV: OR = 1.76, CI = 1.66 - 1.88, P = 0.002). It is worth noting that an increase in the level of markers of systemic inflammation (hs-CRP: OR = 5.57, CI = 3.38 - 7.87, P = 0.010; IL-6: OR = 4.80, CI = 2.72 - 6.88, P = 0.001; TNF-α: OR = 2.56, CI = 1.43 - 4.73, P = 0.002) contributes to a high risk of developing paroxysmal AF in patients with HFmrEF (Table 2).

Risk factors associated with persistent AF

In the analysis of possible risk factors in HFmrEF patients with persistent AF, significant risk factors relative to the control group were the frequency of HCs (OR = 1.56, CI = 1.041 - 1.971, P = 0.001) and increased BMI (OR = 1.97, CI = 0.98 - 2.21, P = 0.044). The OR values for left atrial diameter (LAD) and LAV were also significantly increased (OR = 3.69, CI = 2.58 - 4.82, P = 0.002; OR = 3.80, CI = 2.65 - 4.09, P = 0.040, respectively). An analysis of echocardiological data has revealed that left ventricular (LV) diastolic dysfunction is a possible risk factor in HFmrEF patients with persistent AF, compared to those with paroxysmal AF. Statistically significant increases were observed in interventricular septum thickness (IVST, OR = 1.69, CI = 1.48 - 1.98, P = 0.042), early diastolic filling wave (E peak, OR = 3.05, CI = 3.01 - 3.05, P = 0.012), and isovolumetric relaxation time (IVRT, OR = 3.94, CI = 3.90 - 4.99, P = 0.016). Moreover, in patients with persistent AF, impaired LV systolic function is important. The risk of persistent AF was associated with increased left ventricle end-diastolic diameter (LVEDD, OR = 1.76, CI = 1.58 - 1.99, P = 0.046), left ventricle end-diastolic volume (LVEDV, OR = 1.93, CI = 1.89 - 2.09, P = 0.019), and some reduction in EF (OR = 1.30, CI = 1.08 - 1.57, P = 0.05). A significant increase in the levels of OR markers of inflammation was also revealed (hs-CRP: OR = 6.37, CI = 5.24 - 8.59, P = 0.002; IL-6: OR = 5.58, CI = 4.71 - 7.87, P = 0.001; TNF-α: OR = 2.51, CI = 2.51 - 4.68, P = 0.002), which may also contribute to the high risk of developing persistent AF in patients with HFmrEF. Moreover, an increase in the OR of profibrotic TGF-β1 (OR = 3.84, CI = 2.10 - 6.23, P = 0.005), in contrast to paroxysmal AF, may also be a possible risk factor for the development of persistent AF in patients with HFmrEF (Table 3).

Table 2. The Analysis of OR Values at a 95% CI of Various Clinical Hemodynamic and Structural-Functional Parameters and Markers of Inflammation and Fibrosis in HFmrEF Patients With Paroxysmal AF Compared to the Control Group

Indices	HFmrEF with paroxysmal AF (n = 103)		
	OR	95% CI	P value
Sex	0.24	0.10 - 0.58	0.07
Age	1.18	1.08 - 1.28	0.05*
SBP	1.00	0.94 - 1.05	0.987
DBP	1.09	1.01 - 1.17	0.017*
HR	1.03	0.98 - 1.08	0.182
HC	1.17	1.07 - 1.43	0.01*
TIA	0.65	0.14 - 2.93	0.583
IHD	1.16	0.39 - 3.42	0.788
MI	1.6	0.65 - 4.33	0.285
Pmax	3.92	3.88 - 3.96	0.002*
Pdis	3.91	3.87 - 3.95	0.002*
QRS	0.10	0.96 - 1.04	0.989
BMI	1.13	0.93 - 1.27	0.031*
LAD	0.86	0.70 - 1.06	0.167
LAV	1.76	1.66 - 1.88	0.002*
LVEDD	0.92	0.71 - 1.20	0.558
LVEDV	0.99	0.94 - 1.04	0.811
LVESD	0.98	0.89 - 1.08	0.770
IVST	0.94	0.68 - 1.31	0.751
LVPWT	0.96	0.64 - 1.45	0.877
EF	1.11	0.94 - 1.30	0.188
E peak	1.00	0.96 - 1.03	0.959
A peak	1.00	0.93 - 1.08	0.927
E/A	1.05	0.04 - 2.32	0.975
DT	0.99	0.97 - 1.02	0.777
IVRT	0.99	0.95 - 1.03	0.661
hs-CRP	5.57	3.38 - 7.87	0.010*
IL-6	4.80	2.72 - 6.88	0.001*
TNF-α	2.56	1.43 - 4.73	0.002*
TGF-β1	0.57	0.00 - 4.2	0.995

*P ≤ 0.05. AF: atrial fibrillation; A peak: late diastolic filling wave; BMI: body mass index; DBP: diastolic blood pressure; DT: deceleration time; E peak: early diastolic filling wave; E/A ratio: the ratio of the E peak to the A peak; EF: ejection fraction; HFmrEF: heart failure with mildly reduced ejection fraction; HCs: hypertensive crises; HR: heart rate; hs-CRP: high-sensitivity C-reactive protein; IHD: ischemic heart disease; IL-6: interlekine-6; IVRT: isovolumetric relaxation time; IVST: interventricular septum thickness; LAD: left atrial diameter; LAV: left atrial volume; LVEDD: left ventricle end-diastolic diameter; LVEDV: left ventricle end-diastolic volume; LVESD: left ventricle end-systolic diameter; LVESV: left ventricle end-systolic volume; LVPWT: left ventricle posterior wall thickness; MI: myocardial infarction; Pdis: P-wave dispersion; Pmax: P-wave maximum; SBP: systolic blood pressure; TIA: transitory ischemic attacks; TNF-α: tumor necrosis factor-α; TGF-β1: transforming growth factor-β1; OR: odds ratio; CI: confidence interval.

Discussion

Considering the fact that AF and HF often occur together, much attention is paid to assessing the quality of life, possible risk factors and concomitant diseases that contribute to atrial remodeling, thereby leading to a worsening of the course and prognosis of AF.

It has been demonstrated that left atrial dysfunction, as well as their structural abnormalities, play an important role in the initiation of AF, i.e., electrical and structural remodeling of the atria contributes to the development and progression of AF [16, 18]. Currently, existing data undeniably indicate the

Table 3. The Analysis OR Value of Various Clinical Hemodynamic and Structural-Functional Parameters, as Well as Markers of Inflammation and Fibrosis in HFmrEF Patients With Persistent AF Compared With the Control Group

Indices	HFmrEF with persistent AF (n = 90)		
	OR	95% CI	P values
Sex	0.30	0.12 - 0.74	0.09
Age	1.06	0.98 - 1.14	0.101
SBP	0.98	0.94 - 1.04	0.661
DBP	1.00	0.94 - 1.07	0.801
HR	0.96	0.92 - 1.01	0.142
HC	1.56	1.04 - 1.97	0.001*
TIA	0.69	0.14 - 2.93	0.583
ICD	1.32	0.45 - 3.83	0.608
MI	2.20	0.81 - 5.95	0.120
Pmax	4.81	4.07 - 5.94	0.001*
Pdis	4.90	4.86 - 5.93	0.001*
QRS	0.97	0.93 - 1.01	0.168
BMI	1.97	0.98 - 2.21	0.044*
LAD	3.80	2.65 - 4.09	0.040*
LAV	3.69	2.58 - 4.82	0.002*
LVEDD	1.76	1.58 - 1.99	0.046*
LVEDV	1.93	1.89 - 2.09	0.019*
LVESV	0.96	0.88 - 1.06	0.480
IVST	1.69	1.48 - 1.98	0.042*
LVPWT	0.83	0.55 - 1.24	0.368
EF	1.30	1.08 - 1.57	0.05*
E peak	3.05	3.01 - 3.09	0.012*
A peak	0.93	0.86 - 1.00	0.059
E/A	1.05	1.02 - 2.55	0.720
DT	0.97	0.95 - 1.00	0.071
IVRT	3.94	3.90 - 4.99	0.016*
Hs-CRP	6.37	5.24 - 8.59	0.002*
IL-6	5.78	4.71 - 7.87	0.001*
TNF-α	2.51	2.37 - 4.68	0.002*
TGF-β1	3.84	2.10 - 6.23	0.005*

*P ≤ 0.05. AF: atrial fibrillation; A peak: late diastolic filling wave; BMI: body mass index; DBP: diastolic blood pressure; DT: deceleration time; E peak: early diastolic filling wave; E/A ratio: the ratio of the E peak to the A peak; EF: ejection fraction; HFmrEF: heart failure with mildly reduced ejection fraction; HCs: hypertensive crises; HR: heart rate; hs-CRP: high-sensitivity C-reactive protein; IHD: ischemic heart disease; IL-6: interlekine-6; IVRT: isovolumetric relaxation time; IVST: interventricular septum thickness; LAD: left atrial diameter; LAV: left atrial volume; LVEDD: left ventricle end-diastolic diameter; LVEDV: left ventricle end-diastolic volume; LVESD: left ventricle end-systolic diameter; LVESV: left ventricle end-systolic volume; LVPWT: left ventricle posterior wall thickness; MI: myocardial infarction; Pdis: P-wave dispersion; Pmax: P-wave maximum; SBP: systolic blood pressure; TIA: transitory ischemic attacks; TNF-α: tumor necrosis factor-α; TGF-β1: transforming growth factor-β1; OR: odds ratio; CI: confidence interval.

participation of inflammation in the pathogenesis of AF. Moreover, AF is known to have a strong association with HF, as many studies have shown that AF and HF often coexist, share common predisposing factors, and may worsen the overall prognosis [19-21]. We examined clinical, structural, and biochemical predictors of paroxysmal/persistent AF in HFmrEF patients and compared them with similar patients without AF. The results of our studies show that the tendency to obesity is one of the possible risk factors for the occurrence of AF in patients with HF. Overweight people have a higher incidence, prevalence, severity and progression of AF than people of normal weight. Obese patients often have multiple risk factors for developing AF, which can improve in response to weight loss; therefore, a consolidated approach to weight loss and management of AF risk factors is preferable [22]. A meta-analysis of 10 studies involving 108,996 patients found that for every 5% increase in weight, the incidence of AF increased by 13% (hazard ratio (HR) = 1.13, 95% CI = 1.04 - 1.23, P < 0.01). The authors of this study concluded that weight gain is associated with an increased risk of AF [23, 24]. Our data suggest that patient BMI is a significant predictor of the occurrence of paroxysmal and persistent AF in patients with HFmrEF.

Recent studies have demonstrated a correlation between changes in the anatomical structure of the atria and the level of inflammatory cytokines [25, 26]. This phenomenon has been accepted as a new insight into the study of the pathogenesis of AF, especially in patients with HF [27].

Comparison of risk factors associated with paroxysmal and persistent AF suggests that predictive factors have different effects on the occurrence and progression of AF in patients with HFpEF. In paroxysmal AF, special attention should be paid to the frequency of HCs, and markers of inflammation (OR). In the persistent form of AF, possible risk factors include inflammatory markers as well as fibrosis markers.

Our comparison of possible risk factors associated with paroxysmal and persistent AF suggests that predictor factors contribute differently to the occurrence and progression of AF. Thus, the OR of indicators of atrial electrical remodeling (Pmax and Pdis) turned out to be quite informative in the analysis, which can emphasize the particular importance of atrial damage in the occurrence of AF.

Based on the study of the relationship between left ventricular diastolic function (peak E, peak A, E/A ratio and IVRT deceleration time) and the risk of AF, it turned out that these parameters do not play an important role in the occurrence of paroxysmal AF but are decisive in persistent AF.

Conclusions

Higher age, BMI, frequency of HCs as well as atrial electrical remodeling play an important role in the occurrence of paroxysmal/persistent AF in patients with HFmrEF.

LV diastolic dysfunction and left atrial geometry changes are possible risk factors of AF occurrence of paroxysmal/persistent AF in patients with HFmrEF.

An increase in the concentration of inflammatory markers contributes to the appearance of paroxysmal/persistent AF in

patients with HFmrEF. An increase in the level of a profibrotic marker increases the likelihood of persistent AF in these patients

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Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

All subjects provided written informed consent.

Author Contributions

LH and SG designed and performed the study. PZ, HH, and SG drafted the manuscript and did critical editing. LH, PZ and SG assisted and supported in sample collection and subsequent analysis with statistics. SG and PZ carefully supervised this manuscript preparation and writing.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

AF: atrial fibrillation; A peak: late diastolic filling wave; BMI: body mass index; BP: blood pressure; CI: confidence interval; DBP: diastolic blood pressure; DT: deceleration time; E peak: early diastolic filling wave; E/A ratio: the ratio of the E peak to the A peak; EF: ejection fraction; HC: hypertensive crisis; HF: heart failure; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with educed ejection fraction; HR: heart rate; hs-CRP: high-sensitivity C-reactive protein; IHD: ischemic heart disease; IL-6: interlekine-6; IVRT: isovolumetric relaxation time; IVST: interventricular septum thickness; LAD: left atrial diameter; LAV: left atrial volume; LVEDD: left ventricle end-diastolic diameter; LVEDV: left ventricle end-diastolic volume; LVESD: left ventricle end-systolic diameter; LVESV: left ventricle end-systolic volume; LVPWT: left ventricle posterior wall thickness; OR: odds ratio; Pdis: P-wave dispersion; Pmax: P-wave maximum; SBP: systolic blood pressure; TNF-α: tumor necrosis factor-α; TGF-β1: transforming growth factor-β1

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