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Risk Factors Contributing to the Progression of Paroxysmal and Persistent Atrial Fibrillation in Heart Failure Patients with Mid-Range Ejection Fraction

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Running Title: Atrial fibrillation in heart failure patients

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ABSTRACT

Aims: Heart failure (HF) is frequently accompanied by atrial fibrillation (AF), a combination that worsens the outcomes of both diseases. Despite advances in the treatment of AF, it remains a serious and unsolved problem for clinicians and researchers. The aim of this study was to examine risk factors for incidents of paroxysmal and persistent AF in patients having heart failure with mid-range ejection fraction (HFmrEF).

Methods. Overall, 71 patients with HFmrEF and non-valvular AF, including paroxysmal and persistent types, were enrolled in this study. As a control group, 42 HFmrEF patients without AF were also enrolled. All patients underwent detailed physical examination, including resting electrocardiography, echocardiography, and 24-hour ambulatory Holter monitoring. Levels of the inflammation markers high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α) and the fibrotic marker transforming growth factor-β1 (TGF-β1) were measured by ELISA and expressed as odds ratios.

Results: We show that paroxysmal AF was associated with higher diastolic blood pressure, whereas both paroxysmal and persistent forms of AF were associated with more frequent occurrence of hypertensive crisis episodes and greater body mass index. Progression from paroxysmal to persistent AF was associated with significant ventricular remodeling. Persistent and paroxysmal AF were associated with higher levels of inflammatory markers when compared to HFmrEF patients having no AF. In addition, TGF-β1 was significantly increased in HFmrEF patients having persistent but not paroxysmal AF.

Conclusions: Occurrence of AF, first paroxysmal and then persistent, in HFmrEF patients is associated with left ventricular remodeling and the appearance of systemic inflammatory and fibrotic markers. Changes in those parameters may be indicators by which to identify patients at increased risk of atrial fibrillation. Further studies are needed to determine the prognostic validity of these markers.

Keywords: heart failure, mid-range ejection fraction, atrial fibrillation, cardiac inflammation, cardiac fibrosis, risk factors.

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List of Abbreviations:

SBP-systolic blood pressure; DBP-diastolic blood pressure; HR-heart rate; HCr- hypertensive crisis; TIA- transitory ischemic attacks; IHD-ischemic heart disease; MI- myocardial infarction; BMI-body mass index; LAD-left atrial diameter; LAV-left atrial volume; LV ED-left ventricle end-diastolic diameter; LV EDV- left ventricle end-diastolic volume; LV ESD- left ventricle end-systolic diameter; IVST-interventricular septum thickness; LV PWT- left ventricle posterior wall thickness; EF-ejection fraction; DT-deceleration time; IVRT-isovolumetric relaxation time; hsCRP-high sensitive C reactive protein; IL-6-interlekine-6; TNF-α- tumor necrosis factor- α; TGF- β1 - transforming growth factor-β1.

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Declaration of interest

None

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INTRODUCTION

Heart failure (HF) is emerging as a pandemic, one with wide epidemiological heterogeneity between regions and countries(1).Worldwide, the number of HF cases doubled from 33.5 million in 1990 to 64.3 million in 2017, and the global prevalence remains high(2). HF is associated with structural and functional myocardial abnormalities(3-5). Major pathogenic mechanisms contributing to HF include increased hemodynamic overload, ischemia-related dysfunction, mutations in contractile proteins, ventricular remodeling, and altered neurohumoral stimulation(6-8). Unlike other common cardiovascular diseases such as ischemic heart disease (IHD) or hypertension, HF has a multitude of causes, which hinders precise classification and treatment(9-11). Comparison of clinical characteristics, comorbidities, outcomes, and prognosis among patients with HF having either preserved ejection fraction (>50%, pEF), mid-range ejection fraction (40-49%, mrEF), or reduced ejection fraction (<40%, rEF) leads to consideration of HFmrEF as an intermediate phenotype, neither normal nor preserved, which often resembles HF with reduced ejection fraction more than HF with preserved ejection fraction(12-14). HFmrEF was first recognized as a new HF phenotype by the European Society of Cardiology (ESC) in 2016(15). Of more than 6.5 million HF patients in the US, between 13% and 24% had HFmrEF(16). The latest studies suggest that patients with HFmrEF seem to benefit from therapies established to improve outcomes for those with reduced ejection fraction(17-20). Nonetheless, the characteristics of HFmrEF and its potential for therapy remain understudied. Atrial fibrillation (AF) is both the most commonly sustained and the most heterogeneous type of arrhythmia. There is plausible published evidence linking its initiation and progression to inflammation and fibrosis(21-24). Despite the fact that AF and HF represent separate diseases, these conditions are increasingly found to overlap and are both associated with high morbidity and mortality; furthermore, patients with concomitant HF and AF suffer from even worse symptoms and poorer prognosis(25, 26). Data from the Framingham Heart Study suggests that AF occurs in more than half of individuals with HF, and that HF occurs in more than one third of individuals with AF(27). Thus, HF and AF are commonly encountered together, are closely interrelated with similar risk factors, and each predispose to the other(27). Yet while HF with mrEF is well-described, determinants and outcomes of HFmrEF with concomitant AF remain unclear(27, 28). In this study, we sought to determine common risk factors associated with progression of AF in HFmrEF patients.

MATERIAL AND METHODS

Ethical Approval of Study Participants. Blood samples were collected from heart failure patients in the Department of Arrhythmia at the Research Institute of Cardiology Hospital under

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a protocol approved by the Institutional Review Board of M. Heratsy Yerevan State Medical University, Yerevan, Armenia, and with informed consent from the patients.

Study patients. Clinical characteristics of the patients are presented in **Table 1.** The study was a retrospective analysis of 113 HF patients with mrEF who were hospitalized in the Department of Arrhythmia of Research Cardiology Institute (Yerevan, Armenia). After successful cardioversion, 71 patients (age 62±7.6) with non-valvular paroxysmal and persistent AF were enrolled. Another 42 HFmrEF patients without AF were enrolled as a control group. The inclusion criteria also included presence of ischemic or hypertensive heart disease. Ischemic etiology was defined based on documented history of myocardial infarction or coronary angiography. Exclusion criteria included: HF due to valvular heart disease, chronic obstructive pulmonary disease, systemic inflammatory diseases, and diabetes. Patients were followed up with in accordance with the usual practice of the center. All participants underwent a detailed physical examination that included resting 12-lead electrocardiography (ECG) recording, echocardiography, and 24-hour ambulatory Holter monitoring. Blood pressure was calculated as an average of three independent measurements. Body mass index (BMI) was calculated as weight divided by height and expressed as kg/m^2. All examined patients were asked to complete a questionnaire about lifestyle (smoking, drinking, nutrition, etc.) and the presence of potential comorbidities (**Table 1**).

Materials. 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 ELISA kits according to instructions from the manufacturer. ELISA kits for analysis of IL-6, TNFα, and TGF-β1 were purchased from BioSource (Belgium), and for hs-CRP from DRG International Inc. (USA).

Echocardiography. The conventional trans-thoracic echocardiogram «MedisonSONOX-6» (Hungary) was used to measure left ventricular ejection fraction according to standard criteria. Echocardiographic measurements of chamber and vessel dimensions and cardiac systolic and diastolic functions were obtained by experienced cardiologists according to established guidelines.

Biochemical blood measurements. Quantifications were determined using standard laboratory procedures established at the Research Cardiology Institute. Plasma levels of inflammation

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markers hs-CRP, IL-6, TNFα, and TGF-β1 were determined by ELISA 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 obtained data were modeled by binary logistic regression using the index odds ratio (OR) associated with each risk factor. To assess OR significance, point differences with 95% confidence intervals were determined for all comparisons. A *p*-value <0.05 was considered significant. Studies were conducted on the basis of simple randomized protocols using the universal statistical package SPSS 13.0.

RESULTS:

Clinical characteristics of the study participants. Patient characteristics are presented in **Table 1**. We found that HFmrEF patients with paroxysmal or persistent AF were significantly older than patients without AF. No significant differences in sex distribution were observed. In general, patients with AF had greater BMI relative to those without AF ($p<0.05$, **Table 1**). Furthermore, patients with persistent AF had greater BMI than those with paroxysmal AF. The groups were similar in terms of the proportion of patients with smoking and drinking habits. Resting heart rate (HR) was also similar in all patients examined, but showed a modest but significant increase in patients with paroxysmal AF compared to both those with persistent AF and the control group. Resting systolic blood pressure (SBP) was significantly higher in patients with AF compared with patients without AF, and peak SBP was higher in patients with persistent AF relative to both those with paroxysmal AF and the control group ($p<0.05$). Resting diastolic blood pressure (DBP) was unchanged between groups, but peak DBP was significantly higher in patients with paroxysmal AF than in either patients with persistent AF or controls.

Risk Factors Associated with Paroxysmal AF. Variables associated with an increased risk of paroxysmal AF in HFmrEF patients (n=32) included: 1) middle age (from 49 to 72) with odds ratio of 1.8 and 95% confidence interval (CI) 1.08-1.28, $p = 0.001$; 2); high DBP, with OR 1.09, CI 1.01-1.17, $p = 0.017$; high frequency of hypertensive crises, with OR 1.17, CI 1.07-1.43, $p = 0.001$; and high BMI, with OR 1.13, CI 0.93-1.27, $p = 0.031$. According to electrocardiographic findings, P-maximum (Pmax) and P-wave dispersion (Pdis) were significantly prolonged, and were 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 the echocardiographic measurements, a greater risk of paroxysmal AF was associated with a larger left atrial volume (LAV; OR 1.76 [CI 1.66-1.88, $p = 0.002$]). Importantly, we found that high

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risk for paroxysmal and for persistent AF were both associated with increased levels of systemic inflammatory markers: hs-CRP, OR 5.57 [CI 3.38-7.87, $p = 0.010$] and the cytokines IL-6, OR 4.80 [CI 2.72-6.88, $p = 0.001$], and TNF-α, OR 2.56 [CI 1.43-4.73, $p = 0.002$] (**Table 2 and Fig.1A**).

Risk Factors Associated with Persistent AF. When analyzing individual risk factors in HFmrEF patients with persistent AF (**Table 3** and **Fig.1B**), significant risk factors relative to the control group included the frequency of hypertensive crises (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 volume (LAV) were also significantly increased, with OR 3.69 [CI 2.58-4.82, $p = 0.002$] and OR 3.80 [CI 2.65-4.09, $p = 0.040$], respectively.

Left ventricular diastolic dysfunction was observed in HFmrEF patients having persistent but not paroxysmal AF, which included elevated peak velocity of the early diastolic filling wave (E peak; OR 3.05 [CI 3.01-3.05, $p = 0.012$]) and prolonged isovolumic relaxation time (IVRT; OR 3.94 [CI 3.90-4.99, $p = 0.016$]). Impairment of left ventricular systolic function was also observed in patients with persistent AF relative to controls; risk of persistent AF was associated with enlarged end diastolic diameter (EDD), high end diastolic volume (EDV), increased interventricular septum thickness (IVS), and a slightly elevated ejection fraction, with respective OR values 1.76 [CI 1.58-1.99, $p = 0.046$], 1.93 [CI 1.89-2.09, $p = 0.02$], 1.69 [CI 1.48-1.98, $p = 0.042$], and 1.30 [CI 1.08-1.57, $p = 0.005$]. In addition to accumulation of systemic inflammatory markers, risk factors for persistent AF also included increased plasma levels of TGF-β1, a pro-fibrotic and immunomodulatory molecule, with OR 3.84 [CI 2.10-6.23, $p = 0.005$].

DISCUSSION

AF is the most heterogeneous arrhythmia with regard to the spectrum of resulting symptoms. Currently, much attention is paid to assessing quality of life and comorbid conditions that contribute to remodeling of the heart, thereby leading to worsening outcomes.

It has been shown that LA and LV function and mitral regurgitation play important roles in the initiation of AF(29, 30). These factors can lead to structural remodeling of the atrium, which causes development and progression of AF. Furthermore, existing evidence is indisputable concerning the involvement of inflammation in the pathogenesis of AF; managing its initiating agents can lead to improvement in patients with this type of arrhythmia. Finally, AF is known to have a close relationship with HF, as several studies have shown that AF and HF often coexist, share common predisposing factors and perpetuate one another(26, 31-33)—especially in the

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case of HF with mrEF. Nonetheless, there is still varying assessment of and ambiguity regarding the clinical characteristics and prognostic value of AF in HFmrEF.

We examined clinical, structural, and biochemical predictors of new-onset AF in HF patients with mrEF and compared them against mrEF patients without AF. It has been suggested that association of AF with HF may be modified by clinical factors such as sex, advanced age, type II diabetes, arterial hypertension, and history of myocardial infarction(34, 35). However, in our study, we did not observe any sex-related differences across the groups. Consistent with our observations, data from BiomarCaRE study(36) also suggest no sex differences in plasma levels of C-reactive protein or of N-terminal pro B-type natriuretic peptide: the population-attributable risk from all factors combined was 41.9% in women and 46.0% in men(36). Some authors consider men to be more susceptible to the development of AF(37); however, there is evidence that the onset of AF is simply delayed in women—on average, women develop AF ten years later than men.

Our data suggest that one risk factor for AF is the tendency of obesity. Overweight populations have higher incidence, prevalence, severity, and progression of AF compared with their normal-weight counterparts(38). Obese patients often present multiple risk factors for AF that improve in response to weight loss; this makes preferable a consolidated approach of weight loss and AF risk factor management and raises overweight and obesity as potential targets for intervention. In the same vein, stable weight loss decreases AF burden and its recurrence following treatment, and reverse structural remodeling in response to weight loss suggests improvement in arrhythmia profile. A meta-analysis of ten studies with 108 996 patients overall showed that for every 5% weight gain, the incidence of AF increases by 13% (hazard ratio [HR] 1.13, 95% CI 1.04-1.23, $p<0.01$). Strikingly, a 5% loss in body weight was not associated with any significant change in the incidence of AF (HR 1.04, 95% CI 0.94-1.16, I2=73%, n=40 704). The authors of that study concluded that weight gain is associated with increased risk of AF(39, 40). Obesity-related risk of AF appears to impact men more than women (OR per standard deviation increase 1.18, 95% CI [1.12–1.23] in women versus 1.31, 95% CI [1.25–1.38] in men; $p<0.001$)(37, 39, 40). However, these studies did not take into consideration the clinical form of AF, nor the degree of HF. Our data show that patient BMI represents a significant risk factor for both paroxysmal and persistent AF.

Recent studies have demonstrated a correlation between changes in the anatomical structure of the atria and levels of inflammatory cytokines, a phenomenon that has been adopted as a new angle in studying the pathogenesis of AF, especially in patients with mrHF(37, 40, 41). Inflammation markers IL-6 and hs-CRP have been previously linked to AF(42, 43). Comparison of the risk factors associated with paroxysmal and persistent AF suggests that contributions of

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predictor factors to the onset and progression of AF vary. Thus, with the progression of paroxysmal to persistent AF, special attention should be paid to the duration of AF (OR 6.07 [CI 5.86-7.00, $p = 0.002$]) and to markers of inflammation and fibrosis, namely hsCRP (OR 5.79 [CI 4.37-7.32, $p = 0.000$]) and TGF-β1 (OR 6.39 [CI 4.02-8.38, $p = 0.005$]). The OR indicator was found to be quite informative for analysis of electrical remodeling of the atria (Pmax and Pdis), since these parameters were equally dysregulated in the settings of paroxysmal and persistent AF; this might highlight particular importance of atrial damage in the progression of AF.

From analyzing the association of left ventricular diastolic function (E peak, A peak, E/A ratio, DT IVRT) with AF risk, it appears that these parameters play no role in the paroxysmal form of AF but become crucial in its progression to the persistent form.

In summary, our principal findings are as follows:

1. For parameters of atrial electrical remodeling (Pmax and Pdis), odds ratios are significantly increased in the progression from paroxysmal to persistent AF, potentially indicating an important role of heterogeneous atrial lesions in that progression.
2. Concerning functional and structural changes in the left atrium, our analysis has shown that with the progression from paroxysmal AF to the persistent form, the significance of LAD and LAV OR values increases substantially. Comparative analysis showed that for LV systolic characteristics such as LVEDD, LVEDV, and LVESV, if the OR value in the context of paroxysmal AF does not have specific changes, then in patients with persistent AF, it increases significantly. This indicates the important role of atrial functional and structural changes in AF progression.
3. In patients with paroxysmal AF, the OR values of inflammatory markers such as hs-CRP, IL-6, and TNF-α were statistically significant, and in patients with persistent AF, the reliability of these indicators increases. Moreover, in persistent AF, the fibrosis marker TGF-β1 had significantly increased OR compared with the paroxysmal form; thus, inflammation and fibrosis can possibly become biomarkers for AF in these patients.

We believe that identification and assessment of major risk factors in HFmrEF patient populations is of particular interest from the perspective of preventing the occurrence of AF and its progression to persistent form in patients with HF.

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Figure Legends

Figure 1. OR values and 95% confidence interval of various clinical, hemodynamic and structural functional parameters, and markers of inflammation and fibrosis in HFmrEF patients with paroxysmal (left) and persistent (right) AF in relation to the control group. *, $p<.05$.

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Table 1 Baseline Demographics and Clinical Characteristics in all observed patients with HFmrEF with and without AF. Data represented as mean (range). *, p<0.05 vs. HFmrEF with no AF; #, p<0.05 vs. HFmrEF with paroxysmal AF.

Indices, units	HFmrEF no AF	HFmrEF/ paroxysmal AF	HFmrEF/ persistent AF
Sample size	n=42	n=32	n=39
Age, years	56 49 - 74	54 47-71	57# 51-73
Male, %	56.2	50.8	52.4
BMI kg/m²	28.8 27-32	30.1* 27-34	31.9# 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 HR, bpm	75.6 68-89	76.7 72-91	74.6 65-90
Peak HR, bpm	116.8 92-131	121.7* 92-133	115.8# 96-123
Resting SBP (mmHg)	141.9 125-155	148.9* 131—160	139.9# 131-150
Peak SBP (mmHg)	164.1 145-180	164.8 140-185	170.9# 40-180
Resting DBP (mmHg)	83.7 75-95	78.1 70-90	84.7 75-95
Peak DBP (mmHg)	92.9 80-110	95.9* 80-105	95.9* 80-110

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Table 2. Analysis of OR values at 95% confidence interval of various clinical hemodynamic and structural-functional parameters, and markers of inflammation and fibrosis in HFmrEF patients with paroxysmal AF in relation to the control group.

	HFmrEF with paroxysmal AF (n=32)		
Indices	**OR**	**95% CI**	**P-value**
Sex	0.24	0.10-0.58	0.07
Age years	1.18	1.08-1.28	**0.01***
SBP mm/Hg	1.00	0.94-1.05	0.987
DBP mm/Hg	1.09	1.01-1.17	**0.017***
HR bpm	1.03	0.98-1.08	0.182
HrC %	1.17	1.07-1.43	**0.001***
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 (kg/m²)	1.13	0.93-1.27	**0.031***
LAD (mm)	0.86	0.70-1.06	0.167
LAV (mL)	1.76	1.66-1.88	**0.002***
LVEDD (mm)	0.92	0.71-1.20	0.558
LVEDV (mL)	0.99	0.94-1.04	0.811
LVESD (mm)	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

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IVRT	0.99	0.95-1.03	0.661
hsCRP (mg/l)	5.57	3.38-7.87	**0.010***
IL-6 (pg/ml	4.80	2.72-6.88	**0.001***
TNF- α (pg/ml	2.56	1.43-4.73	**0.002***
TGF- β1 (pg/ml	0.57	0.00 – 4.2	0.995

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Table 3. 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 control group.

	HFmrEF with Persistent AF (n=39)		
Indices	**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
HrC %	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 (kg/m²)	1.97	0.98-2.21	**0.044***
LAD (mm)	3.80	2.65-4.09	**0.040***
LAV (ml)	3.69	2.58-4.82	**0.002***
LV EDD mm	1.76	1.58-1.99	**0.046***
LVEDV (ml)	1.93	1.89-2.09	**0.019***
LV ESV (ml)	0.96	0.88-1.06	0.480
IVST	1.69	1.48-1.98	**0.042***
LV PWT	0.83	0.55-1.24	0.368

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EF%	1.30	1.08-1.57	**0.005***
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***
hsCRP mg/l	6.37	5.24-8.59	**0.002***
IL-6 pg/ml	5.78	4.71-7.87	**0.001***
TNF- α pg/ml	2.51	2.37-4.68	**0.002***
TGF-β1 pg/ml	3.84	2.10-6.23	**0.005***

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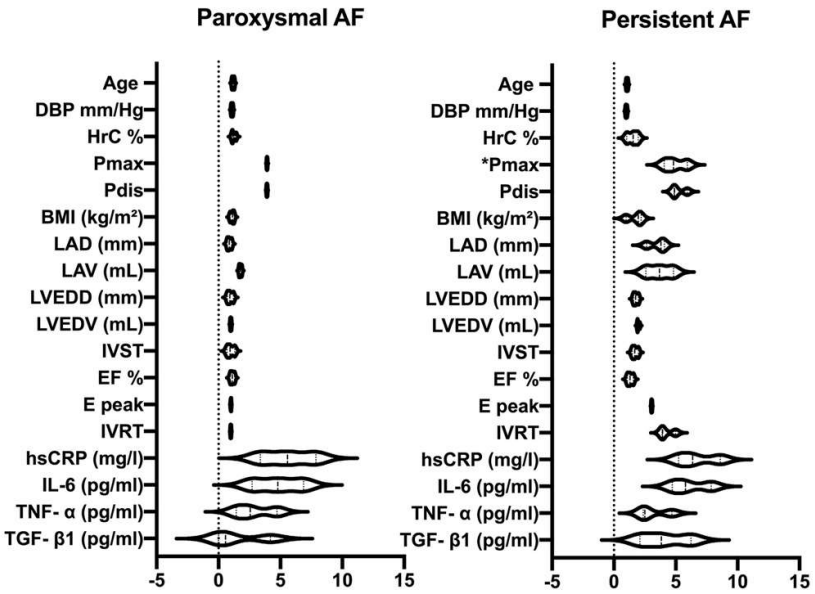

Figure 1.