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Subclinical inflammation, endothelial dysfunction and atrial electrical remodeling in early-onset paroxysmal atrial fibrillation without comorbidities

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Abstract

Objective: Early-onset paroxysmal atrial fibrillation (PAF) in individuals without conventional cardiovascular risk factors has traditionally been labeled as "lone AF." Recent evidence suggests that subtle structural, electrical, and functional abnormalities may still exist. This study evaluated atrial conduction, diastolic function, endothelial function, and systemic inflammation in early-onset PAF patients without structural heart disease or overt comorbidities.

Methods: In this cross-sectional study, 40 patients aged 18–65 years with documented early-onset PAF were compared with 40 age and sex matched healthy individuals in sinus rhythm. All subjects underwent measurement of P wave dispersion and signal-averaged P wave duration, echocardiographic assessment of diastolic parameters, evaluation of endothelial function using flow-mediated dilation (FMD), and analysis of systemic inflammation via high-sensitivity C-reactive protein (hsCRP).

Results: Patients with PAF demonstrated significantly increased P wave dispersion (51.63 ± 11.17 ms vs. 35.13 ± 6.15 ms; $p < 0.001$) and prolonged signal-averaged P wave duration (146.75 ± 19.68 ms vs. 124.40 ± 9.05 ms; $p < 0.001$). Diastolic dysfunction was evident, characterized by a reduced E/A ratio and elevated septal E/E′. Left atrial volume index was significantly higher in the PAF group (29.79 ± 3.94 mL/m^2 vs. 28.23 ± 1.74 mL/m^2; $p = 0.025$). Endothelial function was impaired, as reflected by lower FMD values (5.27 ± 1.94% vs. 6.65 ± 1.78%; $p = 0.001$), while hsCRP levels were significantly higher in the PAF group (0.40 [0.30–0.55] vs. 0.24 [0.20–0.30] mg/dL; $p < 0.001$). Multivariate analysis identified signal-averaged P wave duration, P wave dispersion, mitral E wave velocity, septal E/E′, and left atrial volume index as independent predictors of PAF.

Conclusion: Even in the absence of overt cardiovascular disease, early-onset PAF is associated with meaningful disturbances in atrial conduction, diastolic performance, endothelial function, and systemic inflammation. These findings support the presence of early atrial cardiomyopathy and underscore the need for comprehensive cardiovascular evaluation in younger PAF patients.

Keywords: paroxysmal atrial fibrillation, trial remodeling, inflammation, endothelial dysfunction, diastolic function, signal-averaged ECG

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults, affecting approximately 1–2% of the general population, with its prevalence increasing with age [1,2]. AF is associated with significant cardiovascular morbidity and mortality, including ischemic stroke, heart failure, and reduced quality of life, and it often necessitates long-term pharmacological treatment [3,4]. Established risk factors include hypertension, structural heart disease, heart failure, diabetes mellitus, thyroid disorders, and advancing age [3-5].

Historically, the term "lone atrial fibrillation" was used to describe AF in younger individuals (typically under 60 years) without structural heart disease or other identifiable causes [6]. However, recent guidelines discourage the use of this term due to its limited clinical utility and the growing understanding that subclinical factors often contribute to AF development, even in the absence of overt comorbidities [7,8]. Instead, the focus has shifted toward characterizing the clinical and biological profile of patients without traditional risk factors rather than labeling them as having "lone AF" [9].

Contemporary insights into AF pathophysiology highlight a multifactorial etiology involving atrial remodeling, oxidative stress, systemic inflammation, genetic predisposition, and autonomic imbalance [10-12]. These mechanisms promote structural and electrical changes in atrial tissue that facilitate the initiation and maintenance of the arrhythmia.

AF recurrence and progression are strongly associated with atrial remodeling processes, which include structural, electrical, and contractile alterations. Inflammation, endothelial dysfunction, diastolic dysfunction, and heterogeneous atrial conduction may act individually or synergistically to promote this remodeling [10-13].

Although individual studies have evaluated the relationship between paroxysmal AF and inflammation, left ventricular (LV) diastolic function, endothelial function, and intra-/inter-atrial conduction times, there is a lack of comprehensive research that investigates these parameters collectively and assesses their interplay.

The aim of this study is to investigate the roles of inflammation, endothelial function, intra- and inter-atrial conduction properties, and diastolic function in patients with paroxysmal AF without overt structural heart disease, compare these parameters with age- and sex-matched controls in sinus rhythm, and explore their interrelations.

Methods

Study population

This cross-sectional study included 40 patients aged 18 to 65 years who presented with palpitations to the Hacettepe University Faculty of Medicine, Department of Cardiology, and were diagnosed with paroxysmal atrial fibrillation (PAF) documented by 24-hour Holter monitoring (minimum AF episode duration: ≥30 seconds). Only patients without identifiable structural heart disease, hypertension, or systemic comorbidities were included, representing a cohort with early-onset AF of unknown etiology. A control group of 40 age- and sex-matched healthy individuals with no history of arrhythmia or systemic disease was also enrolled.

Detailed clinical histories were taken. Participants with suspected obstructive sleep apnea (based on structured patient and family interviews), a family history of AF, or any clinical or subclinical cardiovascular or systemic condition were excluded. Demographic data, anthropometric measurements, physical examinations, and baseline laboratory tests were collected.

Exclusion criteria included: any structural heart disease, coronary artery disease, cardiomyopathy, moderate-to-severe valvular disease, thyroid dysfunction, pulmonary disease, hypertension, diabetes mellitus, liver or renal dysfunction, autoimmune or connective tissue disorders, active or chronic inflammatory conditions, malignancy, regular medication use (including anti-inflammatory or antiarrhythmic drugs), and smoking.

Data collection and measurements

Electrocardiographic evaluation

Standard 12-lead surface ECG and signal-averaged ECG (SAECG) recordings were obtained using the General

Electric MAC 5000 system while subjects were in sinus rhythm. After 15 minutes of rest in the supine position, P wave durations were measured. P wave onset was defined as the first deflection from the isoelectric line, and offset as the return to baseline. Leads with unclear P wave morphology were excluded, and measurements from at least 10 analyzable leads were required to ensure reliability. All included participants met this criterion, and no subjects were excluded due to insufficient ECG lead quality.

P wave durations were averaged from three consecutive beats. P maximum (Pmax), P minimum (Pmin), and P wave dispersion (Pd = Pmax − Pmin) were calculated. All ECG measurements were independently assessed by two observers, with intra- and inter-observer variability for Pmax and Pd being <5%.

SAECG P wave durations were derived from orthogonal leads after filtering (band-pass 40–250 Hz; 50 Hz notch filter). A composite signal of 250–350 beats was averaged to reduce noise, and duration was measured using a vector magnitude algorithm.

Transthoracic echocardiography (TTE)

TTE was performed using a 2.5 MHz transducer (GE Vingmed System Six) during sinus rhythm in the left lateral decubitus position. Standard parasternal and apical views were acquired. Measurements included left atrial (LA) diameter, left ventricular (LV) dimensions, wall thickness, and ejection fraction. LA volume was indexed to body surface area (LAVI). Echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) [14].

LV diastolic function was evaluated via pulsed-wave Doppler at the mitral inflow tract, measuring early (E) and late (A) diastolic velocities, E/A ratio, deceleration time (DT), and isovolumetric relaxation time (IVRT). At least three beats at end-expiration were averaged.

Color M-mode Doppler was used to assess mitral inflow propagation velocity (Vp). The slope of early diastolic flow was measured from the mitral valve annulus apically.

Tissue doppler imaging (TDI)

TDI was performed in the apical four-chamber view. Early (E'), late (A'), and systolic (S) myocardial velocities were recorded at the septal and lateral mitral annulus.

Inflammatory marker: High-sensitivity c-reactive protein (hsCRP)

Serum hsCRP was measured via nephelometry using the IMMAGE High Sensitivity CRP Kit (Beckman Coulter) in the central biochemistry laboratory.

Assessment of endothelial function: Flow-mediated dilation (FMD)

Endothelial function was evaluated by measuring brachial artery flow-mediated dilation (FMD) following guidelines from the International Brachial Artery Reactivity Task Force. Participants fasted for 8–12 hours and avoided caffeine and alcohol for 12 hours prior to the test. A 10 MHz linear array transducer was used.

After measuring baseline brachial artery diameter, a forearm cuff was inflated 50 mmHg above systolic pressure for 5 minutes and then deflated. Arterial diameter was re-measured 60 seconds after deflation. FMD was calculated as:

FMD (%) = [(post-hyperemia diameter − baseline diameter) / baseline diameter] × 100

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Hacettepe University Ethics Committee (Approval No: LUT 12/44 – 30), and the research was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) and MedCalc Statistical Software, Version 11.4.2 (MedCalc Software Ltd., Ostend, Belgium). The normality of distributions was assessed with the Kolmogorov–Smirnov test. Continuous variables were expressed as

mean ± SD or median (IQR), and categorical variables as counts and percentages.

Independent samples t-test or Mann–Whitney U test was used for comparing continuous variables, and Chi-square or Fisher's exact test for categorical variables. Variables associated with AF status were first analyzed using univariate logistic regression. Significant variables were included in a multivariate logistic regression model. ROC curve analyses were performed for parameters such as Pd, SAECG P wave duration, LAVI, E/E' septal, and E velocity. Correlations were examined using Pearson or Spearman coefficients as appropriate. A p-value < 0.05 was considered statistically significant.

Results

A total of 80 participants were enrolled in the study, including 40 patients with early-onset paroxysmal atrial fibrillation without identifiable comorbidities and 40 age- and sex-matched healthy controls. There were no significant differences between the two groups in terms of age (47.68 ± 8.47 vs. 48.95 ± 7.09 years; p = 0.468), sex distribution (p = 0.104), or body mass index (BMI; p = 0.180) (Table 1).

Transthoracic echocardiographic assessment demonstrated significantly larger left atrial dimensions in the PAF group. Left atrial diameter was significantly increased in patients with PAF compared to controls (3.50 ± 0.33 cm vs. 3.31 ± 0.38 cm; p = 0.018). Left atrial volume (LAV) (54.8 ± 7.3 mL vs. 50.5 ± 6.8 mL; p = 0.007) and left atrial volume index (LAVI) (29.79 ± 3.94 mL/m^2 vs. 28.23 ± 1.74 mL/m^2; p = 0.025) were also significantly higher in the PAF group (Table 2). Left ventricular ejection fraction and other systolic parameters were similar between groups.

Assessment of diastolic function revealed impaired left ventricular filling in the PAF group. Peak E wave velocity was significantly lower in patients with PAF compared with controls (69 [60–78] cm/s vs. 85 [74–96] cm/s; p = 0.040), along with a reduced E/A ratio (1.0 ± 0.22 vs. 1.15 ± 0.31; p = 0.019). Deceleration time (DT) (238.55 ± 50.11 ms vs. 218.45 ± 34.4 ms; p = 0.040) and isovolumetric relaxation time (IVRT) (115.00 ± 28.84 ms vs. 99.28 ± 14.37 ms; p = 0.033) were significantly prolonged in the PAF group (Table 3).

Table 1. Baseline characteristics of the study population

Variables	PAF (n = 40)	Control (n = 40)	P Value
Age (years)	47.68 ± 8.47	48.95 ± 7.09	0.468
Gender (Female)	22 (55.0%)	29 (72.5%)	0.104
Systolic Blood Pressure (mmHg)	123.75 ± 7.32	125 ± 7.34	0.504
Diastolic Blood Pressure (mmHg)	80.3 ± 6.09	80.5 ± 5.97	0.893
Heart Rate (beats/min)	76.03 ± 13.19	75.95 ± 7.66	0.975
Body Mass Index (BMI, kg/m^2)	26.76 ± 2.25	27.45 ± 2.28	0.180
Body Surface Area (BSA, m^2)	1.84 ± 0.18	1.79 ± 0.18	0.124
Total Cholesterol (mg/dL)	185.88 ± 27.40	187.95 ± 25.70	0.728
Triglycerides (mg/dL)	113.50 (100-130)	125.5 (110-140)	0.273
LDL (mg/dL)	110.38 ± 20.29	115.58 ± 19.19	0.242
HDL (mg/dL)	51.5 (48-55)	52.5 (49-56)	0.567
Glucose (mg/dL)	87.83 ± 11.03	91.65 ± 8.17	0.082
Urea (mg/dL)	14.62 ± 3.85	14.18 ± 5.44	0.672
Creatinine (mg/dL)	0.80 ± 0.13	0.74 ± 0.14	0.057
ALT (U/L)	20.5 (18-25)	23 (20-28)	0.086
AST (U/L)	19.96 ± 4.63	21.33 ± 3.33	0.133

Variables are presented as mean ± SD or median (IQR) according to distribution assessed by the Kolmogorov–Smirnov test.

Table 2. Baseline echocardiographic findings

Variables	PAF (n = 40)	Control (n = 40)	P Value
LVEDD (cm)	4.66 ± 0.38	4.62 ± 0.31	0.653
LVESD (cm)	2.99 ± 0.33	2.86 ± 0.31	0.063
EF (%)	65 (62-68)	66 (63-69)	0.086
FS (%)	35 (33-37)	36 (34-38)	0.090
IVS (cm)	1.00 (0.95-1.05)	0.91 (0.87-0.95)	0.096
PW (cm)	1.00 (0.95-1.05)	0.90 (0.86-0.94)	0.148
LA Diameter (cm)	3.50 ± 0.33	3.31 ± 0.38	0.018
LA Volume (mL)	54.8 ± 7.3	50.5 ± 6.7	0.007
LAVI (mL/m^2)	29.79 ± 3.94	28.23 ± 1.74	0.025
LVM (g)	176.38 ± 27.17	167.88 ± 30.78	0.194
LVMI (g/m^2)	95.81 ± 14.25	94.43 ± 16.72	0.692
sPAP (mmHg)	22.68 ± 4.33	23.13 ± 4.19	0.638

EF: Ejection Fraction, FS: Fractional Shortening, IVS: Interventricular Septum, PW: Posterior Wall (Thickness) LA: Left Atrium, LAV: Left Atrial Volume, LAVI: Left Atrial Volume Index, LVEDD: Left Ventricular End-Diastolic Diameter, LVESD: Left Ventricular End-Systolic Diameter, LVM: Left Ventricular Mass, LVMI: Left Ventricular Mass Index, sPAP: Systolic Pulmonary Artery Pressure
Variables are presented as mean ± SD or median (IQR) according to distribution assessed by the Kolmogorov–Smirnov test.

Table 3. Diastolic function parameters

Variables	PAF (n = 40)	Control (n = 40)	P Value
Peak E wave velocity (cm/s)	69 (60-78)	85 (74-96)	0.040
Peak A wave velocity (cm/s)	68.5 (60-77)	67.5 (58-77)	0.528
E/A ratio	1.00 ± 0.22	1.15 ± 0.31	0.019
DT (ms)	238.55 ± 50.11	218.45 ± 34.40	0.040
IVRT (ms)	115.00 ± 28.84	99.28 ± 14.37	0.033
Vp (cm/s)	57 ± 16	59 ± 10	0.451
E/Vp ratio	1.31 (1.20-1.42)	1.44 (1.33-1.55)	0.408
Lateral E′ (cm/s)	10.47 ± 3.61	13.94 ± 1.91	0.001
Lateral A′ (cm/s)	9.65 ± 1.82	10.70 ± 2.71	0.045
Lateral S (cm/s)	6.82 (6.3-7.3)	7.20 (6.7-7.7)	0.832
Lateral E′/A′ ratio	1.13 ± 0.44	1.38 ± 0.40	0.009
Septal E′ (cm/s)	8.90 ± 2.25	12.73 ± 1.69	0.001
Septal A′ (cm/s)	8.99 ± 1.84	10.13 ± 2.97	0.042
Septal S (cm/s)	6.90 ± 1.23	7.39 ± 1.63	0.131
Septal E′/A′ ratio	1.04 ± 0.37	1.37 ± 0.44	0.001
E/Septal E′	8.11 ± 1.74	6.38 ± 1.85	0.001
E/Lateral E′	7.08 ± 1.70	5.82 ± 1.73	0.002
Average E′ (cm/s)	9.68 ± 2.73	13.33 ± 1.26	0.001
E/Average E′	7.47 ± 1.48	6.03 ± 1.64	0.001

DT: Deceleration Time, IVRT: Isovolumetric Relaxation Time, Vp: Mitral Flow Propagation Velocity
Variables are presented as mean ± SD or median (IQR) according to distribution assessed by the Kolmogorov–Smirnov test.

Tissue Doppler imaging demonstrated significantly lower septal and lateral E′ velocities in the PAF group (septal E′: 8.90 ± 2.25 cm/s vs. 12.73 ± 1.69 cm/s; p = 0.001; lateral E′: 10.47 ± 3.61 cm/s vs. 13.94 ± 1.91 cm/s; p = 0.001). Accordingly, septal and average E/E′ ratios were significantly higher in patients with PAF (septal E/E′: 8.11 ± 1.74 vs. 6.38 ± 1.85; p = 0.001; average E/E′: 7.47 ± 1.48 vs. 6.03± 1.64; p = 0.001) (Table 3).

Electrocardiographic analysis revealed significantly prolonged atrial conduction parameters in the PAF group. P wave dispersion was markedly increased in patients with PAF (51.63 ± 11.17 ms vs. 35.13 ± 6.15 ms; p = 0.001). Signal-averaged ECG P wave duration was also significantly longer in the PAF group (146.75 ± 19.68 ms vs. 124.40 ± 9.05 ms; p = 0.001), as was maximum P wave duration (Pmax) (112.13 ± 16.68 ms vs. 98.00 ± 7.75 ms; p = 0.001) (Table 4).

Endothelial function assessed by flow-mediated dilation was significantly impaired in the PAF group (5.27 ± 1.94% vs. 6.65 ± 1.78%; p = 0.001), whereas baseline brachial artery diameters did not differ between groups (Table 5).

Inflammatory status, as reflected by high-sensitivity C-reactive protein (hsCRP), was significantly elevated in patients with PAF (median 0.40 mg/dL [0.30–0.55] vs. 0.24 mg/dL [0.20–0.30]; p = 0.001). P wave dispersion showed a strong positive correlation with hsCRP levels (r = 0.810; p = 0.001), while signal-averaged ECG P wave duration was moderately correlated with hsCRP (r = 0.364; p = 0.001). P wave dispersion and P wave duration were also moderately correlated with each other (r = 0.613; p = 0.001). Septal E/E′ ratio demonstrated significant positive correlations with both P wave dispersion (r = 0.317; p = 0.004) and P wave duration (r = 0.269; p = 0.016) (Figure 1).

Flow-mediated dilation was inversely correlated with LAVI (r = –0.245; p = 0.028), hsCRP (r = –0.401; p < 0.001), P wave dispersion (r = –0.400; p = 0.001), and P wave duration (r = –0.230; p = 0.040). LAVI showed weak but significant correlations with both P wave dispersion (r = 0.295; p = 0.009) and septal E/E′ ratio (r = 0.221; p = 0.049).

Univariate logistic regression analysis identified several parameters significantly associated with the presence of early-onset PAF, including left atrial dimensions, diastolic function indices, electrocardiographic markers of atrial conduction, hsCRP, and FMD (Table 6). In multivariate logistic regression analysis, signal-averaged ECG P wave duration (OR = 1.161; 95% CI: 1.01–1.34; p = 0.040), P wave dispersion (OR = 1.322; 95% CI: 1.01–1.75; p = 0.045), septal E/E′ ratio (OR = 21.121; 95% CI: 1.90–234.40; p = 0.013), mitral E wave velocity (OR = 0.76; 95% CI: 0.61–0.94; p = 0.012), and LAVI (OR = 1.964; 95% CI: 1.16–3.18; p = 0.038) emerged as independent predictors of early-onset PAF without comorbidities (Table 7).

Table 4. P wave analysis data from 12-lead surface ECG and signal-averaged ECG

Variables	PAF (n = 40)	Control (n = 40)	P Value
Pmax (ms)	112.13 ± 16.68	98.00 ± 7.75	0.001
Pmin (ms)	60.5 ± 14.31	62.88 ± 6.59	0.345
Pd (ms)	51.63 ± 11.17	35.13 ± 6.15	0.001
SAECG P wave duration (ms)	146.75 ± 19.68	124.40 ± 9.05	0.001

SAECG: Signal averaged ECG

Table 5. Baseline brachial artery diameters and flow-mediated dilation values of the groups

Variables	PAF (n = 40)	Control (n = 40)	P Value
FMD (%)	5.27 ± 1.94	6.65 ± 1.78	0.001
Baseline brachial artery diameter (cm)	3.89 (3.7-4.1)	3.74 (3.55-3.95)	0.182

FMD: Flow-Mediated Dilation

Variables are presented as mean ± SD or median (IQR) according to distribution assessed by the Kolmogorov–Smirnov test.

Receiver operating characteristic curve analyses demonstrated strong discriminatory performance for several parameters. P wave dispersion yielded an area under the curve (AUC) of 0.906 ($p < 0.001$), while signal-averaged ECG P wave duration showed an AUC of 0.857 ($p < 0.001$). Optimal cut-off values, along with sensitivity and specificity, are presented in Figure 2 and Figure 3.

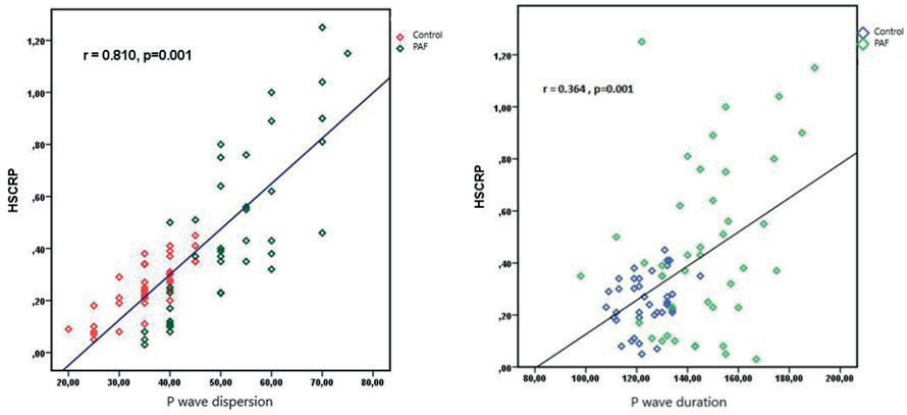

Figure 1. Correlation of hsCRP levels with P wave duration and P wave dispersion. The figure illustrates significant positive correlations between hsCRP levels and both P wave duration and P wave dispersion.

Table 6. Univariate logistic regression analysis of risk factors for PAF

Variables	OR	P Value	95% Confidence Interval(CI)
LA diameter	4.748	0.023	1.245 – 18.112
LAV	1.093	0.010	1.021 – 1.169
LAVI	1.206	0.032	1.016 – 1.406
Peak E wave velocity	0.975	0.038	0.951 – 0.998
E/A ratio	0.129	0.022	0.022 – 0.749
DT	1.011	0.045	1.008 – 1.022
IVRT	1.035	0.007	1.009 – 1.060
Lateral E′	0.662	0.001	0.543 – 0.807
Septal E′	0.377	0.001	0.245 – 0.578
E/Septal E′	1.764	0.001	1.285 – 2.422
E/Lateral E′	1.550	0.003	1.157 – 2.077
E/Average E′	1.837	0.001	1.302 – 2.593
Pmax	1.094	0.001	1.044 – 1.147
SAECG P wave duration	1.115	0.001	1.061 – 1.173
Pd	1.316	0.001	1.157 – 1.497
FMD (%)	0.644	0.004	0.477 – 0.871
hsCRP	101.7	0.001	6.166 – 1679.21

Table 7. Multivariate logistic regression analysis of risk factors affecting PAF

Variables	OR	P Value	95% Confidence Interval (CI)
SAECG P wave duration	1.161	0.040	1.01 – 1.34
Pd	1.322	0.045	1.01 – 1.75
E/E' (septal)	21.121	0.013	1.90 – 234.40
Peak E wave velocity	0.76	0.012	0.61 – 0.94
LAVI	1.964	0.038	1.16 – 3.18

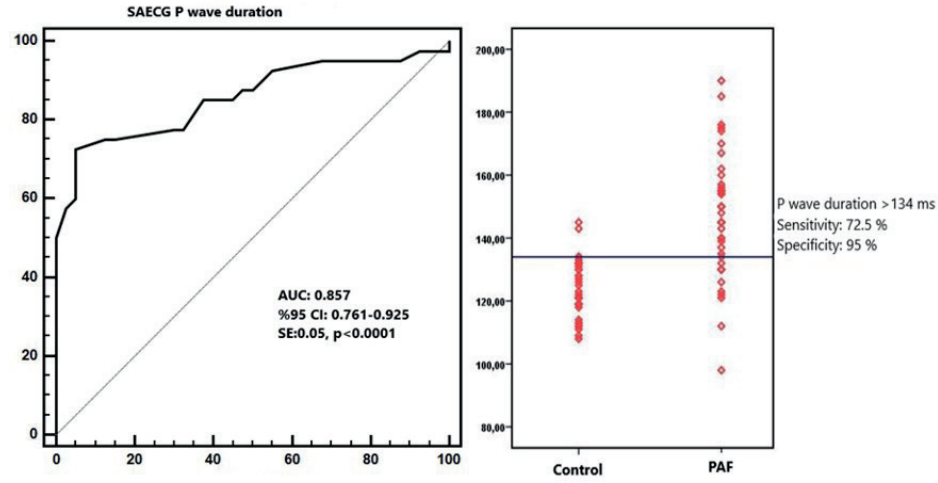

Figure 2. ROC analysis and cut-off value of SAECG P wave duration for predicting the development of PAF

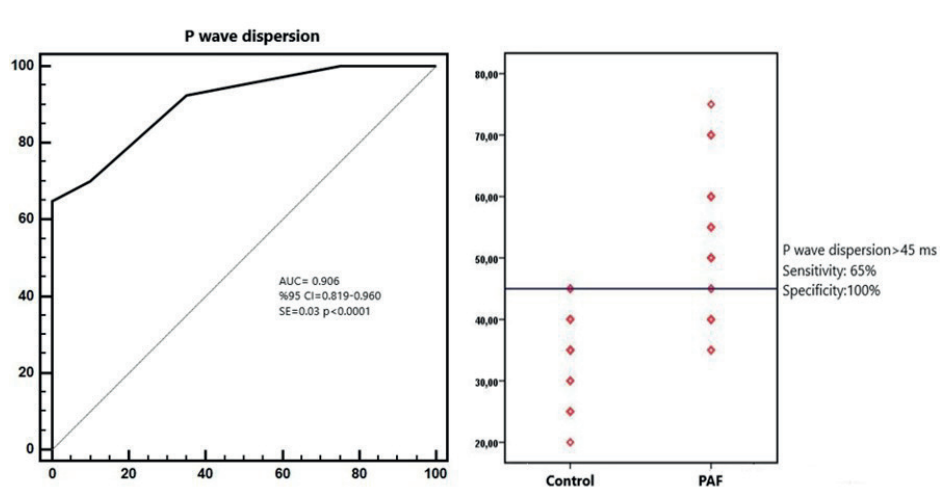

Figure 3. ROC analysis and cut-off value of P wave dispersion for predicting the development of PAF

Discussion

In this study, we investigated atrial conduction properties, left ventricular diastolic function, endothelial function, and systemic inflammation in patients with early-onset PAF without overt structural heart disease or traditional comorbidities. Our findings reveal that even in the absence of identifiable cardiovascular risk factors, PAF is associated with significant alterations in atrial electrophysiology, subclinical diastolic dysfunction, impaired endothelial function, and elevated inflammatory markers.

Patients with PAF exhibited increased P wave dispersion and prolonged signal-averaged P wave duration markers of intra and inter-atrial conduction heterogeneity that reflect early atrial electrical remodeling. These conduction abnormalities were significantly correlated with elevated hsCRP levels, supporting the role of inflammation in AF pathogenesis. Inflammatory cytokines can promote atrial fibrosis and conduction slowing through the activation of profibrotic pathways (e.g., TGF-β) and inflammasome-mediated myocyte injury [15,16]. Recent mechanistic studies confirm that NLRP3 inflammasome activation contributes to atrial electrical instability, while targeted inhibition of inflammasome signaling reduces AF vulnerability [17,18].

Interestingly, recent studies evaluating atrial electromechanical conduction and left atrial functional properties in patients undergoing interventions for atrial fibrillation have demonstrated that even in the absence of overt comorbidities, subtle atrial remodeling and functional impairment can be detected [19,20]. Although these studies primarily focused on echocardiographic and mechanical parameters rather than surface ECG indices, their findings complement our results by supporting the presence of early atrial remodeling in apparently healthy individuals with AF. Together, these observations reinforce the concept that atrial electrical abnormalities identified in our study coexist with subclinical structural and functional changes of the left atrium.

We also observed impaired left ventricular diastolic function in the PAF group, evidenced by reduced E wave, lower E/A ratios, prolonged deceleration time and isovolumetric relaxation time, and elevated E/E′ ratios. These findings suggest increased left atrial pressure and wall stress, which can lead to atrial dilation and fibrosis—mechanical contributors to AF onset and maintenance [21,22]. Notably, the strong correlations between E/E′ and both conduction parameters and hsCRP underscore the interplay between mechanical dysfunction, electrical instability, and systemic inflammation.

Endothelial function, as measured by FMD, was significantly reduced in the PAF group. FMD showed inverse correlations with LAVI, hsCRP, and conduction parameters, indicating that endothelial dysfunction may not only reflect systemic vascular pathology but also actively contribute to AF pathogenesis. Impaired nitric oxide bioavailability, increased oxidative stress, and altered vascular tone in endothelial dysfunction may augment systemic inflammation and atrial remodeling [23,24]. Furthermore, recent studies suggest that microvascular ischemia of the atrial myocardium, even in the absence of epicardial coronary artery disease, may promote low-grade fibrosis and create a vulnerable substrate for AF [25]. Emerging evidence also suggests that endothelial senescence may exacerbate inflammation and structural remodeling in AF-prone atria [26].

Additionally, the HALP score has been evaluated as a predictor of AF recurrence after ablation, showing that hematologic and inflammatory parameters can reflect underlying atrial vulnerability [27]. This aligns with our findings where elevated hsCRP correlated with conduction heterogeneity, suggesting that systemic inflammatory status may contribute to early atrial remodeling even in young, low-risk patients.

These results align with emerging data suggesting that patients formerly described as having “lone AF” may, in fact, exhibit early signs of atrial cardiomyopathy. Advanced imaging techniques such as speckle-tracking echocardiography and cardiac MRI have revealed atrial fibrosis, mechanical dysfunction, and reduced strain in AF patients without overt comorbidities [28,29]. The elevated LAVI and diastolic abnormalities in our study support the presence of subtle structural remodeling in this ostensibly healthy population.

Genetic predisposition is another key consideration. Recent genome-wide association studies (GWAS) have identified common variants in ion channel and transcription factor genes associated with AF, particularly in early-onset cases. These variants may predispose to conduction abnormalities and increased

atrial susceptibility to inflammatory or hemodynamic stressors [30]. Thus, the conduction changes observed in our patients may reflect a genetically determined atrial substrate. Recent Mendelian randomization studies have also linked genetically predicted IL-6 receptor signaling and CD40 ligand activity with increased AF risk, suggesting an inherited inflammatory susceptibility [31].

Additionally, heightened autonomic nervous system (ANS) activity especially increased vagal tone has been implicated in triggering paroxysmal AF in structurally normal hearts. In young individuals, autonomic imbalance may play a critical initiating role in arrhythmogenesis and influence AF patterns, particularly in the absence of other comorbidities [32].

Importantly, inflammation represents a potentially modifiable contributor to AF. Anti-inflammatory strategies, including colchicine and interleukin-1 antagonists, have demonstrated efficacy in reducing AF recurrence post-cardiac surgery and catheter ablation [33,34]. Given the strong association between hsCRP and conduction indices in our study, targeting inflammatory pathways may hold promise for early intervention in patients with subclinical atrial remodeling. Novel approaches targeting macrophage activity and osteopontin signaling have shown promising anti-fibrotic effects in experimental AF models [35]. Novel inflammatory markers such as interleukin-6, galectin-3, and soluble ST2 are being evaluated as potential biomarkers and therapeutic targets for atrial cardiomyopathy [36].

Although participants were selected to exclude known risk factors, subclinical contributors such as undiagnosed sleep apnea, visceral adiposity, alcohol consumption, or sedentary lifestyle may still influence atrial structure and electrophysiology. Future studies incorporating detailed lifestyle assessments and wearable monitoring could help capture these subtle influences [37]. Environmental triggers such as air pollution and heat exposure have also been identified as transient risk factors for AF events, even in young or low-risk populations [38].

Limitations

This study has several limitations. Its cross-sectional design precludes causal inference. The modest sample size may limit generalizability, and unmeasured confounders such as undiagnosed sleep-disordered breathing, masked hypertension, or lifestyle factors could have influenced the results. Additionally, we assessed inflammation using hsCRP alone, which, while widely validated, does not capture the full complexity of inflammatory signaling. Advanced imaging and genetic testing were not available to further characterize atrial structure or predisposition.

Conclusion

In summary, early-onset PAF in individuals without traditional cardiovascular risk factors is associated with a distinct pathophysiological profile that includes subclinical diastolic dysfunction, systemic inflammation, atrial electrical heterogeneity, and endothelial dysfunction. These findings reinforce the concept of early atrial cardiomyopathy and highlight potential targets for risk stratification and early therapeutic intervention. Future prospective studies should assess whether targeting inflammation and mechanical dysfunction can delay AF progression or improve long-term outcomes in this population.

Author contributions

Conception and design: A.Ü.K., K.A.; Data acquisition: A.Ü.K., T.K., A.B.; Data analysis: A.Ü.K.; Data interpretation: A.Ü.K., T.K., A.B.; Drafting of the manuscript: A.Ü.K., T.K., A.B.; Critical revision of the manuscript: K.A. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Hacettepe University Ethical Commitee (Date: June 5, 2012, Decision/ Protocol No: LUT 12/44-30). Informed consent was obtained from all participants involved in this study.

Data availability statement

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

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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