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Risk of atrial fibrillation in primary immunodeficiencies: evaluation of atrial electromechanical delay and P-wave dispersion

Mustafa Ilker Inan[a]*, Yasemin Akgul Balaban[b], Ahmet Faruk Yagcı[c], Cihad Kaya[c], Ezgi Sonmez[d], Fikriye Kalkan[e], Fevzi Demirel[d], Sait Yeşillik[d], Barış Bugan[c], Ozgur Kartal[d]

[a]*Immunology and Allergy Department, Kütahya City Hospital, Kütahya, Turkiye*
[b]*Immunology and Allergy Department, Zonguldak Atatürk State Hospital, Zonguldak, Turkiye*
[c]*Cardiology Department, Gulhane Training and Research Hospital, Ankara, Turkiye*
[d]*Immunology and Allergy Department, Gulhane Training and Research Hospital, Ankara, Turkiye*
[e]*Immunology and Allergy Department, Ankara Bilkent City Hospital, Ankara, Turkiye*

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Abstract
Background: Primary immunodeficiency diseases (PIDs) are an expanding group of rarely observed immune system disorders. Various clinical conditions, such as autoimmunity, immune dysregulation, and inflammation, could affect multiple organ systems in PID patients. The heart may be one of these organs; however, studies on this topic are rare. Atrial fibrillation (AF) is a significant cause of mortality and morbidity in the community and an increased P-wave dispersion (PWD) and atrial electromechanical delay (AED) are well-known markers indicating a predisposition to AF. We aimed to determine whether AED and/or increased PWD predict the early risk of AF in PID patients.
Methods: This single-center, prospective controlled study included 61 PID and 60 control group patients. All participants underwent resting electrocardiography, echocardiography, and atrial electromechanical conduction time (AECT) monitoring using tissue Doppler imaging evaluated by an experienced cardiologist.
Results: The PID group had a statistically significantly higher Pmax, Pmin, and PWD values, compared to the control group (102 [92-108] vs. 88 [82-99] ms, P < 0.001; 74 [70-80] vs. 68 [62-72] ms, P < 0.001; 26 [22-30] vs. 21 [18-26] ms, P = 0.001, respectively). Right atrial delay and interatrial delay were discovered to be statistically significantly higher in PID group (4 [2-6] vs. 2 [2-4] ms, P < 0.001; 6 [4-8] vs. 4 [4-6] ms, P = 0.039, respectively). Left atrial delay was also discovered to be high in the PID group, although this difference was not statistically significant (6 [4-6] vs. 4 [3-6] ms; P = 0.05).
Conclusion: We demonstrated that the well-known predictors of AF, AECT, and PWD were increased in PID patients. This result aids in the follow up and survival of PID patients, who

***Corresponding author:** Dr. Mustafa Ilker Inan, MD, Division of Immunology and Allergy, Kütahya City Hospital, Evliya Çelebi Mah. Eken Paşa cd. No:19, Merkez, Kütahya 43100, Turkiye. *Email address*: m.ilkerinan@gmail.com

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experience multiple complications, by enabling the early identification of AF-related mortality and morbidity risk.
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Introduction

Primary immunodeficiency diseases (PIDs), also known as inborn errors of immunity, are an expanding group of clinically heterogeneous immune system disorders.[1] According to the affected components of innate and adaptive immune responses, PIDs are classified into 10 different groups by the International Union of Immunological Societies.[2] They have a broad clinical spectrum of manifestations but are typically characterized by a compromised immune system, resulting in increased susceptibility to recurrent or chronic infections. Autoimmunity, atopic diseases, lymphoproliferative diseases, and malignancies are the other common manifestations.[3]

Atrial fibrillation (AF) is a rhythm disorder characterized by disorganized atrial electrical activity and uncoordinated atrial contractions.[4] AF is a significant cause of mortality and morbidity in the community, particularly because of heart failure, stroke, and other thromboembolic events.[5,6] Atrial electromechanical conduction time (AECT) defines the period between electrical depolarization and atrial contraction, in other words, the time interval between the onset of electrocardiographic P-wave and the onset of late diastolic wave in tissue Doppler imaging. A prolonged AECT demonstrates atrial electromechanical delay (AED).[7-9]

Prolongation of maximum P-wave duration (Pmax) recorded from multiple different surface electrocardiogram (ECG) leads, an increase in P-wave dispersion (PWD), which is defined as the difference between the maximum and minimum P-wave duration (Pmin), and AED are well-known markers indicating a predisposition to AF.[10,11] Several studies have shown that AED predicts the risk of developing AF, even in patients with normal sinus rhythm.[8,9,12,13] The presence of comorbid conditions affecting multiple organ systems in PID patients and the observation of cardiovascular system involvement, including arrhythmias, in our previous study led us to design this study.[14,15] We aimed to determine whether AED and/or increased PWD predict the early risk of AF in patients with PID.

Materials and Methods

Study design and population

The study was a prospectively planned, cross-sectional, controlled study. The study protocol was approved by the Clinical Research Ethics Committee of Gulhane Training and Research Hospital (2023/46). All participants included in the study were aged ≥18 years. Written informed consent was obtained from all patients.

Patients who were followed up with a diagnosis of PID were included in the study group. Patients who did not provide written informed consent, those without normal sinus rhythm on resting ECG, and those with a poor echocardiographic window were excluded from the study. All secondary causes of immunodeficiency were evaluated and excluded. None of the patients was using any medication that could cause secondary hypogammaglobulinemia. Routine biochemical examinations, serum immunoglobulins (Ig), IgG subgroups, and flow cytometric examinations were performed in all PID patients at the time of the study. All cases underwent echocardiography (ECHO) by an experienced cardiologist. Also, resting ECG results were evaluated.

The control group consisted of individuals who presented to the cardiology outpatient clinic and had normal cardiac evaluation results, including ECG and ECHO. None of the control patients had a diagnosis of PID, and none had a family history of PID. There was no history of recurrent, severe, chronic, unexplained, or unusual infections, autoimmune diseases, malignancies, or lymphoproliferative disorders that could suggest PID in any of them. The European Society for Immunodeficiencies warning signs for adult PIDs were also inquired from all in the control group.[16] Participants with any of these findings were not included in the control group.

Electrocardiographic evaluation

In all, 12-lead surface ECG recordings (50 mm/s, 0.05 mV/mm) were obtained from each patient at rest. Then, ECG records were transferred to a digital platform for more precise measurements. The onset of P-wave is defined as the point of first detectable upward or downward deflection from the isoelectric line for positive or negative waveforms, respectively. All P-wave durations were measured in the 12-lead ECG, and PWD was obtained by subtracting Pmin from Pmax.

Echocardiographic and tissue doppler echocardiographic measurements

All individuals included in the study underwent echocardiographic examination in the left lateral decubitus position using a 3.5-MHz probe and the echocardiography device (Philips Epiq 7, Philips Medical Systems, Bothell, WA). The echocardiographic examination was performed with monitoring of DII lead. The systolic and diastolic internal diameters of the left ventricle, interventricular septal diastolic thickness, and left ventricular posterior wall diastolic thickness were measured using the M-mode method from the parasternal long-axis view, following commonly applied procedures. The anteroposterior diameter of the left atrium (LA) was measured as the longest diameter

behind the posterior wall of the aorta and the posterior wall of LA at the end of systole, using the parasternal long-axis view. In the apical four-chamber view, the sampling point was placed between the tips of the mitral leaflets, and a pulsed-wave Doppler was used to obtain mitral inflow velocity–time curve. From this curve, peak velocities of E and A waves during early diastolic filling and during late diastole with contraction of LA (A-wave), and deceleration time of E-wave were measured. Valve functions of the patients were assessed. All these measurements were obtained by averaging three consecutive cardiac cycles. The estimated systolic pulmonary artery pressure (SPAP) was obtained from the amount of tricuspid regurgitation using the modified Bernoulli equation, in addition to the estimated right atrial pressure. SPAP was accepted normal up to 25 mmHg, pulmonary hypertension (PHT) was defined as SPAP >25 mmHg.

Atrial electromechanical conduction time evaluation

Apical four-chamber tissue Doppler images were obtained at the end of expiration to determine AECT using tissue Doppler imaging. In the apical four-chamber view, the sampling point was placed on the lateral mitral annulus (LMA), septal mitral annulus (SMA), and lateral tricuspid annulus (LTA), and systolic and diastolic waves representing mitral and tricuspid annular motion were visualized. The peak velocities of positive S'-wave (LMA S', SMA S', and LTA S') during ventricular systole, negative E'-wave (LMA E', SMA E', and LTA E') during early diastolic filling, and negative A'-wave (LMA A', SMA A', and LTA A') during late diastole caused by left atrial contraction were measured. Then the sample point was placed on the mid-segment of the lateral and septal walls of LA and the middle segment of the lateral wall of the right atrium (RA), and the negative A-wave (denoted as A") caused by left and right atrial contraction was measured during late diastole and its peak velocity. Time intervals from the onset of P-wave in lead DII to the onset of the A" waves were measured to calculate mitral [P-A"(M)], septal [P-A"(S)], and tricuspid [P-A"(T)] time intervals. Differences between these three time intervals were used to calculate left and right intra-atrial and interatrial conduction times. The results were compared to determine whether there was AED between the patient and the control groups.

Statistical analysis

The data analysis of the study was performed using the IBM SPSS version 25.0 software. Descriptive statistics for continuous variables were presented as mean ± standard deviation (mean±SD), median, 1st quartile, 3rd quartile, and the minimum and maximum values. Categorical variables were expressed as counts and percentages. The normality of the data distribution was assessed using the Shapiro–Wilk or Kolmogorov–Smirnov test. For independent two-group comparisons of continuous variables, the homogeneity of variances was evaluated using Levene's test. Two independent group comparisons were made with independent sample *t*-test when the assumptions of normality and homogeneity of variances were met, Welch's *t*-test when the assumption of normality was met but the assumption of homogeneity was not met, and Mann–Whitney U test when the assumption of normality was not met. Comparisons between categorical variables were assessed using the Pearson's Chi-square test, and if necessary, Fisher's Exact and Exact Chi-square tests were used. Relationships between continuous variables were examined using the Spearman's correlation test, as the normality assumption was not met. A significance level of $P < 0.05$ was considered statistically significant.

Results

A total of 61 PID patients and 60 control group patients were included in the study. The median age of PID group was 35 (min.–max.: 18–76) years, while it was 33.5 (min.–max.: 20–74) years in the control group (P = 0.156). There was no statistically significant difference between these two groups in terms of age, gender, and comorbid conditions that could pose a risk for cardiovascular disease. Baseline characteristics of PID and control groups are summarized in Table 1.

Table 1 Baseline characteristics of the study population.

	PIDs (n = 61)	Controls (n = 60)	P value
Age in years, median (Q_1–Q_3)	35 (29–54)	33.5 (24.5–43)	0.156[a]
Female, n (%)	29 (48.3)	26 (42.6)	0.528[b]
Coronary artery disease, n (%)	4 (6.6)	2 (3.3)	0.68[c]
Hypertension, n (%)	4 (6.6)	3 (5)	0.323[c]
Diabetes mellitus n (%)	4 (8.3)	1 (1.7)	0.365[c]
Family history of heart disease, n (%)	19 (31.1)	9 (15)	0.035[b]
Comorbid diseases, n (%)	42 (68.9)	5 (8.3)	<0.001[b]
SBP (mmHg), mean±SD	124.98±17.88	118.78±7.76	0.016[e]
DBP (mmHg), mean±SD	73.05±11,67	65.73±9.1	<0.001[d]

Notes: [a]Mann–Whitney U test; [b]Pearson's Chi-square test; [c]Fisher's Exact test; [d]Independent sample *t*-test; [e]Welch's *t*-test.
DBP: diastolic blood pressure; PIDs: primary immunodeficiency diseases; SBP: systolic blood pressure; SD: standard deviation.

Although 6.6% of patients in the PID group and 5% of patients in the control group had a history of hypertension, both systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were significantly higher in the PID group (124.98±17.88 vs. 118.78±7.76, P = 0.016; 73.05±11.67 vs. 65.73±9.1, P < 0.001, respectively).

The mean follow-up period of PID patients was 8.44±7.8 years. Among these patients, 39.3% (n = 24) had autoimmune diseases, 34.6% (n = 21) had bronchiectasis, 37.3% (n = 22) had splenomegaly, and 26.7% (n = 16) had hepatomegaly. All patients were receiving immunoglobulin replacement therapy. The immunological parameters and clinical features of the PID group are summarized in Table 2.

C-reactive protein (CRP) and low-density lipoprotein (LDL) levels were significantly higher in the PID group, compared to the control group. Although total cholesterol (TC) and triglyceride (TG) levels were higher and high-density lipoprotein (HDL) levels were lower in the PID group, these differences were not statistically significant (Table 3).

The PID group had a statistically significantly higher Pmax, Pmin, and PWD values, compared to the control group (102 [92-108] vs. 88 [82-99], P < 0.001; 74 [70-80] vs. 68 [62-72], P < 0.001; 26 [22-30] vs. 21 [18-26], P = 0.001, respectively), which were shown in Table 4.

While comparing AECT parameters between two groups, RA delay, interatrial (IA) delay, the interval with tissue Doppler imaging from the onset of P-wave on the surface ECG to the beginning of late diastolic wave (PA) measurement of LA (PA-LA), PA measurement of RA (PA-RA), and PA measurement of interatrial septum (PA-IAS) were discovered to be statistically significantly higher in the PID group (Table 4, Figure 1). Although LA delay tended to be higher in the PID group, the difference was not statistically significant (P = 0.05).

No significant differences were observed in other echocardiographic findings, except SPAP and right ventricular tricuspid annular pulmonary systolic excursion (RV TAPSE). The PID group had a higher SPAP (20 [16-25] vs. 16 [15-20]; P < 0.001) and a lower RV TAPSE value (23 [22-25] vs. 25 [24-26]; P < 0.001), compared to the control group patients (Table 5).

Table 2 Clinical and laboratory findings of primary immunodeficiency patients.

	PIDs (n = 61)
Duration of disease (years), mean±SD	8.44±7.8
Delay in diagnosis (years), median (min.-max.)	3 (0-40)
BMI, mean±SD	23.41±4.8
Autoimmune disease, n (%)	24 (39.3)
Allergic disease, n (%)	14 (23)
Malignancies, n (%)	5 (4.1)
Lymphadenopathy, n (%)	11 (18.6)
Bronchiectasis, n (%)	21 (35)
Hepatomegaly, n (%)	16 (26.7)
Splenomegaly, n (%)	22 (37.3)
IgG (mg/dL), mean±SD	991.54±463.25
IgM (mg/dL), median (Q_1-Q_3)	23.9 (6.4-46.4)
IgA (mg/dL), median (Q_1-Q_3)	6.3 (3-50.7)
IgG1 (g/L), mean±SD	6.55±3.06
IgG2 (g/L), median (Q_1-Q_3)	2.8 (1.92-3.69)
IgG3 (g/L), median (Q_1-Q_3)	0.25 (0.15-0.38)
IgG4 (g/L), median (Q_1-Q_3)	0.15 (0.06-0.24)
CD19 (%), median (Q_1-Q_3)	4.63 (1.24-9.4)
CD4 (%), mean±SD	40.34±11.56
CD8 (%), mean±SD	41.06±14.13
CD16 (%), median (Q_1-Q_3)	6.46 (4-12.8)
CD56 (%), median (Q_1-Q_3)	9.1 (4.7-15.1)

Notes: BMI: body mass index; CD: cluster of differantiation; Ig: immunoglobulin; PIDs: primary immunodeficiency diseases; SD: standard deviation.

Table 3 Comparison of laboratory findings.

	PIDs (n = 61)	Controls (n = 60)	P value
Leukocytes (×10^3 cells/uL), median (Q_1-Q_3)	6.1 (4.3-8.2)	7,31 (6.71-8.84)	0.005[a]
Hemoglobin (g/dL), mean±SD	13.48±2.27	14.21±1.72	0.05[b]
Platelet (×10^3 cells/uL), mean±SD	251.64±126.90	274.05±56.43	0.212[b]
MCV (fL), mean±SD	82.98±8.38	87.65±6.43	<0.001[b]
Lymphocytes (×10^3 cells/uL), median (Q_1-Q_3)	1.55 (1.17-2.23)	2.26 (1.88-2.71)	<0.001[a]
ESR (mm/h), median (Q_1-Q_3)	7 (3-17)	7 (4.5-8)	0.724[a]
CRP (mg/L), median (Q_1-Q_3)	5.5 (2.1-12.1)	1.45 (0.7-4.1)	<0,001[a]
Cholesterol (mg/dL), median (Q_1-Q_3)	189.5 (153-213.5)	164 (146-192.5)	0.053[a]
HDL (mg/dL), median (Q_1-Q_3)	42 (35-54.5)	46 (41-59.5)	0.216[a]
LDL (mg/dL), mean±SD	109.07±37.47	94.75±32.17	0.029[c]
Triglyceride (mg/dL), median (Q_1-Q_3)	125.5 (84.5-176)	117.5 (97.5-152.5)	0.797[a]
TSH (μIU/mL), mean±SD	2.17±1.8	1.55±0.81	0.018[b]

Notes: [a]Mann-Whitney U test, [b]Welch's *t*-test, [c]Independent sample t test.
CRP: C-reactive protein; ESR: erytrocyte sedimantation rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MCV: mean corpusculer volume; PIDs: primary immunodeficiency diseases; SD: standard deviation; TSH: thyroid stimulating hormone.

Table 4 Comparison of electrocardiogram and atrial electromechanical parameters.

	PIDs (n = 61)	Controls (n = 60)	P value
Heart rate (beats/min), mean±SD	78.70±11.75	76.05±10.29	0.189[b]
Pmax (ms), median (Q_1-Q_3)	102 (92-108)	88 (82-99)	<0.001[a]
Pmin (ms), median (Q_1-Q_3)	74 (70-80)	68 (62-72)	<0.001[a]
PWD (ms), median (Q_1-Q_3)	26 (22-30)	21 (18-26)	0.001[a]
PA-LA (ms), median (Q_1-Q_3)	34 (28-38)	30 (28-33)	0.008[a]
PA-RA (ms), median (Q_1-Q_3)	30 (28-36)	26 (24-30)	<0.001[a]
PA-IAS (ms), median (Q_1-Q_3)	32 (26-34)	26 (24-31)	0.001[a]
LA delay (ms), median (Q_1-Q_3)	6 (4-6)	4 (3-6)	0.050[a]
RA delay (ms), median (Q_1-Q_3)	4 (2-6)	2 (2-4)	<0.001[a]
IA delay (ms), median (Q_1-Q_3)	6 (4-8)	4 (4-6)	0.039[a]

Notes: [a]Mann-Whitney U test; [b]ındependent sample *t*-test.
IA: interatrial; IAS: interatrial septum; LA: left atrium; PA: interval with tissue Doppler imaging, from the onset of P-wave on the surface ECG to the beginning of the late diastolic wave (Am wave); PA-IAS: PA measurement of IAS; PA-LA: PA measurement of LA; PA-RA: PA measurement of RA; PIDs: primary immunodeficiency diseases; Pmax: longest P-wave duration; Pmin: shortest P-wave duration; PWD: P-wave dispersion; RA: right atrium; SD: standard deviation.

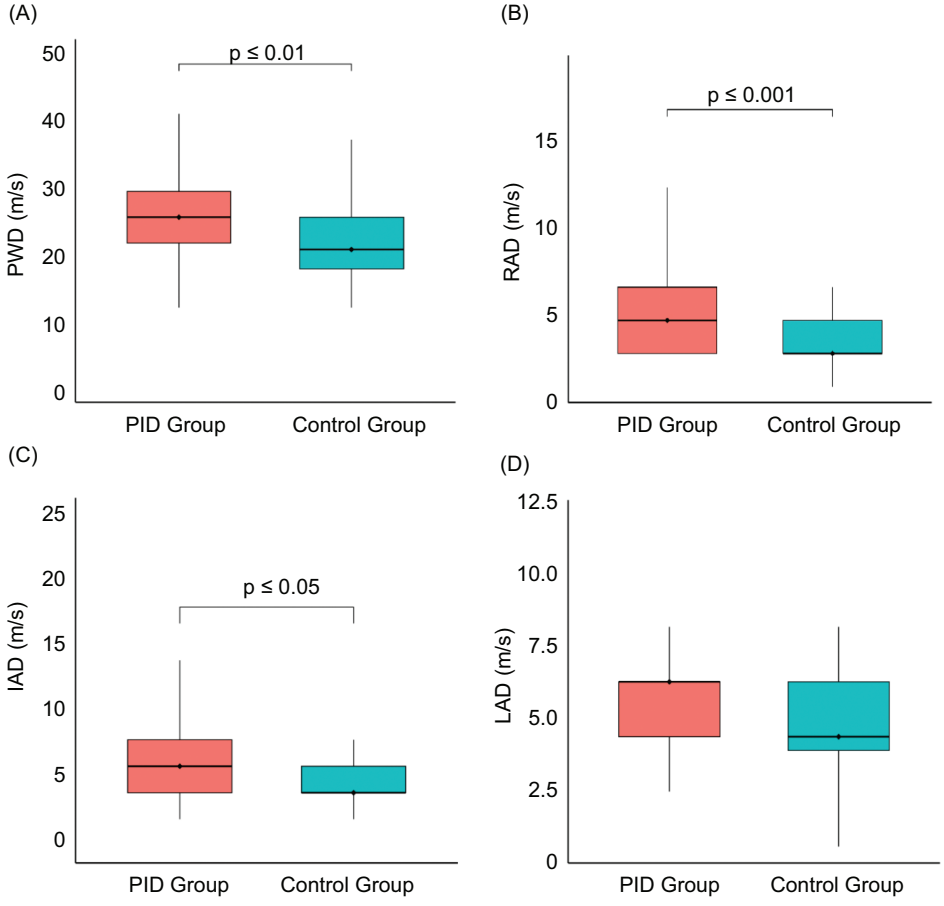

Figure 1 P-wave dispersion and atrial electromechanical conduction periods in PID and control group patients. (A) P-wave dispersion, (B) right atrial delay, (C) interatrial delay, and (D) left atrial delay.

Discussion

In this study, we demonstrated that AECT and PWD, known to be predictors of AF, were increased in PID patients. These findings may indicate subclinical atrial dysfunction and an early sign of arrhythmias in PID patients, who are prone to multiple complications. Considering that the prevalence of AF is expected to double in the next few decades because of an aging population, an increasing burden of comorbidities, greater awareness, and new detection

Table 5 Comparison of echocardiographic findings.

	PIDs (n = 61)	Controls (n = 60)	P value
LVIDd (mm), median (Q_1-Q_3)	44 (42-46)	45 (41.5-46)	0.745[a]
LVIDs (mm), median (Q_1-Q_3)	29 (27-30)	28.5 (26-30)	0.198[a]
IVSd (mm), median (Q_1-Q_3)	9 (8-10)	9 (8-10)	0.908[a]
PWd (mm), median (Q_1-Q_3)	8 (8-9)	9 (8-9)	0.316[a]
As. Ao (mm), median (Q_1-Q_3)	31 (29-34)	30 (28-32)	0.107[a]
Ann. Ao (mm), median (Q_1-Q_3)	20 (19-21)	20 (19-22)	0.904[a]
LA (mm), median (Q_1-Q_3)	31 (28-34)	32 (30-34)	0.301[a]
RA (mm), median (Q_1-Q_3)	29 (27-32)	29 (27.5-32)	0.954
RV (mm), median (Q_1-Q_3)	31 (28-33)	30 (28-32.5)	0.602[a]
RV TAPSE (mm), median (Q_1-Q_3)	23 (22-25)	25 (24-26)	<0.001[a]
SPAP (mmHg), median (Q_1-Q_3)	20 (16-25)	16 (15-20)	<0.001[a]
EF (%), median (Q_1-Q_3)	65 (65-65)	65 (65-65)	0.557[a]

Notes: [a]Mann-Whitney U test.
Ann. Ao: annuler aorta; As. Ao: ascending aorta; EF: ejection fraction; IVSd: interventricular septum diameter; LA: left atrium; LVIDd: left ventricular end-diastolic diameter; LVIDs: left ventricular end-systolic diameter; PIDs: primary immunodeficiency diseases; PWd: left ventricular posterior wall thickness diameter; RA: right atrium; RV: right ventricle; SD: standard deviation; SPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular pulmonary systolic excursion.

technologies, the significance of our findings becomes even more meaningful.[5]

In another recent study we investigated the frequency of arrhythmia and cardiac diseases in PID patients. Holter monitoring revealed a higher frequency of supraventricular and ventricular arrhythmias in PID patients compared to the control group.[15] Since AF is one of the leading causes of hospitalization, morbidity, and mortality, we designed the current study to assess the risk of AF using AED as an objective marker based on our previous findings.[5,15] As a result, we demonstrated that AECT were prolonged in PID patients, supporting the findings of our initial study.

We investigated the relationship between accompanying bronchiectasis, autoimmune disease, organomegaly, and delay in diagnosis in PID patients with PWD, RA delay, LA delay, and IA delay. However, although we did not find statistically significant results, we observed that RA delay was longer in patients with bronchiectasis, and IA delay was longer in patients with autoimmune diseases and in those with organomegaly.

It has been stated that autoimmune and inflammatory disorders play a role in the development of arrhythmias and AF.[17,18] The immune system may contribute to cardiac arrhythmias through autoantibodies and/or inflammatory cytokines, while immune cells, particularly macrophages, can interact with fibroblasts and myocytes, leading to conduction abnormalities.[19-22] The commonly observed two clinical conditions, chronic inflammation and autoimmunity, may increase susceptibility to AF in PID patients.[23-25] Autoimmune diseases were detected in 39.3% of our patients, which were mainly autoimmune cytopenia and autoimmune thyroiditis. Supporting our findings and this hypothesis, studies have demonstrated prolonged AECT and increased PWD in various autoimmune and inflammatory diseases.[26-30]

Subclinical and clinical thyroid disorders are discovered to be associated with ischemic and structural heart diseases, as well as rhythm disorders, including AF.[31-33] In our study, 10 patients (16.4%) in the PID group had a history of autoimmune thyroiditis, whereas none of the patients in the control group had such a history of thyroid disorders (P = 0.001). Additionally, thyroid-stimulating hormone (TSH) levels in the PID group were discovered to be significantly higher compared to the control group (P = 0.018; Table 3). From a pathophysiological perspective, considering both autoimmunity and thyroid hormone dysfunction, autoimmune thyroiditis may have contributed to the positive findings observed in our study. Indeed, a study conducted on patients with subclinical thyroid dysfunction discovered that AECT was long, compared to the control group and showed a positive correlation with TSH levels.[34]

High blood pressure is another risk factor that increases susceptibility to AF development[5] In our study, we discovered that both SBP and DBP were significantly higher in the PID group compared to the control group (Table 1). High blood pressure values in our patient group, because of the ongoing inflammatory process, may also have contributed to the risk of AF development.

Chronic airway, parenchymal, and vascular pulmonary manifestations are commonly observed in PIDs.[35] We discovered that SPAP values were higher and RV TAPSE measurements were lower in the PID group, compared to the control group, despite none of our patients having a prior history of diagnosed PHT. Also, 34.6% of the patients had bronchiectasis, and RA delay was longer in patients with bronchiectasis. The presence of chronic lung diseases primarily affecting the right heart in these patients explains the statistical significance of the RA delay parameters. Besides the more significant RA delay findings, this study suggests that if these patients remain untreated, uncontrolled inflammation could lead to much more pronounced abnormalities in all conduction parameters.

Considering that hyperlipidemia is a significant risk factor for cardiovascular diseases, it can be anticipated that, in addition to the increased occurrence of cardiovascular diseases, hyperlipidemia may indirectly lead to a higher

risk of AF.[36,37] In our study, compared to the control group, we observed a statistically significant increase in LDL levels in the PID group, along with a nonsignificant increase in TC and TG levels, and a nonsignificant decrease in HDL levels.

Although studies on lipid levels in PID patients are rare and show variable results, a recent study evaluating cardiovascular risk factors in patients with primary antibody deficiency discovered that 72.5% of the patients had lipid metabolism disorders, including increased TC (45.5%), increased LDL (47%), increased TG (32%), and decreased HDL (28.5%), which is consistent with the findings of our study.[38] In another controlled cohort study, serum TG and very low density lipoprotein (LDL) levels were higher in the PID patient group, while no statistically significant differences were observed in other lipid profiles.[39]

Unlike other lipoproteins, HDL is reported to have anti-inflammatory properties.[40,41] In a study comparing 102 common variable immunodeficiency (CVID) and 28 control patients, serum HDL levels were discovered to be significantly lower in the patient group, and this was suggested to contribute to increased inflammation in CVID patients.[42] In another study comparing 24 PID and 12 control patients, it was discovered that the patient group had lower HDL levels along with higher serum CRP levels.[43] In our study, consistent with these findings, serum CRP levels were significantly higher in the PID group, while HDL levels were lower, although not statistically significant.

Small population size and being conducted at a single center are the primary limitations of the current study. Owing to the diagnosis of PIDs could be at advanced ages and the wide age range in which the disease can manifest, our patients had a broad age distribution. However, considering that this is a rare disease, it should not be forgotten that gathering this acceptable patient group is both challenging and highly valuable in a single center. Additionally, we ensured that the age range of the control group was similar to the patient group. As the same diseases were also present in the PID patient group, we did not exclude participants with cardiovascular disease and AF risk factors, such as diabetes mellitus, hypertension, and coronary artery disease, from the selection of the control group, rather than including completely healthy volunteers. Another limitation is the lack of long-term follow-up to determine whether the observed AECT delays ultimately lead to the development of AF in this patient group.

Conclusion

As a result of this study, two main effects may lead to cardiovascular outcomes in PID patients. One is the indirect effects of systemic inflammatory process, and the other is the direct effect on the right heart because of infections and lung involvement. The results of our study will aid in the follow-up and survival of PID patients, who experience multiple complications and whose cardiac conditions have not been well defined until now, by enabling the early identification of AF-related mortality and morbidity risk. However, multicenter, large-scale, randomized controlled studies are necessary to validate our results.

Author's Contribution

INAN MI: design of the study; acquisition, analysis and interpretation of data; writing, drafting, revising of the manuscript. BALABAN YA: acquisition, analysis and interpretation of data, revising of the manuscript. YAGCI AF: design of the study, acquisition and analysis of data; KAYA C: design of the study, acquisition and analysis of data; SONMEZ E: acquisition of data; KALKAN F: acquisition of data; DEMIREL F: acquisition of data; YESILLIK S: interpretation of data; revising of the manuscript; BUGAN B: design of the study, acquisition and analysis of data, revising of the manuscript; KARTAL O: design of the study; analysis and interpretation of data and revising of the manuscript. All authors made final approval of the version and agreed to be accountable for all aspects of the work.

Conflict of Interest

Authors declared no conflict of interest.

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