Evaluation of the Relationship between Atrial Septal Aneurysm and Cardiac Arrhythmias via P-Wave Dispersion and Signal-Averaged P-Wave Duration

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Objective: The aim of the study was to investigate the relationship between atrial septal aneurysms (ASAs) and cardiac arrhythmias via signal-averaged P-wave duration (SAPWD) and P-wave dispersion (Pd).

Methods: Sixty-six patients with ASA served as the study group (group 1; 28 men and 38 women; mean age, 34 ± 10 years) and 62 healthy volunteers served as the control group (group 2; 29 men and 33 women; mean age, 31 ± 8 years) in the current study. ASAs were diagnosed by transthoracic echocardiography based on the criteria of a minimal aneurysmal base of ≥ 15 mm; and an excursion of ≥ 10 mm. All subjects were evaluated by 24-hour Holter monitoring, 12 lead body surface electrocardiogram for P-wave analysis, and signal-averaged electrocardiogram for P-wave duration (PWD).

Results: There was no significant difference between the study and control groups in terms of age, gender, left atrium diameter, and left ventricular ejection fraction. Supraventricular arrhythmias (SVAs) were detected in 29 patients with ASA (43.9%) and 5 controls (8.1%; $P < 0.001$). The mean Pd in patients with ASA was significantly longer compared to the control group (14.1 ± 8 ms vs 7.0 ± 2.9 ms; $P < 0.001$). Similarly, the mean SAPWD in group 1 was significantly longer compared to group 2 (127.4 ± 17.6 ms vs 99.8 ± 12.3 ms; $P < 0.001$).

Conclusion: Prolonged SAPWD and Pd were determined to indicate electrical disturbances in the atrial myocardium, and predict the increase in the prevalence of SVA in patients with ASA.

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atrial septal aneurysm; P-wave dispersion; P-wave duration; supraventricular arrhythmias

Atrial septal aneurysm (ASA) is a saccular deformity located in the atrial septum.¹ Although ASA is a well-recognized cardiac anomaly, the clinical significance of ASA has not yet been fully elucidated. ASA has been reported to be associated with congenital heart diseases, including patent foramen ovale (PFO), atrial septal defects (ASDs), ventricular septal defects (VSDs), valvular prolapsus (VP), patent ductus arteriosus (PDA), Ebstein's anomaly, tricuspid and pulmonary atresia, as well as acquired heart diseases, such as thromboembolic

stroke, systemic and pulmonary hypertension, cardiac arrhythmias, and thrombus formation.^{1–3}

The relationship between cryptogenic stroke and atrial septal anomalies in young patients has been studied, and several factors which might potentially be associated with stroke in patients with ASA have been identified in many studies to date.^{4–6} Though the most significant underlying cause of stroke due to pathology involving the atrial septum is paradoxical embolism, it has also been suggested that paroxysmal atrial arrhythmias might lead to

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thrombus formation within the atria in patients with ASA and this might also result in cerebral thromboembolism.⁷

In addition to invasive electrophysiological methods, some parameters obtained from surface electrocardiogram (ECG) recordings are used for determining patients at risk for the development of atrial arrhythmias. Among these parameters, the P-wave duration (PWD) and P-wave dispersion (Pd) are the most frequently used parameters in clinical cardiology. It has been demonstrated that both parameters indicate heterogeneous and discontinuous conduction of sinus impulses within the atrial myocardium and are electrocardiographic markers reflecting intra- and inter-atrial conduction delay in many clinical studies to date.^{8–13}

Patients with ASA have not been optimally evaluated regarding these two parameters. In the present study, the relationship between two pathologies, ASA and cardiac arrhythmias, both of which may predispose to thromboembolic stroke, were investigated. For this purpose, 24-hour ambulatory Holter monitoring, signal-averaged P-wave duration (SAPWD), and Pd were evaluated in patients diagnosed with ASA via transthoracic echocardiography (TTE) and the relationship between these parameters was investigated.

MATERIALS AND METHODS

Eighty-two patients diagnosed with ASA on TTE performed in the Echocardiography Laboratory for various clinical reasons between May 2006 and June 2008, 66 patients (38 females and 28 males) without any health problems were included in the study.

To determine the possible underlying cardiac, thromboembolic, and neurologic pathologies in patients diagnosed with ASA in the Echocardiography Laboratory, a detailed history was obtained from all subjects regarding coronary artery disease (CAD), congenital heart disease with a shunt, valvular heart disease, peripheral artery disease (PAD), hypertension, diabetes mellitus, hyperlipidemia, smoking, arrhythmias, syncope, and strokes. Detailed systemic and neurologic examinations were performed in all patients with ASA. Of the patients with ASA, those who had CAD, left ventricular systolic dysfunction, valvular heart disease, and congenital heart disease with a shunt were excluded since these pathologies may lead to an increased risk for arrhythmias. Patients who had a history of

a stroke and who had any neurologic symptoms or any abnormalities on the neurologic examination were also excluded.

Among 82 patients with ASA, 25 patients were further evaluated by TEE; small ASD (<0.6 cm) was detected in 2 patients and PFO was detected in 14 patients. No accompanying cardiac pathology was noted in the remaining 9 patients evaluated by TEE. Patients diagnosed with PFO or ASD by TEE were excluded from the study.

Blood biochemistry analysis, a 12-lead body surface ECG, a signal-averaged electrocardiogram (SAECG), and 24-hour ambulatory Holter monitoring were performed in all patients with ASA. Sixty-two healthy individuals (33 females and 29 males) without a history of stroke and a peripheral embolus, CAD, congenital heart disease with a shunt, valvular heart disease, and left ventricular systolic dysfunction were served as the control group. Similar to the patients with ASA, the control group also underwent TTE, 12-lead body surface ECG, SAECG, and 24-hour ambulatory Holter monitoring. Thus, the present study population consisted of a group of patients with ASA (group 1) and a control group of healthy volunteers (group 2). The study protocol approved by the local ethics committee and a written informed consent was obtained from all subjects.

Transthoracic Echocardiography

All patients with ASA and the controls were first evaluated by TTE. TTE was performed using a (General Electric Vingmed System Five echocardiography device, Horten, Norway) and a 2.5 MHz transducer, while the subjects were in the left lateral decubitus position. Parasternal long-axis, parasternal short-axis, apical four-chamber view, apical five-chamber view, and subcostal views were obtained from all subjects. All subjects were asked to breathe normally during the TTE.

Left atrium and aortic diameters were measured in the parasternal long-axis view using M-mode echocardiography in accordance with the American Society of Echocardiography's Guidelines as the distance from the anterior margin to the posterior margin. The left ventricular end-systolic and end-diastolic diameters, as well as the left ventricular ejection fraction values, were measured in the parasternal long-axis view using M-mode echocardiography. The aortic peak flow velocity was measured from the apical five-chamber view,

and the pulmonary peak flow velocity was measured from the parasternal short-axis view using pulsed Doppler.

ASA was diagnosed using the following criteria: (a) minimal aneurysmal base of ≥ 15 mm; and (b) an excursion of ≥ 10 mm into the right or left atrium, or the total of bilateral excursion of ≥ 10 mm, as suggested by Olivares-Reyes et al.¹

Transesophageal Echocardiography (TEE)

TEE was performed in patients with a wide base and a highly mobile ASA determined in TTE. The presence of a possible shunt between the atria before and after the Valsalva maneuver was evaluated by agitated saline infusion via a large diameter intravenous line through the right antecubital vein in order to investigate possible pathologies, including ASD or PFO. TEE was performed in another session for optimal evaluation of patients with a large ASA among whom contrast passage was detected. TEE was performed using a (General Electric Vingmed System Five echocardiography device) with a 7.5 MHz multiplanar probe. At the mid-esophageal depth, the interatrial septum was evaluated by a four-chamber view at 0°, an aortic short-axis view at 45°, and a bicaval view at 120°. Two-dimensional echocardiography, color Doppler, and pulse-wave Doppler were used for diagnosing PFO and ASD, and a shunt between the atria before and after the Valsalva maneuver was evaluated by agitated saline infusion via the right antecubital vein. The presence of at least three bubbles in the left atrium within four cardiac cycles following contrast appearance in the right atrium was considered positive in terms of a shunt for the diagnosis of PFO.

Electrocardiography

Using a General Electric MAC 5000 Resting ECG Analysis System device (GE Marquette Medical systems, Milwaukee, WI, USA), a 12-lead surface ECG and orthogonal derivations, as well as SAEKG recordings at a speed of 50 mm/s and 1 mV/cm calibration, were obtained from all subjects in the supine position following 15 min of rest. The subjects were asked to breathe normally and not to cough or speak during the recordings. In the ECG recording, in order to calculate the Pd, the PWD was measured as the distance between the points at which the beginning of the P-wave deflexion in-

tersected the isoelectric line and the point at which the end of the P wave intersected the isoelectric line using a magnifying lens. Derivations at which the beginning or end of the P wave could not be precisely determined were excluded from the analysis. Following the determination of Pmax and Pmin, Pd was calculated by subtracting the Pmin value from the Pmax value. The PWD in the SAEKG was obtained from the average of at least 250 P waves performed with orthogonal derivations recorded by the MAC 5000 device at a 0.05–0.20 μ V noise level and 40–250 Hz band-pass filtering.

24-Hour Ambulatory Holter Monitoring

Twenty-four-hour ambulatory Holter monitoring was performed on all patients and the control group using an Ela Medical Spider View digital Holter recording system (Ela Medical Corp., Montrouge, France) The data obtained from this three-channel recording system was digitally evaluated using an Ela Medical Synescope program in terms of the presence of atrial and ventricular arrhythmias. The supraventricular arrhythmias accepted as clinically significant were as follows: frequent supraventricular extrasystoles (SVEs; an atrial early beat frequency of $\geq 2000/24$ hours), paroxysmal atrial fibrillation (PAF), paroxysmal atrial flutter, or other paroxysmal supraventricular tachycardias (i.e., atrioventricular nodal re-entrant tachycardia and atrioventricular re-entrant tachycardias). Ventricular arrhythmias were classified according to the modified Lown criteria.¹⁴ Lown grade ≥ 2 was considered clinically significant.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) 11.5 for Windows (Chicago, IL, USA) was used for statistical analysis of the data. Variables with skew distribution are expressed as median (minimum-maximum), and categorical variables are expressed as percentage. An independent samples *t*-test was used for comparison of mean values of the normally distributed numerical variables; the Mann-Whitney *U* test was used for comparison of median values of skewed distributed numerical variables. The Pearson chi-square test was used to compare categorical variables between the groups and to determine the correlation, and continuity correction was performed if necessary. Receiver operating characteristic (ROC) curve analysis was used to

Table 1. Demographic Characteristics of Groups 1 and 2

Characteristics	Group 1 (n = 66)	Group 2 (n = 62)	P Value
Age (years)* (min and max)	34 ± 10 (18–61)	31 ± 8 (18–46)	0.113
Gender (Male/Female), n (%)	28/38 (42.4/57.6)	29/33 (46.7/53.3)	0.376
Current smoking n (%)	6 (9)	5 (8.1)	0.338
Left atrial diameter (mm)*	32.1 ± 3.5	32.5 ± 2.6	0.474
Left ventricle end-diastolic diameter (mm)*	46.1 ± 3.7	46.9 ± 3.9	0.251
Left ventricle end-systolic diameter (mm)*	31 ± 0.8	31.1 ± 1.1	0.446
Left ventricle ejection fraction (%)*	66.5 ± 3.6	65.4 ± 3.3	0.532
SAPWD (ms)*	127.4 ± 17.6	99.8 ± 12.3	<0.001
Pd (ms)*	14.1 ± 8	7.0 ± 2.9	<0.001

*Mean ± SD: Mean standard deviation; SAPWD: Signal-averaged P wave duration; Pd: P wave dispersion.

determine the duration of the Pd and PWD that would best differentiate groups with or without atrial arrhythmias, and the optimal cut-off points. Supraventricular arrhythmias were analysed using a binary logistic regression model including age, ASA diameter, ASA excursion, left atrial diameter, Pd and SAPWD. Results were expressed as P-values with a 95% confidence interval and Odds ratios (OR) for the independent predictors. A P-value of <0.05 was considered statistically significant.

RESULTS

The mean age of the 66 patients with ASA (group 1; 28 males and 38 females) was 34 ± 10 years (range, 18–61 years) and the mean age of the control group (group 2; 29 males and 33 females) was 31 ± 8 years (range, 18–46 years). No statistically significant difference existed between the two groups in terms of age and gender ($P > 0.05$; Table 1).

No statistically significant difference was found between groups 1 and 2 in terms of the mean left atrial diameter (32.1 ± 3.5 mm and 32.5 ± 2.6 mm, respectively; $P = 0.474$), the left ventricle end-systolic diameters (31 ± 0.8 mm and 31 ± 1.1 mm, respectively; $P = 0.446$), the end-diastolic diameters (46.1 ± 3.7 mm and 46.9 ± 3.9 mm, respectively; $P = 0.251$), and the left ventricle ejection fractions (66.5 ± 3.6% and 66.4 ± 3.3%, respectively; $P = 0.532$; Table 1).

All subjects were in sinus rhythm at baseline and there were no pathologic findings in any of the resting ECGs. While the mean SAPWD was 127.4 ± 17.6 ms in group 1, the duration was 99.8 ± 12.3 ms in group 2. A statistically significant difference existed between groups 1 and 2 in terms of SAPWD ($P < 0.001$; Fig. 1). The mean Pd was 14.1 ± 8 ms

in group 1 and 7.0 ± 2.9 ms in group 2. A statistically significant difference existed between groups 1 and 2 in terms of Pd ($P < 0.001$; Fig. 2).

On 24-hour ambulatory Holter monitoring, frequent SVEs were noted in 18 patients (27.3%), PAF attacks in 7 patients (10.6%), and supraventricular tachycardia attacks in 4 patients in group 1. The number of patients with supraventricular arrhythmias (SVAs) was 29 (43.9%). Frequent SVEs were noted in only five patients (8.1%) in group 2. A statistically significant difference existed between groups in terms of the prevalence of SVA ($P < 0.001$). All arrhythmias noted in the two groups were of supraventricular origin and no clinically significant ventricular arrhythmias were observed in any of the subjects.

When group 1 was divided into 2 subgroups as patients with or without SVA, the ASA diameter and the maximal excursion of the ASA were

Figure 1. Signal-averaged P-wave durations for groups 1 and 2.

Figure 2. P-wave dispersion values in groups 1 and 2.

significantly greater in the subgroup with arrhythmias compared to the subgroup without arrhythmias ($P < 0.001$ and 0.001 , respectively; Table 2). ROC analysis was performed in the subgroups to determine the cut-off values for the Pd and SAPWD in an attempt to differentiate the patients with or without atrial arrhythmias in group 1. The cut-off value for the Pd was accepted as 12.5 ms, which led to an 86% sensitivity and 91% specificity to differentiate the two subgroups with a positive predictive value of 89.7% and a negative predictive value of 92.5%. The cut-off value for the SAPWD was 123.5 ms, which led to a 55% sensitivity and 81% specificity to differentiate the two subgroups with a positive predictive value of 70.8% and a negative predictive value of 80.6%.

Due to possibility of the interrelationship among independent predictors associated with SVA, we used a multivariate logistic regression analysis to determine the independent predictors of SVA. In the multivariate regression analysis, SAPWD (OR = 1.60; 95% CI: 1.10–2.45; $P < 0.01$) and Pd

Figure 3. Multivariate regression analysis for supraventricular arrhythmias.

(OR = 1.10; 95% CI: 1.05–1.20; $P < 0.05$) were the only independent predictors for the development of SVA (Fig. 3).

DISCUSSION

The relationship between ASAs and cardiac arrhythmias was analyzed in the present study in terms of predisposing factors for thromboembolic stroke in patients with ASA. For this purpose, 24-hour ambulatory Holter monitoring, SAPWD measurements, and Pd analysis were performed in patients with ASA. According to our knowledge, the present study is the first using these three parameters together in terms of investigating the prevalence and causes of arrhythmias in young, healthy patients with ASA.

The relationship between ASAs and cardiac arrhythmias have been evaluated in many retrospective studies and case reports; however, there are only a few prospective studies on the relationship.^{15–19} The results of the Holter data are similar to the series consisting of 50 cases reported by Schneider et al.¹⁷ The prevalence of SVA has been reported to be 40% (atrial fibrillation [AF; 18%], atrial flutter [4%], atrioventricular nodal re-entrant tachycardia [8%], and miscellaneous [18%]). While the prevalence of SVA has been reported to be 57% by Longhini et al.,¹⁹ Morelli et al.¹⁸ have reported the prevalence of SVA to be 45% in a smaller series.

One of the main findings of the present study was that the most common SVAs in patients with ASA are frequent SVEs. Greater than 2000 SVEs were detected in 18 patients (27.3%) in group 1 within 24 hours. In a study involving 90 patients with frequent PAF attacks, Vincenti et al.²⁰ have

Table 2. The Relationship between Arrhythmia and ASA Diameters and ASA Maximal Excursion in Patients with ASA

	SVA [+], (n = 29)	SVA [–], (n = 37)	P
ASA diameter (mm)*	21 ± 3.0	15.8 ± 0.63	<0.001
Maximal excursion of the ASA (mm)*	13 ± 3.4	10.9 ± 0.95	<0.001

*Mean ± SD: Mean standard deviation; ASA: Atrial septal aneurysm; SVA: Supraventricular arrhythmia.

noted that nearly half of the PAF attacks were induced following a supraventricular ectopic beat. In another study conducted by Haissaguerre et al.,²¹ it has been similarly shown that AF attacks were triggered by frequent extrasystoles originating from the area surrounding the pulmonary veins. The results of the present study suggested that the heterogeneity of atrial macro- and microgeometry caused by ASA may lead to changes in electrophysiological dynamics of the atrial myocardium, which in turn leads to more frequent atrial extrasystoles and induces AF attacks.

SVAs, and especially AF, are common types of arrhythmias in cardiology practice. It has been shown in several studies that the duration of intra- and interatrial conduction of sinus impulses is longer in patients who have a sinus rhythm and frequent PAF attacks.^{22,23} Prolongation of conduction has been documented both by 12-lead surface ECG and by SAECG recordings to have a longer PWD.²⁴ It has been demonstrated in two studies that sinus impulses are conducted in a heterogeneous and anisotropic manner within the atrial tissue due to an irregular physical structure and differentiated microstructure of the atrial myocardium.^{25,26} In addition to the effects of atrial geometry on impulse conduction, some intra- and intercellular factors may also lead to conduction disorders, such as specific conduction delays in several regions within the atrial tissue.²³ Due to the potential ability of this heterogeneity in structural and electrophysiological characteristics to induce unidirectional conduction block on premature impulses, the risk of re-entry is increased in the atrial tissue.²⁷

The reasons for an increased prevalence of arrhythmias in patients with ASA have not been clearly demonstrated. In this study, there were no secondary causes which might lead to an accompanying structural cardiac abnormality, CAD, hypertension, or atrial dilatation which could explain the increased prevalence of arrhythmias in patients with ASA compared to the control group. As an increased Pd and PWD have been reported in patients with secundum-type ASD by Guray et al.,²⁸ it has been suggested that there may be an increase in the risk of AF in interatrial septal anomalies with a shunt. Therefore, patients with ASA and interatrial septal pathologies with shunts, such as ASD and PFO, were excluded from the present study. Thus, the Holter results in this study were not affected by parameters like the presence of ASD and PFO. The fact that the demographic characteris-

tics of the ASA group, consisting predominantly of healthy young adults, were similar to the control group suggests that the presence of ASA is the only factor that could explain the increase in the prevalence of SVA.

Another important finding of this study was the detection of a statistically significant association between the ASA diameter and excursion, and SVAs in the group of patients with ASA. The results of this study support the hypothesis that SVAs in patients with ASA might be induced by ASA's capability of changing the physical and electrophysiological characteristics of the atrial myocardium, which in turn leads to inter- and intraatrial conduction disorders.

Invasive electrophysiological studies certainly provide the most valuable data for evaluating atrial electrophysiological characteristics in order to investigate the occurrence and maintenance of AF. However, electrophysiological studies are highly complex, time-consuming, and expensive procedures that are not suitable for screening the general population. Therefore, the presence of more simple electrocardiographic predictors is needed for determining the risk for AF.

In a study conducted on a patient population with PAF by Aytemir et al.,²⁹ it has been reported that a Pd threshold value of 36 ms would differentiate the patient group from control group with 77% sensitivity and 82% specificity. In the present study, it was found that the Pd was significantly increased in patients with ASA compared to the control group. This finding was in agreement with the results of the study conducted by Janion et al.¹⁵ on a patient population with ASA using the same parameter. However, unlike this study, the study population of Janion et al.¹⁵ was comprised of much older patients, with a mean age of 54.3 ± 14.4 years. The incidence of AF is doubled every decade after 50 years of age. It has been reported that while the prevalence of AF ≥ 40 years of age is 2–3%, this rate increases to $>6\%$ in people ≥ 80 years of age.³⁰ In one study conducted in patients without CAD by Turhan et al.,³¹ the Pd values were significantly higher in subjects ≤ 45 years of age compared to those subjects who were ≥ 65 years. The mean age of patients with ASA was determined to be 34 ± 10 years in the present study. A lower mean age in the present study population compared to the Janion et al. study¹⁵ eliminates both the age-related risk increase in the prevalence of AF and the effect of age on the Pd.

PWD is currently considered a suitable method for assessing global atrial conduction. In one study conducted by Aytemir et al.²⁹ on a patient population with PAF, a PWD threshold value of 106 ms has been reported to differentiate patients from controls with a sensitivity of 83% and a specificity of 72%. In studies conducted in patients with sinus rhythm using a signal-averaged ECG, it has been demonstrated that prolongation in the PWD is a risk factor for the development of PAF independent from the presence of structural heart disease.³²⁻³⁴ The SAECEG was used to evaluate the PWD in the present study. This method was preferred in an attempt to perform the standard measurement of PWD, to eliminate possible measurement errors by the researchers and to obtain high-resolution P waves. This study is the first to compare the SAPWD in patients with ASA and in a control group. In this study, it was found that the SAPWD was significantly increased in patients with ASA compared to the control group.

Study Limitations

Since ASAs were frequently detected as incidental findings in several of the subjects and they were healthy individuals, it was not possible to perform TEE in all subjects due to the semiinvasive nature of the procedure. Only individuals at risk in terms of interatrial septal pathologies with shunts were evaluated by TEE in a separate session. Nevertheless, comorbidities have been excluded by only history taking and physical examination. Although all subjects were evaluated by 24-hour ambulatory Holter monitoring, a 24-hour period might not be sufficient to detect the exact prevalence of arrhythmia. Therefore, we believed that monitoring subjects for a longer period of time by other ambulatory methods might provide more accurate data.

CONCLUSION

The prevalence of SVA was significantly increased in patients with ASA. This increase in the prevalence of arrhythmias suggests that ASAs lead to intra- and interatrial conduction abnormalities. Being noninvasive, inexpensive, and simple techniques, Pd and SAPWD may provide significant contributions to assess the risk for paroxysmal supraventricular arrhythmia in patients with ASA.

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