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Electrical Remodeling Following Atrial Septal Defect Closure in Adults: A Prospective Cohort Study.

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Abstract

Background: Atrial septal defects (ASDs) are a common type of congenital heart anomaly, accounting for approximately 10% of all such defects. The closure of an ASD with a substantial left-to-right shunt can lead to enhanced functional capacity and a reduction in arrhythmias. However, the closure of ASDs in adult patients carries certain risks, including the potential development of pulmonary edema and heart failure.

Objectives: The study aimed to assess atrial electrical function in adult patients with ASD before and 3 months after either transcatheter or surgical closure.

Material and methods: A prospective cohort study was conducted involving 40 adult patients (age ≥ 40 years) diagnosed with ostium secundum ASD and 20 age-matched healthy individuals serving as controls. The primary objective of this study was to investigate and compare the atrial electrical function in patients with ASD, both before and 3 months following the closure of the defect.

Results: The mean duration of the P wave in the case group was significantly higher than the mean duration of the P wave in the control group (p-value 0.001). A highly statistically significant difference in the mean QRS duration in the case group was higher than in the control group (p-value <0.001). A highly statistically significant difference between ECG parameters (HR, P wave duration, QRS width & QTc interval) before and after ASD closure (p-value <0.001). Also, there was a highly statistically significant difference before and after ASD closure (p-value < 0.001) regarding inter-atrial and intra-atrial conduction time (PA) involving PA lateral, septal & tricuspid in addition to atrial electromechanical delay (EMD).

Conclusions: The atrial geometrical and electrical reverse remodeling was evident at 3 months following ASD closure. Atrial enlargement is a substrate for developing atrial arrhythmia. Finally, ASD closure in older patients is safe and effective.

Keywords: ASD, Congenital Heart Defects, Atrium, Closure, Trans-catheter, QTc, Surgery.

Abbreviations: **AF/A Fib**: Atrial fibrillation, **IAEMD**: Inter-atrial electromechanical delay, **ILEMD**: Left intra-atrial electromechanical delay, **IREMD**: Right intra-atrial electromechanical delay, **LUPV**: Left upper pulmonary vein, **LV**: Left ventricle, **PA**: Atrial conduction time, **RV**: Right ventricle, **TOE/TEE**: Transesophageal echocardiography.

Introduction

Atrial septal defect (ASD) is a common form of congenital heart disease observed in adults. (1) This condition is treatable through surgical or percutaneous intervention, and patient outcomes after both approaches have been reported to be excellent. (2, 3) Notably, percutaneous device closure of ASD is often considered the primary line of treatment due to its advantages, including a low rate of complications, shorter anesthesia time, and reduced hospital stay duration. (4, 5)

ASD is often asymptomatic during childhood and remains undetected and untreated until adulthood. During this time, left-to-right shunting causes biatrial remodeling and left atrial (LA) dysfunction. (6) Consequently, patients over 40 years of age with untreated ASD often experience atrial tachyarrhythmias, including atrial fibrillation (AF). AF is estimated to occur in at least 20% of individuals who are older and have increased pulmonary arterial pressure or systemic hypertension. (7) When accompanied by AF, ASD closure alone is insufficient to restore sinus rhythm and may be associated with a risk of stroke and worsening of heart failure. (8)

This is attributed to the abrupt elevation in left ventricular preload following ASD closure in a non-compliant left ventricle (LV), which can be secondary to the mechanical response to chronic right ventricular (RV) volume overload, leading to LV compression, abnormal diastolic-systolic relations of the interventricular septum, and chronic LV underfilling with increased left atrial (LA) pressure, resulting in "masked LV restriction." Alternatively, these complications may arise from comorbid conditions such as systemic hypertension, coronary heart disease, or age-related LV diastolic dysfunction. (9)

To mitigate these potential complications, cardiac catheterization before ASD closure is necessary, and if the left ventricular end-diastolic pressure (LVEDP) is found to be high, a balloon occlusion test should be performed before the closure procedure. (10)

Previous studies have raised concerns that electrophysiological disorders of the atrial septum may arise from the ASD itself or the surgical correction of the defect. (11) There are also reports that atrial stiffness may increase after percutaneous device or surgical closure of ASD, affecting functional changes in the LA and related outcomes. However, when clinicians choose the method of ASD closure (surgical or percutaneous), they typically do not consider the potential changes in LA function after the procedure. (12)

The electrocardiogram (ECG) is a noninvasive, widely used, and inexpensive tool that can be employed during the long-term follow-up of ASD patients, particularly to help predict the occurrence of rhythm disorders and sudden cardiac death. (13)

The present study aimed to assess the electrical function of the atria in adult patients with ASD, both before and 3 months after the closure of the defect, either through transcatheter or surgical intervention.

Material and methods

Ethical considerations

The study participants who met the established criteria were informed by the authors about the objectives of the investigation, and their participation was solicited only after they had provided verbal consent. All the patients participated in the study voluntarily. The data collection instruments were anonymous, and verbal consent was obtained from the participants to take part in the study. Participants were made aware of their right to decline or withdraw from the study at any point, following the ethical principles outlined in the Helsinki Declaration of 1983. The research protocol was reviewed and approved by the Medical Research Ethics Committee of Kafr Elsheikh University.

Sample size:

A Convenient sample was used to enroll the cases in the study, 40 ASD adult patients who met the pre-established inclusion criteria were recruited from the cardiology departments of Kafr Elsheikh University Hospital and the National Heart Institute in Egypt, and 20 healthy age-matched individuals in the control group.

Design:

A prospective cohort study has been used to analyze and compare the electrical changes in adult patients with ASD before and 3 months after closure.

Study population and procedure

The study included a total of 60 participants. The participants were divided into two groups: 40 adults with ostium secundum atrial septal defect (ASD) who were candidates for either surgical or transcatheter ASD closure, and 20 age-matched individuals without ASD to serve as the control group.

The ASD patients were recruited from the outpatient cardiology department of Kafr Elsheikh University Hospital during their regular monitoring and follow-up visits, conducted from November 2021 to December 2023. At baseline, before the ASD closure procedure, all participants underwent a comprehensive evaluation, including electrocardiography (ECG), echocardiography, laboratory investigations, and chest X-ray. The control group consisted of 20 healthy adults matched for age.

The study inclusion criteria for cases were a) adult patients ≥ 40 years old with hemodynamically significant ostium secundum ASD, and b) adequate follow-up. The criteria for exclusion of cases were a) patients with ASD other than secundum type, b) other congenital defects, c) impaired LV systolic function, d) high pulmonary vascular resistance, e) renal impairment, f) patients with allergy to contrast media, and g) patients with poor echo window.

The inclusion criteria of the control group: a) Same age group of patients without any structural or congenital heart diseases.

When selected candidates for the study were determined, an explanation of the study aspects was provided and permission for their participation in the study was obtained. The instruments were self-administered. Each patient's data included: a full clinical evaluation, socio-demographic characteristics (e.g., gender, age, weight, height, and BMI), ECG (P wave duration, PR interval, QRS duration, and QTc interval), echocardiography, chest X-ray and laboratory investigations (BUN, serum creatinine, CBC, virology, INR, HbA1c and LDL). All participants were examined before the ASD closure and close follow-up was done 24 hours, one week, one month, and 3 months after the defect closure.

Data from Conventional Echocardiography:

Based on the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI). Using Philips Epic 7C Echocardiography machine equipped with S5-1, X5-1 transthoracic transducers, TDI technology, and X7-2t TEE probe. All echocardiographic studies were performed with the subjects in the left lateral decubitus position.

***Tissue Doppler Imaging**:*

PW Doppler over mitral & tricuspid inflow velocities: peak early diastolic velocity (E) wave, peak late diastolic velocity (A) wave, E wave deceleration time (DT) & E/A ratio. Tissue Doppler of lateral, septal mitral & lateral tricuspid annuli. Assessment of intra-atrial and inter-atrial electro-mechanical delay for ASD cases. **(Figure 1)**

On the tissue Doppler trace, atrial conduction time (PA) was accepted as the time passing from the beginning of the P wave on ECG to the A′ wave on tissue Doppler trace and estimated from lateral mitral annulus named as lateral PA, form septal mitral annulus named as septal PA, and from RV tricuspid annulus named as tricuspid PA.

Inter-atrial electromechanical delay (IA-EMD) was described as the time difference between the lateral mitral annulus of LV and the tricuspid annulus of RV.

The left intra-atrial electromechanical delay (ILeft-EMD) was described as a PA time difference between the lateral mitral annulus of LV and the septal mitral annulus of LV.

The right intra-atrial electromechanical delay (IRight-EMD) was described as the PA time difference between the septal mitral annulus of LV and the tricuspid annulus of RV, respectively.

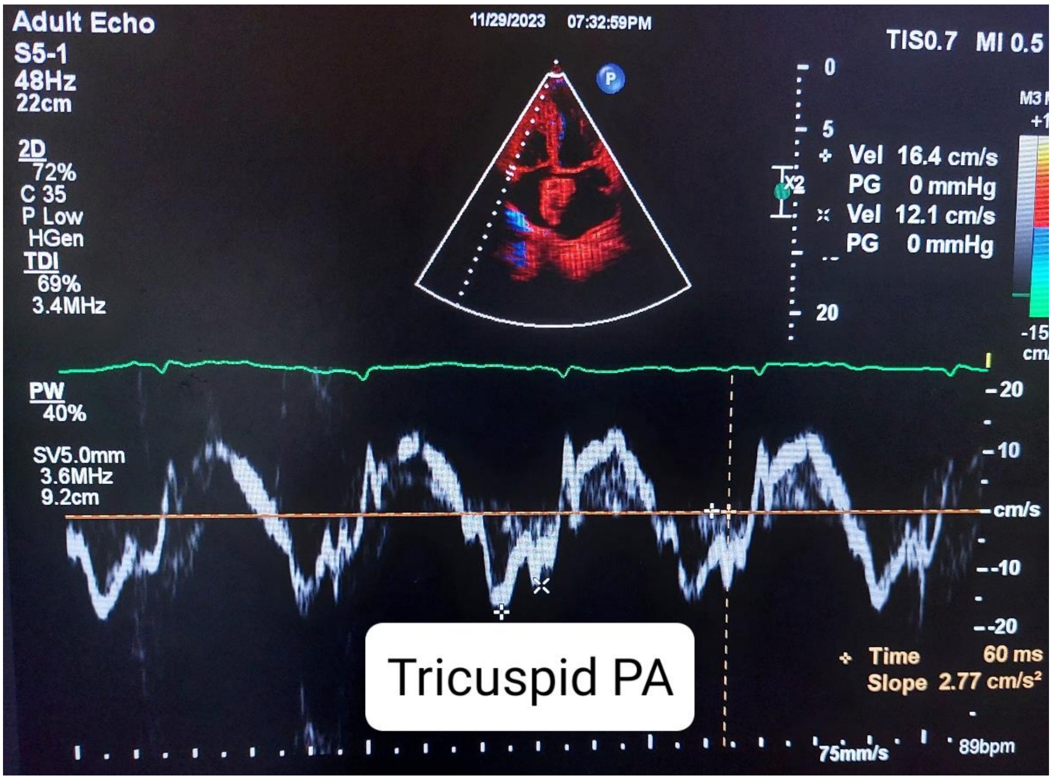

Figure (1): The evaluation of atrial conduction times using Doppler echocardiography.

Electrocardiographic study:

The electrocardiographic (ECG) recordings were obtained using the ECG-3150 machine manufactured by Nihon Kohden. A 12-lead ECG was recorded at a speed of 50 mm/s and an amplitude of 1 mV/cm, both before and 3 months after the ASD closure procedure, to evaluate the following electrical parameters.

The P-wave duration was defined as the distance between the junction of the baseline with the point of earliest and latest P-wave activity. The longest P-wave duration was noted as the P-wave maximum (Pmax), in any of the 12 ECG leads (14).

The QRS duration was defined as the widest QRS complex duration in any lead, as measured from the first deflection to the last deflection crossing the isoelectric line (14). The QTc interval was defined as the interval between the beginning of the QRS complex and the end of the T-wave, corrected for the patient's heart rate using the Bazett formula (15).

Presence of another common independent ECG sign in patients with ASD is the "crochetage" pattern (a notch near the apex of the R-wave in the inferior limb leads) **(Figure 2)**

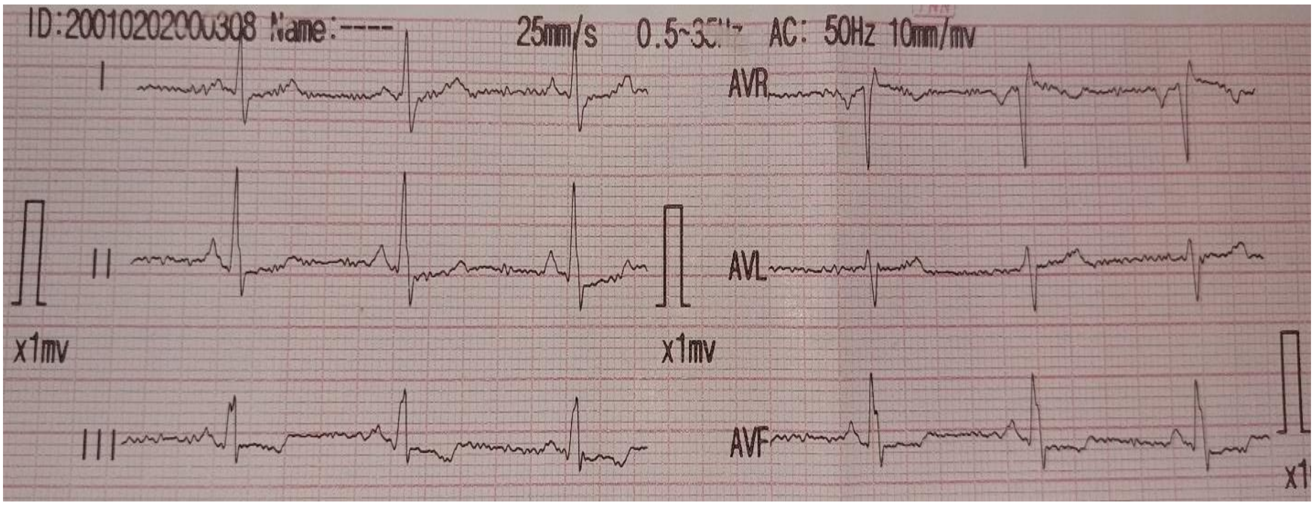

Figure (2): ECG shows Crochetage pattern in a case with ASD from our study.

ASD closure:

Percutaneous transcatheter ASD closure was performed when the anatomical characteristics and the surrounding rims were deemed adequate, under general anesthesia with guidance from fluoroscopic and transesophageal echocardiographic (TEE) imaging. Heparin (100 IU/kg) was administered in every case. To avoid oversizing the device, repeated measurements were obtained in different views using both TEE and real-time 3D echocardiography in addition to sizing balloon usage to measure the defect diameter. For all cases that were candidates for transcatheter closure, we proceeded using the left upper pulmonary vein (LUPV) deployment technique using different ASD occluders e.g. Amplatzer septal occluder, Figulla Flex II ASD occluder (occlutech), Ceraflex ASD occluder (Lifetech) and MemoPart ASD occluder.

For patients with defects that were not suitable for transcatheter closure due to deficient rims, surgical closure was performed using a patch technique.

Statistical Analysis:

Data were collected, coded, and analyzed using Microsoft Excel software and then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis with inferential and descriptive procedures. According to the type of data qualitative represented by number and percentage, and the quantitative continues group is represented by mean ± SD, the following tests were used to test differences for significance; difference and association of qualitative variable by Chi-square test (X2). Differences between quantitative independent groups by t-test paired by paired t, correlation by Pearson's correlation. Results are presented as the 95% confidence interval (95% CI) and regression coefficient (β-coefficient). A p-value <0.05 was considered significant.

Results:

The mean ages of the studied groups were (43.70±2.84 years) for the case group and (44.60±3.23 years) for the control group. The case group consisted of 24 females and 16 males, while the control group had 12 females and 8 males. The mean BMI of the case group was slightly higher at (28.25 ± 3.75 kg/m^2) compared to (27.11 ± 2.59 kg/m^2) for the control group. The mean height of the case group was slightly lower at (170.9 ± 7.53 cm) compared to (172.5 ± 5.11 cm) in the control group. **(Table 1)**

Table (1): Demographic and anthropometric data of the studied groups

			Case	Control	t/ X^2	P
Age			**43.70±2.84**	**44.60±3.23**	**1.103**	**0.275**
Height			**170.9±7.53**	**172.5±5.11**	**0.855**	**0.396**
Weight			**83.2±16.02**	**80.85±9.86**	**0.600**	**0.551**
BSA			**1.95±0.21**	**1.94±0.13**	**0.029**	**0.977**
BMI			**28.25±3.75**	**27.11±2.59**	**1.222**	**0.226**
Sex	**Female**	**N**	**24**	**12**		
		%	**60.0%**	**60.0%**		
	Male	**N**	**16**	**8**	**0.0**	**1.0**
		%	**40.0%**	**40.0%**		
Total		**N**	**40**	**20**		
		%	**100.0%**	**100.0%**		

BMI: Body mass index & BSA: Body surface area.
***** P value was set at <0.05 for significant results.

The mean systolic blood pressure (SBP) in the case group was (115.75 ± 14.25 mmHg), which was slightly lower than the control group's (117.0 ± 8.64 mmHg), with no significant difference (p-value 0.720). Regarding risk factors, 34 patients were without risk factors, and 2 patients were hypertensive.

The mean HR in the case group was (93.75 ± 8.15 beat/min.) which is significantly higher than the mean HR of the control group which was (81.25 ± 7.58 beat/min.) (p-value <0.001). The mean duration of the P wave in the case group was (105.30 ± 17.55 msec) which is significantly higher than the mean duration of the P wave in the control group which was (92.90 ± 8.61 msec) (p-value 0.001). **(Table 2)**

The mean duration of the PR interval in the case group was (144.05 ± 22.35 msec) which is slightly lower than the mean duration of the PR interval in the control group which was (147.20 ± 13.18 msec) but with no significant difference between the studied groups (p-value 0.564). The mean QRS duration in the case group was (105.25 ± 9.92 msec) which is significantly higher than the mean QRS duration in the control group which was (92.15 ± 11.79 msec) (p-value <0.001).

Table (2): ECG data comparison between groups

	Case (n=40)	**Control** (n=20)	**T**	**P**
	Mean ± SD	**Mean ± SD**		
HR	**93.75±8.15**	**81.25±7.58**	**5.336**	**<0.001****
P	**105.30±17.55**	**92.90±8.61**	**3.686**	**<0.001****

PR	**144.05±22.35**	**147.20±13.18**	**0.580**	**0.564**
QRS	**105.25±9.92**	**92.15±11.79**	**4.523**	**<0.001****
QTc	**430.15±15.11**	**380.95±17.25**	**11.337**	**<0.001****

HR: Heart rate & QTc: corrected QT interval.
*P value was set at <0.05 for significant results,
**P value <0.001 was set for highly significant results,
P value >0.05 for non-significant results.

All ECG parameters (HR, P-wave duration, QRS width & QTc interval) decreased significantly after ASD closure, there was a highly statistically significant difference between previously mentioned parameters before and after ASD closure (p-value <0.001). **(Table 3)**

Table (3): Comparison between cases regarding ECG data before and after ASD closure

	Pre-closure	**Post-closure**	**Paired t**	**P**
	Mean ± SD	Mean ± SD		
HR	**93.75±8.15**	**72.65±5.74**	**15.134**	**<0.001****
P	**105.30±17.55**	**76.7±7.42**	**23.483**	**<0.001****
PR	**144.05±22.35**	**117.45±14.5**	**14.732**	**<0.001****
QRS	**105.25±9.92**	**85.50±9.1**	**23.525**	**<0.001****
QTc	**430.15±15.11**	**392.7±17.78**	**15.838**	**<0.001****

HR: Heart rate & QTc: corrected QT interval.
*P value was set at <0.05 for significant results,
**P value <0.001 was set for highly significant results.

Atrial conduction time (PA) lateral, septal & tricuspid, left intra-atrial electromechanical delay (ILEMD), right intra-atrial electromechanical delay (IREMD) & inter-atrial electromechanical delay (IAEMD) were compared before and after ASD closure. All previously mentioned parameters decreased significantly after ASD closure, there was a highly statistically significant difference between these parameters before and after ASD closure (p-value < 0.001). **(Table 4)**

Table (4): Atrial electromechanical delay pre and post ASD closure comparison.

	Pre-closure	**Post-closure**	**Paired t**	**P**
	Mean ± SD	Mean ± SD		
PA Lateral	**69.75 ± 4.66**	**48.60 ± 5.40**	**24.773**	**< 0.001****
PA septal	**57.25 ± 5.70**	**39.60 ± 4.53**	**24.569**	**< 0.001****
PA Tricuspid	**48.00 ± 3.89**	**33.40 ± 3.48**	**19.377**	**< 0.001****

ILEMD	**12.50 ± 4.18**	**9.00 ± 3.47**	**9.115**	**< 0.001****
IREMD	**9.55 ± 4.67**	**6.20 ± 2.96**	**5.162**	**< 0.001****
IAEMD	**21.75 ± 4.95**	**15.20 ± 3.75**	**9.324**	**< 0.001****

IAEMD: Inter-atrial electromechanical delay, ILEMD: Left intra-atrial electromechanical delay, IREMD: Right intra-atrial electromechanical delay, and PA: Atrial conduction time.
*P value was set at <0.05 for significant results,
**P value <0.001 was set for highly significant results.

During the follow-up period, two cases reported shortness of breath for 1 week after ASD closure, one case had palpitation, and one case had median sternotomy wound-related pain. **(Figure 3)** The case who had palpitation was interpreted as AF post transcatheter ASD closure.

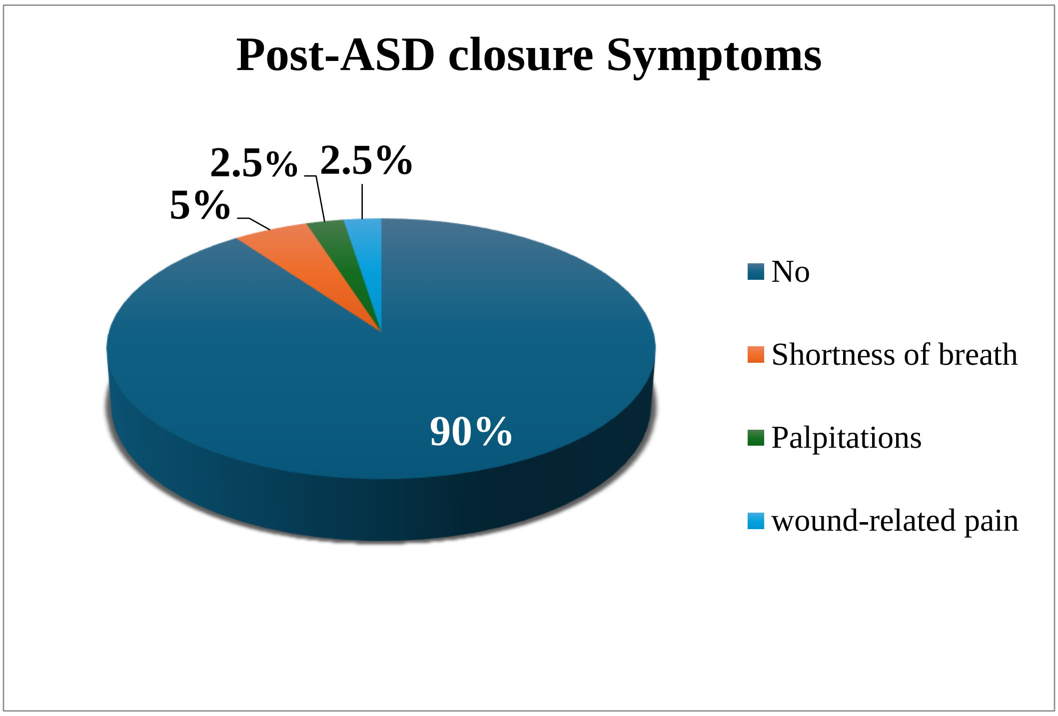

Figure (3): Symptoms after ASD closure.

Discussion*:*

Atrial septal defect (ASD) can manifest in early childhood or remain asymptomatic until adulthood. (16) If left untreated, chronic right ventricular (RV) volume overload due to left-to-right shunting can eventually lead to pulmonary hypertension and Eisenmenger syndrome. Patients who do not undergo ASD closure have worse long-term outcomes, including atrial arrhythmias, reduced functional capacity, and greater degrees of pulmonary hypertension. (17)

Up to 80% of patients with secundum ASD are amenable to device closure, and due to the established safety and efficacy of the procedure, with a very low rate of serious complications (<1%), it has been the first choice for defect closure. (16) Patients who undergo ASD closure before the age of 25 years have the best outcome, while closure after the age of 40 does not seem to alter the incidence of atrial tachyarrhythmias. However, symptomatic improvement and regression in pulmonary artery pressure and RV dimensions were observed in all age groups. (18)

The mean age of the ASD-Surgical and ASD-Device groups in the study by Seo JS et al. in 2021 was (45.5 ± 11.6 years) and (51.3 ± 11.0 years), respectively. Our results agree with those of Seo JS et al., as there was no statistically significant difference between the case and control groups regarding age, body surface area (BSA), body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP). (p-value > 0.05). (19)

Our results also agree with those of Mansour A et al. in 2021, who studied RA and RV electromechanical changes by cardiac magnetic resonance (CMR) 3 months after ASD transcatheter and surgical closure in 30 consecutive adult patients with isolated secundum ASD. They found a reduction in the electrical parameters (resting heart rate, P-wave duration, QRS complex duration, QTc max, and QTD) after ASD closure, as compared to the baseline measurements in both groups. (p-value <0.05). (20)

In our study, there was a highly statistically significant difference between the case and control groups regarding heart rate (HR), P-wave duration, QRS, and QTc, which were higher in the case group than in the control group. However, there was no statistically significant difference in the PR interval between the case and control groups. In our study, HR, P-wave duration, PR interval, QRS width, and QTc interval decreased significantly after ASD closure (p-value <0.001).

This agrees with the findings of Veldtman et al. in 2001 and Gatzoulis et al. in 1996, who showed a significant reduction in the QRS complex duration after ASD device closure, which was explained by the reduction in RV volume overload, geometrical remodeling, and improvement of pulmonary artery pressure with partial reversal of right bundle branch block. (21, 22).

In 2019, Öz A et al. conducted a study to evaluate the mid-term and long-term effects of the transcatheter closure of secundum-type ASD on the lateral atrial conduction time (PA), septal PA, tricuspid PA, left intra-atrial electromechanical delay (ILeft-EMD), right intra-atrial electromechanical delay (IRight-EMD), and inter-atrial electromechanical delay (IA-EMD) measured employing Doppler echocardiography. They observed a statistically significant decrease in these parameters at 6- and 12-month post-device closure and a decrease in the incidence of atrial arrhythmias over time. (23)

We found that the atrial conduction time (PA) lateral, septal, and tricuspid, left intra-atrial electromechanical delay (ILEMD), right intra-atrial electromechanical delay (IREMD), and inter-atrial electromechanical delay (IAEMD) decreased significantly after ASD closure at 3 months post-ASD closure follow-up. (p-value < 0.001).

In our study, there was only one case who had palpitation post-ASD closure, representing 2.5% of all patients involved in the case group. She was a 50-year-old female and her ECG showed acute-onset atrial fibrillation immediately after transcatheter closure, sinus rhythm was restored immediately without treatment, and she was followed up by Holter monitoring for 48 hours post-closure but did not reoccur, it may be due to atrial structural changes secondary to long-standing left-to-right shunting especially in old age patients.

In conclusion, ASD closure in adults (≥40 years) was found to be safe, cost-effective, and efficient, either transcatheter or surgical. This agrees with the findings of O'Byrne ML et al.2018 and Ostovan MA et al. 2016. Along with the added advantage of the less invasive nature of device closure, it was found to be associated with a shorter hospital stay and a smaller number of post-procedure complications. (24, 25)

Limitations:

The study had some limitations, the small number of included patients, and the short duration of follow-up. Also, the percutaneous closure was performed using different devices and we didn't evaluate the effect of a particular device on atrial electrical function.

Conclusion:

The atrial geometrical and electrical reverse remodeling were evident at 3 months following ASD closure and atrial enlargement is a substrate for developing atrial arrhythmia. Finally, ASD closure in older patients is safe and effective.

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