ORIGINAL RESEARCH

Heart, Vessels and Transplantation 2020; 4: 92-98.
Doi: 10.24969/hvt.2020.206

Atrial septal defect patients with greater shunts show susceptibility for ventricular arrhythmias

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Abstract

Objectives: Ventricular arrhythmia episodes are not infrequent in patients with atrial septal defect (ASD). Disturbance in cardiac volume and pressures may lead to enlargement and fibrosis in heart. An interatrial volume displacement through septal defect, briefly interatrial shunt, is the major reason for this complication. Prolongation of the interval between the peak and end of the T wave (Tpeak to Tend, Tp-e) on the 12-lead electrocardiogram (ECG), is utilized as a marker of ventricular arrhythmogenesis during last years. The aim of this study was to assess if there is an impact of shunt ratio on ventricular repolarization in patients with ASD by using Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio.

Methods: Patient records of Samsun Training and Research Hospital were retrospectively analyzed. Electrocardiograms of 133 patients, who were diagnosed as ASD between January 2016 and December 2019 were obtained and scanned. ECG intervals were measured. Shunt ratios, right ventricle diameters and volumes were also acquired. Patients were grouped into two by their calculated shunt ratio, ratio of ≥2.0 is accepted as a high shunt group and <2.0 as a low shunt group.

Results: Both groups' baseline characteristics were similar. Right ventricular dimensions and systolic pulmonary artery pressure were higher in high shunt group. Furthermore, ASD patients with higher shunt ratio had significantly higher ECG measurements than controls, Tp-e: 103.0 (22.1) vs 76.2 (10.2); Tp-e/QT: 0.25 (0.03) vs 0.21 (0.02); Tp-e/QTc: 0.22 (0.03) vs, 0.17 (0.02); for all p<0.001). Of all ECG parameters; Tp-e (r=0.631, p<0.001), Tp-e/QT (r=0.531, p<0.001) and Tp-e/QTc (r=0.614, p<0.001) had moderate correlation with shunt ratio.

Conclusion: T wave peak-to-end interval is a measure of transmural dispersion of repolarization and accepted as a surrogate for increased ventricular arrhythmogenesis risk. Our findings show that ASD patients whose shunt ratio are ≥2.0 show increased risk for arrhythmias.

Key words: atrial septal defect, electrocardiogram, ventricular arrhythmia, risk, ventricular repolarization

(Heart Vessels Transplant 2020; 4; 92-8. doi: 10.24969/hvt.2020.206)

Introduction

Atrial septal defect (ASD) constitutes a significant amount of congenital heart diseases (1). Secundum ASD is the most common type of ASD that causes diversion of blood from systemic to pulmonary circulation. In early stages of life, most patients are asymptomatic. Although some patients are diagnosed early, many of them remain silent until adulthood (2). If the disease stays unnoticed, decrease in exercise capacity, miscellaneous supraventricular arrhythmias, right heart failure, and pulmonary arterial hypertension may occur within years (3, 4). ASD may lead to disruptions in cardiac kinetics dependent on the defect diameter and shunt volume. Shunts which are calculated to be over 2.0 indicate large ASDs with significant blood diversion from left to right atria (5). If atrial and ventricular myocardium is exposed to volume overload, shear stress extends to not only myofibers but also conduction system of heart. Disruptions may manifest as conduction delay within atrium and ventricles (6, 7). Furthermore, the degeneration of cardiac microarchitecture,

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Received: 13.06.2020 **Revised:** 04.07.2020 **Accepted:** 04.07.2020

including enhanced fibrosis, improperly modifies myocardial repolarization (6, 7).

T wave peak to end (Tp-e) interval is recent marker for ventricular susceptibility for arrhythmias and repolarization heterogeneity (8-10). A prolonged Tp-e interval represents a period of susceptibility to ventricular arrhythmias. It was shown that this interval has been associated with increased risk of mortality in various congenital and structural heart diseases (11-15).

There is little information in current literature concerning ventricular arrhythmia susceptibility in ASD.

Our goal is to assess if there is an impact of shunt ratio on transmural repolarization in patients with ASD by using Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio.

Methods

Study participants

Virtual data management system of Samsun Training and Research Hospital was retrospectively analyzed. One hundred and thirty-three patients who had been diagnosed with secundum ASD at outpatient clinic were enrolled. Their electrocardiograms were acquired and scanned. Echocardiographic calculations such as shunt ratio, pulmonary artery pressure and other measurements of right ventricle diameters were gained from previous reports in digital archive. Patients with significant coronary artery lesion, critically ill ASD patients (requiring pulmonary arterial hypertension-specific therapy), moderate or more severe degree valve disease other than tricuspid valve, left ventricular failure, any ASD type other than secundum ASD, left ventricular hypertrophy, atrial fibrillation, right or left bundle block or patients with implanted pacemaker or cardioverter/defibrillator were excluded. Informed consent was obtained from all patients before procedures. Study protocol was endorsed by local scientific board.

Availability of Data and Materials

Supplementary material consisting of supportive data is available from the corresponding author, (OCY), upon reasonable request.

Measurement of Tp-e, QT and QRS Intervals from the 12-Lead ECG

All ECGs were scanned. Utilization of a manual measuring tool and a magnifier for interval measurements; could be either inaccurate or time consuming. ECG papers were scanned and that allowed researcher to make measurements in virtual environment. All intervals were measured by blinded colleague with a virtual caliper on computer interface. Measurements of Tp-e interval were performed from precordial lead V5 as it was described (Fig. 1) (16). From the peak (or the nadir if it was negative) of T wave to the end point where it reaches isoelectric line was measured for Tp-e interval.

The QT interval was measured from the beginning of the QRS complex to where T waves descend onto the isoelectric baseline. When an U wave interrupted the T wave before returning to isoelectric line, the QT interval was measured to the nadir of the bent segment between the T and U waves. The QTc interval was calculated using the Bazett formula: QTc (ms)=QT measured/$\sqrt{RR}$ (sec). QT interval was measured from precordial V5 lead.

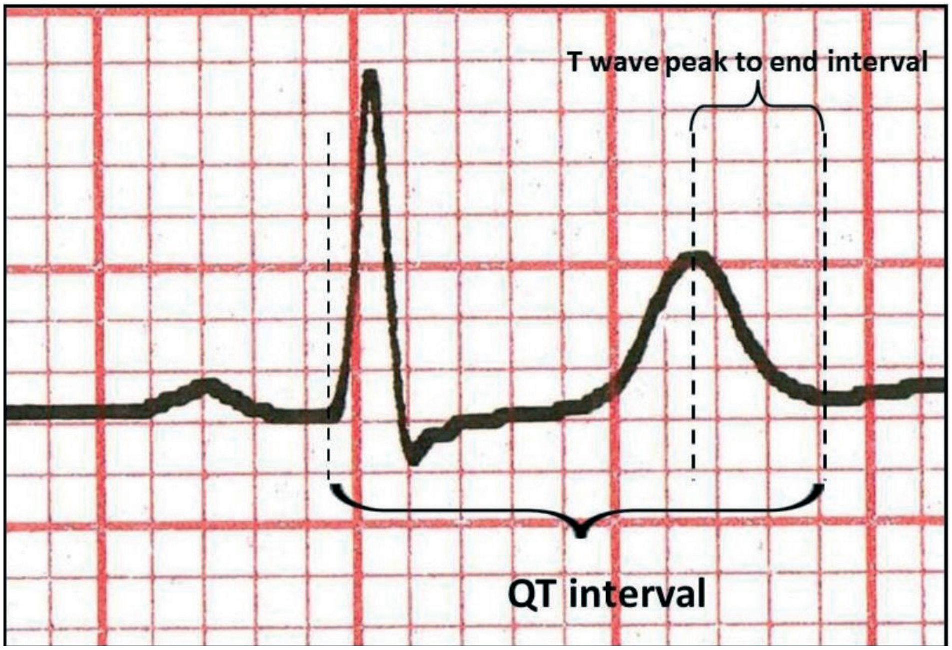

Figure 1. Measurement of intervals on electrocardiogram

Echocardiography

Atrial septal defect shunt ratio was calculated noninvasively by echocardiography (17). Pulmonary perfusion (Qp) was calculated by multiplying right ventricle outflow tract (RVOT) time-velocity integral (in centimeters) and pi number and square of the half of the RVOT diameter (in millimeters). Systemic perfusion (Qs) was calculated by multiplying left ventricular outflow tract time-velocity integral (in centimeters) and pi number and square of the half of the left ventricular outflow tract diameter (in millimeters). Then Qp was divided by Qs to calculate shunt ratio.

Also right ventricular midline/baseline/ end-diastolic base-to-apex distance, end-diastolic and end-systolic volumes, systolic pulmonary artery pressure (SPAP), left ventricular ejection fraction and tricuspid annular plane systolic excursion (TAPSE) were determined. Each echocardiogram was evaluated by 2 blinded sonographers.

Statistical analysis

All analyses were performed using SPSS V 22.0 for Windows (SPSS Inc., Chicago, Illinois, USA). We calculated the minimum number of the individuals that should be sampled with 90% power and 0.05 Type-I error as at least 58 (R 3.0.1. open source program). For parametric and continuous variables, independent-samples t test; for nonparametric and categorical variables, Chi-square test was used for univariate case-control comparisons for all cases vs. controls, respectively. A P value of <0.05 was considered as significant. Spearman correlation coefficient was used for correlation analysis. Association of different variables with electrocardiographic and echocardiographic parameters and shunt ratio were separately calculated in univariate analysis.

Results

Baseline data

A total of 133 patients were grouped into two: 65 patients constituted low shunt ratio group (<2.0), remaining 68 patients formed the group with high shunt ratio (≥2.0). Mean age for patients with high shunt ratio was 40.5 (12.5) and for lower shunt group was 38.9 (12.7) (p=0.463). High shunt group consisted of 47 female patients (72.3%) whereas there were 44 female patients (64.7%) in low shunt group (p=0.358). Twenty three patients (35.4%) of low shunt group had diabetes whereas there were 14 (20.6%) patients with diabetes in high shunt group (p=0.834). High and low shunt groups did not differ in entity of hypertensive individuals (7 vs. 10) and smokers (31 vs. 32).

ECG and echocardiographic variables

Echocardiographic and ECG measurements are listed in Table 1. High shunt group had significantly longer Tp-e, QT and QTc intervals and higher Tp-e/QT and Tp-e/QTc ratios than low shunt group (p<0.001 for all).

Echocardiographic measurements of RV diameters (end-diastolic annulus line diameter, end-diastolic mid-line diameter, end-diastolic base-to-apex distance), RV volumes and SPAP were higher (p<0.001), while TAPSE was significantly lower (p<0.001) in high shunt group as compared to low shunt group. Mean left ventricular ejection fraction was similar in both high and low shunt groups (p>0.05).

Correlations between parameters of transmural repolarization with ECG and echocardiographic variables

Of all ECG parameters; Tp-e (r=0.631, p<0.001), Tp-e/QT (r=0.531, p<0.001) and Tp-e/QTc (r=0.614, p<0.001) had moderate correlation with shunt ratio (Table 2). On the other hand, right ventricular end-diastolic (r=0.783, p<0.001) and end-systolic volumes (r=0.833, p<0.001), TAPSE (r=-0.638, p<0.001) and SPAP (0.677, p<0.001) showed strong correlation with shunt ratio (Table 3).

Discussion

Our results demonstrated that ASD patients whose shunt ratio are ≥2.0 had longer Tp-e intervals and higher Tp-e/QT and Tp-e/QTc ratios than individuals with a lower shunt ratio and there is a positive correlation between shunt ratio and Tp-e interval, Tp-e/QT and Tp-e/QTc ratios

Atrial septal defect is one of the most common congenital heart diseases. Frequency of atrial tachyarrhythmias and conduction diseases is very well studied in this population (18-20). Atrial arrhythmia prevalence shows correlation with size of shunt and occurrence of hemodynamic complications such as pulmonary artery hypertension, as well as with other comorbidities. However, there is a lack of scientific data regarding occurrence of ventricular arrhythmogenesis in this group of patients. Eryu et al. (21) investigated the RR and QT interval variability in a group of ASD patients and found that there was a correlation between these indices and shunt ratio.

Table 1. Comparison of echocardiographic and electrocardiographic parameters between both groups

Parameters	Shunt ratio ≥2.0 (n=68)	Shunt ratio <2.0 (n=65)	p
Mean shunt ratio	2.2 (0.1)	1.3 (0.2)	<0.001
RV1, mm	35.5 (2.4)	32.4 (1.7)	<0.001
RV2, mm	28.0 (2.2)	24.7 (1.4)	<0.001
RV3, mm	66.5 (2.8)	64.0 (1.9)	<0.001
RVEDV, ml	185.4 (13.9)	147.62 (7.0)	<0.001
RVESV, ml	88.46 (7.5)	51.8 (5.4)	<0.001
SPAP, mmHg	35.5 (7.6)	19.3 (5.2)	<0.001
TAPSE, mm	11.2 (2.9)	16.2 (1.6)	<0.001
LVEF, %	60.9 (3.7)	61.0 (4.0)	0.859
QT, msec	409.9 (62.7)	361.4 (35.7)	<0.001
QTc, msec	459.7 (44.0)	428.2 (43.1)	<0.001
Tp-e, msec	103.0 (22.1)	76.2 (10.2)	<0.001
Tp-e/QT ratio	0.25 (0.03)	0.21 (0.02)	<0.001
Tp-e/QTc ratio	0.22 (0.03)	0.17 (0.02)	<0.001

Data are presented as mean (SD)

LVEF - left ventricular ejection fraction, ml - milliliter, mm - millimeter, msec - millisecond, QTc - corrected QT, RV1 - right ventricular end-diastolic annulus line diameter, RV2 - right ventricular end-diastolic mid-line diameter, RV3 - right ventricular end-diastolic base-to-apex distance, RV EDV - right ventricular end-diastolic volume, RVESV - right ventricular end-systolic volume, SPAP - systolic pulmonary artery pressure, TAPSE - tricuspid annular plane systolic excursion, Tp-e- T wave peak to end interval

Table 2. Correlations between electrocardiographic parameters and shunt ratio

Variables	Shunt ratio	
	r	p
QT, msec	0.457	<0.001
QTc, msec	0.375	<0.001
Tpe, msec	0.631	<0.001
Tpe/QT	0.531	<0.001
Tpe/QTc	0.614	<0.001

Table 3. Correlations between echocardiographic parameters and shunt ratio

Variables	Shunt ratio	
	r	p
RV1	0.553	<0.001
RV2	0.569	<0.001
RV3	0.393	<0.001
RVEDV	0.783	<0.001
RVESV	0.833	<0.001
LVEF	0.008	0.926
SPAP	0.677	<0.001
TAPSE	-0.638	<0.001

LVEF - left ventricular ejection fraction, ml - milliliter, mm - millimeter, msec - millisecond, RV1 - right ventricular end-diastolic annulus line diameter, RV2 - right ventricular end-diastolic mid-line diameter, RV3 - right ventricular end-diastolic base-to-apex distance, RVEDV - right ventricular end- diastolic volume, RVESV - right ventricular end systolic volume, SPAP - systolic pulmonary artery pressure, TAPSE - tricuspid annular plane systolic excursion

Authors came to a conclusion that these repolarization indices provided information on alteration of sinus node autonomic control and the pathophysiology of myocardial repolarization. A more recent study (22) was able to show prolonged QT intervals in children with relevant hemodynamic impairment. Authors reach to a conclusion that after closure operation patients' QTc interval shortened significantly. This finding may create a discussion point for our article's intellectual basis. In our study, we utilized another myocardial repolarization index, the Tp-e interval, in concordance with QT interval, to determine ventricular arrhythmia susceptibility in a group of ASD patients with relatively lower shunt ratio.

Miscellaneous methods were utilized in order to assess myocardial repolarization including QT dispersion (QTd), corrected QT dispersion (cQTd), and transmural dispersion of repolarization. Recent studies demonstrated that Tp-e interval can be used as an index of total (transmural, apico-basal, and global) repolarization disparity (23, 24). Increased Tp-e interval might be a useful index to predict ventricular tachyarrhythmias and cardiovascular mortality (25). Furthermore, Tp-e/QT ratio has been suggested to be a more accurate measure for the dispersion of ventricular repolarization compared to QTd, cQTd, and Tp-e intervals, which is independent of alterations in heart rate (26). Also, these markers may be used as an ECG indexes of ventricular arrhythmogenesis and sudden cardiac death (16, 20). Previous studies showed that prolongation of Tp-e interval was associated with increased mortality in various clinical cardiac conditions (11, 12, 14, 16). The novel repolarization indexes Tp-e interval and Tp-e/QT ratio, has not been studied in ASD patients before.

Abnormal hemodynamics in ASD patients may play the most important role in ventricular arrhythmogenesis. Left-to-right shunt increases right atrial and eventually right ventricular volume and pressure load to some extent (1). Abnormal right ventricle workload may promote fibrosis in myocardial tissue that would precede an arrhythmic risk. On the other hand, right ventricular volume and pressure overload shift the interventricular septum towards left ventricle. This displacement precedes an impaired diastolic filling and a reduced stroke volume. This would also provoke fibrosis in ventricle. Our patients with larger shunts had their right ventricular end-systolic and end-diastolic volumes significantly increased, which clearly indicates right heart failure. Another theory for conduction heterogeneity in these patients is that, left ventricular diastolic impairment might lead to autonomic imbalance (27), which would directly affect Tp-e and related intervals. Eryu et al (21) asserted that there was an increase in sympathetic control of the heart or a decrease in parasympathetic control of the heart in children with ASD. In our opinion there should be other factors in charge, which involve microarchitecture and ion channels and signal transmission than macro changes in heart chambers.

Study limitations

The most important restriction of our study is the limited number of patients. Another limitation we did not assess the association between ventricular arrhythmias with Tp-e interval and Tp-e/QT ratio. Also study population could not be followed-up prospectively for ventricular arrhythmic episodes. Large-scale prospective studies are needed to determine the predictive value of prolonged Tp-e interval and increased Tp-e/QT ratio in this population.

Conclusion

Our study revealed that transmural repolarization is more deteriorated in ASD patients with large shunts and dilated right ventricle than individuals with a lower shunt ratio. Tp-e interval and Tp-e/QT ratio might be a useful marker of arrhythmia susceptibility in this group.

Peer-review: External and internal

Conflict of interest: None to declare

Authorship: O.C.Y

Acknowledgments and funding: None to declare

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The lake in high-altitude Kochkor region, Naryn, Kyrgyzstan. Ulan Tursunbekov, Bishkek, Kyrgyzstan.