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Original Article

Flow-Mediated Vasodilatation which is diagnostic method of endothelial dysfunctions change in atrial septal defect patients before and after closure of the ASD

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Abstract

Aim: Atrial septal defect secondary pulmonary hypertension causes disruption of the endothelial structure, resulting in an increase in vasoconstrictor mediators and a decrease in vasodilator mediators. These changes on the endothelial system alter the flow in the pulmonary vein and the systemic vein bed. This also has an effect on flow mediated vasodilatation. Our purpose in this study is to evaluate the endothelial dysfunction after atrial septal defect closure via flow mediated vasodilatation.

Material and Methods: Total 51 patients with pre and one mount after post treatment secundum-type atrial septal defect and 40 healthy volunteers were prospectively enrolled. Atrial septal defect was treated with transcathater closure procedure. Flow mediated vasodilatation was measured to evaluate endothelial function prior to and one month after the defect was closured.

Results: Flow-mediated vasodilatation values were significantly higher in an atrial septal defect's patient than in the healthy volunteer (11.2 ± 1.01 m/s vs. 12.7 ± 1.18 m/s, P < 0.001). Flow-mediated vasodilatation values were significantly reduced at the follow-up one month after the procedure compared to baseline. Moreover, there was a significant negative correlation between pulmonary arterial pressure values and flow-mediated vasodilatation (r=-0.347; p=0.013) in the pretreatment group.

Conclusion: Flow-mediated vasodilatation values were significantly lower in the right cardiac chambers, and the systolic pulmonary arterial pressure was improved. This result has shown us that atrial septal defect closure may benefit from endothelial dysfunction.

Keywords: Atrial septal defect; endothelial dysfunction; flow-mediated vasodilatation

INTRODUCTION

Although adult congenital heart diseases are rare in the normal population, atrial septal defect (ASD) is the most common of these disorders (1). Patients are asymptomatic until adolescence, but heart failure, systemic embolism, transient ischemic attack, pulmonary hypertension, and arrhythmias such as in this disease very important to diagnose and treat them early (2,3).

Endothelial dysfunction and endothelial structural anomaly play an important role in the increase of blood pressure in the pulmonary bed. ASD also does this with endothelial dysfunction, affecting pulmonary hypertension by increasing the release of vasoconstrictor mediators and reducing vasodilator release such as 5 lipoxygenase, nitric oxide and prostacyclin. Most of these mediators increase pulmonary vascular resistance and hypertension by developing and remodeling vascular muscle cells (4, 5).

Atrial septal defect primarily increases blood flow to the pulmonary system followed by remodeling of the pulmonary vessels, resulting in pulmonary hypertension. These histopathological changes cause endothelial dysfunction. This change in the pulmonary vessel and mediators transferred from these vessels into the circulation alter flow-mediated vasodilatation.

There are several methods for evaluating endothelial dysfunction. It can be evaluated as an invasive and non-invasive. The invasive system is injected into the endothelium-dependent vasodilator (6). The non-invasive method is flow-mediated vasodilatation, a diagnostic method associated with vascular modulation mechanisms

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in the arterial system associated with the endothelial system (7). Flow-mediated vasodilatation is measured by arterial vasodilation secondary to the ischemic response. Flow-mediated vasodilatation measurement with the development of equipment, flow-mediated vasodilatation is recognized as a simple, safe and valuable method for assessing endothelial function in clinical practice and is being guided (7).

As a result, in this study show that evaluate endothelial dysfunction after atrial septal defect closure via flow-mediated vasodilatation.

MATERIAL and METHODS

Study population

In this study, total 51 patients (33% males and mean age 36±14) with pre and one mount after post treatment secundum-type atrial septal defect and 40 healthy volunteers (mean age 35.2±8.1) were prospectively enrolled.

Patients were enrolled in patients who had enlarged right heart cavities secondery secundum ASD according to ESC guidelines. Patients with normal Qp / Qs, primum type or sinusvenous type defect, valvular pathology that may contribute to pulmonary hypertension, diabetes, hypertension were excluded.

Patients and healthy volunteers' medical history and medications were recorded. Blood pressure was measured by experienced individuals before transthoracic echocardiography (mean 10 min). This procedure was performed 3 times with 2 min intervals. The mean blood pressure was calculated and recorded.

Echocardiographic study

Echocardiographic study was performed to all patients and healthy volunteers. Atrial septal defect group were evaluated by both transthoracic echocardiography and transesophageal echocardiography before the procedure and by only transthoracic echocardiography one month from discharge. Vivid 7 (GE-Vingmed Ultrasound AS, Horten, Norway) with the echocardiography device, M-mode and two-dimensional echocardiography parameters were applied by using parasternal long-axis in accordance with echocardiography guidelines. Transesophageal echocardiography was performed under sedation using the same device and 6- and 9 MHz transesophageal echocardiography probe. Teichos method was used for the calculation of ejection fraction as suggested by the American echocardiography guide and two-dimensional echocardiographic parasternal long axis view was used for this (8). Pulmonary artery was calculated secondary to valvular insufficiency via the wearer tricuspid valve. Pulmonary artery pressure = Rigth Atrium Pressure +4V2 (V= tricuspid valve regurgitation maximum blood flow rate).

Ultrasound examination

The same examiner performed on all the patients throughout the study. This procedure used pre and post treatment. After resting the patients on their back for ten minutes, the arm was started and the procedure was continued. 7–12 MHz linear-array transducer was used for measured brachial artery diameter. All patients were studied for the same durations. The right brachial artery was used if there was no problem (e.g. occlusion, amputations). The artery diameter was measured at end-diastole. The average of three cardiac cycles was calculated. The brachial artery was evaluated approximately five cm above the antecubital line. Two-dimensional ultrasound images were obtained. A sphygmomanometer placed around the arm to be measured was inflated to at least 200 mmHg for five minutes. When the sphygmomanometer is extinguished, reactive hyperemia and regressive stress are caused by the expansion of the brachial artery. Brachial artery image was taken five minutes after the cuff was open. After sublingual five mg nitroglycerine dose, it was waited for ten minutes and recorded for five minutes to assess vasodilatation from the brachial artery.

Endothelium-dependent vasodilatation (flow-dependent vasodilatation) was expressed as the percentage of change in the brachial artery on average 60 seconds after the sphygmomanometer is lowered (Flow-mediated vasodilatation % = [(Brachial artery diameter after sphygmomanometer is lowered) baseline brachial artery)/ baseline brachial artery] · 100). Likewise, endothelium-independent peripheral vasodilatation (% nitroglycerin%) from nitroglycerin was expressed as a percent change in the brachial artery relative to baseline four minutes after sublingual or intravenous nitrate administration (Nitroglycerine % = [(Brachial artery diameter after nitroglycerine) brachial artery)/baseline brachial artery diameter] · 100).

Transcatheter closure procedure

The whole procedure was performed under local anesthesia and mild sedation, the same procedure performs under the guidance of transesophageal echocardiography. Hemodynamic parameters were recorded throughout the procedure. Pulmonary arterial pressure and left to right shunts were calculated without passing atrial septal defect. The defect diameter was detected transesophageal echocardiography and fluoroscopy, and an appropriate atrial septal defect clouse device was chosen. The occluder device (Amplatzer Septal Occluder USA) was selected and applied 10% more than the measured atrial septal defect cavity. The occluder devices were placed with the help of fluoroscopy and transesophageal echocardiography. Residual leakage, device optimization and compression of the device to adjacent structures were controlled by transesophageal echocardiography. Also, stabilization of the occluder was confirmed by Minasoto and various maneuvers before the occluder was released. After ensuring that the device was placed without any complications, the device was released with appropriate maneuver (9, 10). During the

procedure, anticouagulation and antibiotic prophylaxis was given at the appropriate dose.

Laboratory measurements

Hematological parameters (HBg, WBC, Plt) were taken into tripotassium EDTA based anticoagulated tubes in all patients. Biochemical parameters were taken in the morning after a 12-hour fasting. Biochemical tests (CRT, Glucose, Cholesterol) were performed in an autoanalyzer (Roche Diagnostic Modular Systems, Tokyo, Japan). Anticoagulated blood samples based on tripotassium EDTA were evaluated with the Sysmex K-1000 auto analyzer.

Statistical Analysis

Statistical analyses were performed using SPSS Statistical Package version 21.0 for Windows (SPSS Inc, Chicago, IL, USA). Normally distributed continuous variables were tested by Shapiro - Wilk test. We report continuous data as mean and standard deviation. The distribution of continuous variables between groups was performed using the student t-test or Mann-Whitney U test. Variability between groups was performed by the t test. The chi-square test was used for categorical variables and was calculated as a percentage. The relationship between the variables was analyzed by person correlation analysis. P-value <0.05 was considered significant.

RESULTS

There were 51 patients (mean age 36 ± 14) in pre and post treatment after one mount in the atrial septal defect group. Baseline characteristics are shown in Table 1. Between the two groups, there were no significant differences in baseline laboratory parameters (Table 1). The hemodynamic parameters (heart rate, systolic and diastolic blood pressure) were not significantly different (p=0.718, p=0.664 and p=0.778 respectively). Complete bloods counted parameters, which were hemoglobin, hematocrit, and platelet count were not different between groups.

Table 1. Baseline characteristics

	ASD pre treatment n=51	ASD post treatment n=51	p value
Age (year)	35.9 ± 13.6	-	-
BMI (kg/m^2)	22.6 ± 2.4	22.5 ± 2.9	0.558
Hemoglobin (g/dl)	13.6 ± 1.6	13.1 ± 1.3	0.596
WBC (10^3µL)	8.0 ± 2.0	8.1 ± 1.9	0.798
Platelet count (10^3µL)	260 ± 79	270 ± 89	0.547
Creatine (mg/dl)	1.0 ± 0.2	0.8 ± 0.1	0.190
Glucoze (mg/dl)	98 ± 23	95 ± 19	0.649
Total cholesterol (mg/dl)	177 ± 38	183 ± 41	0.470
LDL (mg/dl)	107 ± 31	114 ± 35	0.323
HDL mg/dl)	45 ± 9	47 ± 9	0.459
Triglyceride (mg/dl)	120 ± 82	110 ± 47	0.474
Hemodynamic parameters			
Systolic blood pressure	121.8 ± 16.5	123.8 ± 19.1	0.664
Diastolic blood pressure	79.2 ± 11.6	77.7 ± 13.1	0.778

BMI: Body mass index, LDL: Low density lypoprotein, HDL: High density lypoprotein

When we evaluated the atrial septal defect population before and after closure of defect, pulmonary artery pressure (45.8±9.3 mmHg to34.2±7.6 mmHg, p<0.001) and right ventricular diameter (4.2±1.2 cm vs. 3.6±0.9 cm, p<0.001) were significantly decreased after one month's treatment (Table 2).

A significant difference was found in the patients with atrial septal defect between tricuspid annular plane systolic excursion value, which was a marker of right ventricular systolic function, measured before the one month after the procedure (P < 0.001) (Table 2).

Table 2. Pre and post-treatment parameters of ASD population

	Pre-treatment	Post-treatment	p value
Systolic PAP (mmhg)	45.9 ± 11.9	34.2 ± 7.6	<0.001
TAPSS	1.94 ± 0.423	2.64 ± 0.414	<0.001
RV diameter (cm)	4.4 ± 0.6	3.7 ± 0.6	<0.001
RA diameter (cm)	4.5 ± 0.5	4.3 ± 0.6	0.102
LVEF %	62.6 ± 5.7	63.2 ± 5.8	0.542

Data are expressed as mean ± standard deviation for normally distributed data. PAP: Pulmonary artery pressure, RV: Right ventricle, RA: Right atrium, LVEF: Left ventricular ejection fraction

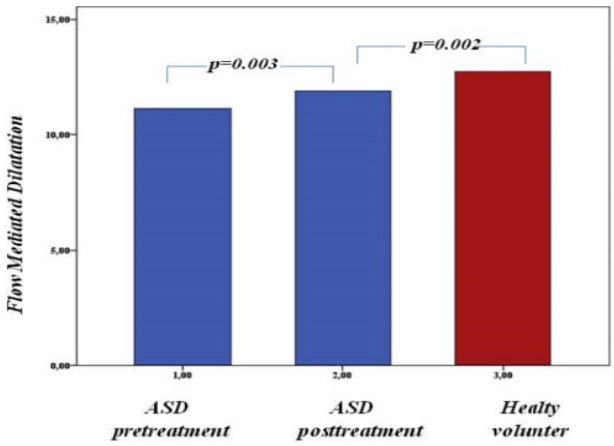

Figure 1. Pre and post treatment, FMD levels after one month in ASD patients

Atrial septal defect population pre and post treatment, flow-mediated vasodilatation levels were significantly increased after one month (11.2±1.01to 11.9±1.20, p=0.003) (Figure 1). Moreover, there was a significant negative correlation between systolic pulmonary artery pressure values and flow-mediated vasodilatation (r=-0.347; p=0.013) in the pretreatment group (Figure 2).

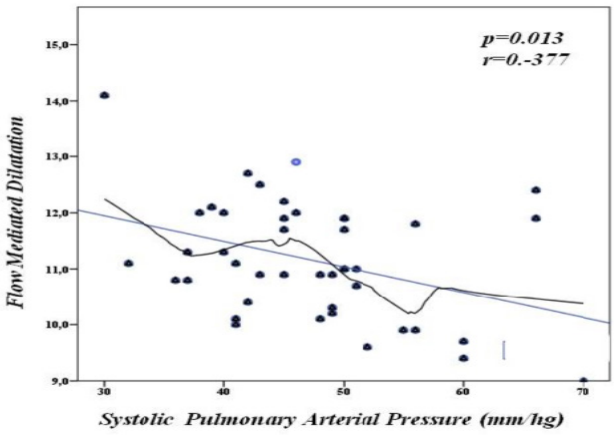

Figure 2. Significant negative correlation between systolic PAP values and FMD

DISCUSSION

Although congenital heart diseases are rare in adults, they often have an atrial septal defect. The mortality rate from untreated, hemodynamically significant atrial septal defect can approach 25% (11). As stated in the American Heart Association guidelines, closure is recommended when enlargement and volume increase is seen in the right heart of a patient with ASD.

Flow-mediated vasodilatation in the brachial or femoral artery is one of the best indirect methods of demonstrating endothelial dysfunction, and numerous studies have demonstrated the usefulness of flow-mediated vasodilatation measurement in risk stratification for cardiovascular diseases (12).

In this study, flow-mediated vasodilatation levels that a sign of endothelial dysfunctions are significantly low in atrial septal defect group pretreatment to posttreatment. Besides, flow-mediated vasodilatation levels are negatively correlated with systolic pulmonary artery pressure in patients with pulmonary hypertension secondary to atrial septal defect.

Pulmonary hypertension is considered the most critical complication of ASD, and it leads to a lack of effort capacity and early mortality (13,14). Excess volume due to the left to right shunt plays a significant role in pulmonary hypertension. Excess volume in the right causes' pulmonary hypertension as a compensation mechanism by increasing pulmonary circulation. Due to increased volume load in the pulmonary bed due to left-to-right shunt due to congenital heart disease ASD and high pressure to which it is exposed, remodeling occurs in the pulmonary vessels, hyperplasia occurs in the layers of the pulmonary vessels, and the balance of vasoconstriction and vasodilatation is impaired (15).

The endothelium carries essential functions in controlling blood flow, maintaining vascular tone, platelet aggregation, adhesion of leukocytes and controlling the coagulation system (16). This role of endothelium is the determinant of cardiovascular diseases (6).

Flow-mediated vasodilatation, a non-invasive method for

demonstrating endothelial dysfunction, is described by Celermajer et al. in 1992 (17). The active mechanism in this diagnostic method is formed by the immediate release of physiologically active substances from endothelial cells after transient ischemia. Nitric oxide is the leading active release mediator in this event, and the increase in vessel diameter is caused by this substance (6). Flow-mediated vasodilatation demonstrates the response of these mediators to endothelium and provides valuable insight into endothelial dysfunction.

Potential mechanisms of endothelial dysfunctions and relationship between flow-mediated vasodilatation and ASD

There is no clear information about the development of systemic endothelial dysfunction in congenital heart diseases and especially in ASD; however, endothelial dysfunction is thought to have increased volume load secondary to left-to-right shunt in these patients and remodeling caused by this load. Studies have shown that pulmonary hypertension is independently increased in patients with endothelial dysfunction (5). It is not known exactly how and with what vasoconstrictive / vasoproliferative events begin. Furthermore, in some hypotheses, apoptosis of calm cells usually occurs at the end of damage to the endothelium, resulting in an unbalanced operation of the intimal region in the pulmonary bed, leading to an uncontrolled increase of proliferative cells. Most of the physiological consequences of pulmonary hypertension would then emanate from the resultant narrowing of the pulmonary artery (4).

Lu H et al. (18) showed that endothelin and nitric oxide levels were significantly higher in increasing pulmonary artery pressure secondary to congenital heart disease and showed that these two molecules could play an important role in the development of pulmonary hypertension. Stevvart et al. (19) showed that in peripheral venous and arterial endothelin levels were significantly higher in the pulmonary hypertension group (seven primary, twenty secondary) than in the control group. In congenital heart disease and diseases with endothelial dysfunction, the balance between nitric oxide and endothelin in plasma is disrupted in favor of endothelin. Increased endothelin levels are associated with vasoconstriction, vascular fibrosis, increased vascular smooth muscle tone and endothelial dysfunction (20). In the present study, flow-mediated vasodilatation levels that are a sign of endothelial dysfunctions were significantly low in ASD and flow-mediated vasodilatation levels were significantly negative correlations with pulmonary artery pressure.

Kaya et al. (21) showed that echocardiographic findings improved, and diameters improved six months the after closure of ASD percutaneously. In this study, flow-mediated vasodilatation levels were significantly increased after transcatheter closure and echocardiography showed a trend towards a reduction in the pulmonary artery pressure in post-treatment patients. Therefore, for the first time we demonstrated that there is a significant relation between flow- mediated vasodilatation levels and pulmonary hypertension secondary to atrial septal defect.

LIMITATIONS

The significant limitations of this study were that data were collected from a single center and the number of patients was low. Other possible limitations of this study may be that there is not a cutoff sign for flow-mediated vasodilatation so that we did not know when flow mediated vasodilatation levels increase to a healthy volunteer level after the closure of the atrial septal defect with the transcatheter approach.

CONCLUSION

Endothelial dysfunction plays a significant role in the pathogenesis of pulmonary hypertension secondary to atrial septal defect and occurs earlier than pulmonary hypertension. So that, endothelial dysfunction which is correlated with decreased flow-mediated vasodilatation levels, may be the other indication of closing atrial septal defect.

Competing interests: The authors declare that they have no competing interest.

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