ABSTRACT

Objective: The aim of the present study was to examine whether endothelial function is affected in patients with atrial septal defect (ASD) of secundum type and to determine the changes that might occur in endothelial function after the defect was closed by the transcatheter method by using the pulse wave velocity (PWV) method.

Materials and Methods: A total of 54 patients with ASD type and 40 healthy individuals were included in the study. All patients underwent transthoracic echocardiography and PWV measurements to evaluate the endothelial function prior to and 1 month after the closure procedure.

Results: PWV values were significantly higher in patients with ASD than in healthy subjects (7.5±1.2 m/s vs. 6.1±1.0 m/s, p<0.001). Systolic pulmonary arterial pressure (PAP), right ventricular diameter, and PWV values were significantly lower at 1 month of follow-up after the procedure than at baseline (p<0.001). However, left ventricular ejection fraction, left ventricular end-diastolic diameter (LVEDD), and tricuspid annular plane systolic excursion values increased significantly after the procedure component (p<0.001, p=0.002, and p<0.001, respectively).

Conclusion: It was observed that following closure of the ASD by the transcatheter route, the PWV values were significantly reduced in the right cardiac chambers, and the systolic PAP was improved. This result has shown us that ASD closure may benefit from endothelial dysfunction.

Keywords: Atrial septal defect, endothelial dysfunction, pulse wave velocity

INTRODUCTION

Atrial septal defect (ASD) is the most common congenital heart disease in adults and comprises 5%–10% of all congenital heart diseases (1). The majority of the patients are asymptomatic until adulthood, but early diagnosis and treatment of this condition are important because of complications, such as pulmonary hypertension (PHT), right heart failure, and arrhythmias (2). It is anticipated that chronically increased pulmonary arterial blood flow may have mechanical effects on the endothelial cells. These mechanical effects include irregularities on the vessel wall and development of pulmonary vascular disease. Increased pulmonary blood flow leads to remodeling of the pulmonary vessel in time (3). This balance mechanism that deteriorates in the pulmonary vascular bed may also affect the systemic vascular bed by increasing the levels of mediators with vasoconstrictor effects. The structural and functional changes in the endothelial cells cause these cells to lose their barrier function, and the serum factors that should not normally be present in this region escape to the subendothelial area. As a result, the balance between vasodilatation and vasoconstriction in the vessels deteriorates, and endothelial dysfunction develops.

Measurement of peripheral arterial stiffness has been a prominent diagnostic tool in assessing endothelial function in recent years. Arterial stiffness represents the elasticity and distensibility characteristics of the arterial wall (4, 5). Disruption in the media layer of the vascular wall causes increased stiffness and decreased distensibility in the vessel. Increased peripheral arterial stiffness is known to be a risk factor for diseases with high mortality and morbidity and to be a marker of target-organ damage. Pulse wave velocity (PWV) is viewed as the gold standard in assessing arterial stiffness (6, 5).

The aim of the present study was to explore the effects of positive hemodynamic changes expected to occur after closing the ASD of secundum type by the percutaneous route on endothelial function using the PWV method.

MATERIALS and METHODS

Patient Population
This was a prospective cohort, simple random sampling study. A total of 54 (18 male and 36 female) volunteer patients with a mean age of 35.6±12.6 years who were diagnosed with secundum type ASD and whose ASD was...
closed using an atrial septal occluder (ASO) device and 40 (14 male and 26 female) healthy volunteers with a mean age of 35.5±8.3 years were included in the study. The healthy group was selected from the group whose routine blood tests were normal, and no significant pathology in echo and electrocardiography was applied to the clinic. The present study was approved by the ethics committee of Erciyes University (approval date 2011/174).

The interatrial septal defects of the patients included in the present study who had secundum type ASD were closed by the transcatheter route using an ASO device. All patients underwent transthoracic echocardiography (TTE) and PWV measurement to evaluate the endothelial function prior to and 1 month after the closing procedure.

Exclusion Criteria
Patients with sinus venous type defect and primum ASD, history of cardiomyopathy, history of congestive heart failure, left or right branch block, malignant hypertension (>180/100 mm Hg), known connective tissue disorders, history of moderate to serious valvulopathy, peripheral arterial disease, chronic obstructive pulmonary disease, active infectious or inflammatory conditions, known malignancy, and systemic conditions involving the aorta were excluded from the present study.

The patients and healthy subjects included in the present study were informed of the procedures that would be conducted in the study. Informed consent was obtained from the participants of the study.

Biochemical Parameters
Total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglyceride, aspartate aminotransferase, and alanine aminotransferase were assayed by a Beckman Coulter analyzer using its specific kits. The level of LDL-cholesterol was calculated using Friedewald’s formula (LDL=TC–HDL–C–[TG/5]). Normal reference values were as follows: total cholesterol 120–200 mg/dL, HDL-cholesterol 40–60 mg/dL, LDL-cholesterol 100–130 mg/dL, and triglyceride 35–150 mg/dL. Blood samples were obtained from the patients to evaluate renal function. Normal reference values were 5–25 mg/dL for blood urea nitrogen and 0.6–1.2 mg/dL for creatinine.

Echocardiographic Examination
All patients and healthy subjects in the present study underwent TTE examination. Echocardiography measurements obtained prior to the closing procedure were compared with those obtained at 1 month after closure. The TTE examination was performed using a Vivid 7 echocardiography instrument (GE Vingmed Ultrasound, Horten, Norway) and a 2.5 MHz transducer by following the criteria recommended by the American Association of Echocardiography. M-mode and two-dimensional (2D) echocardiographic parameters were obtained from the parasternal long axis and apical views with the patients lying on their left side. Transesophageal echocardiographic (TOE) examination was performed under sedation using the same instrument and a 6 MHz TOE probe. The left and right ventricular end-diastolic diameters (LVEDD and right VEDD) and diameters of the left and right atriums were measured from the parasternal long axis and apical four-chamber views using M-mode and 2D echocardiography. The left ventricular ejection fraction (LVEF) was calculated using Teichholz’s formula. Pulmonary arterial pressure (PAP) was calculated through tricuspid regurgitation using the following formula: $PAP = RAP + 4V^2$, where $RAP$ = the right atrial pressure, $V$ = the highest blood velocity of tricuspid regurgitation. Right atrial pressure was calculated utilizing the size of the right atrium and vena cava inferior (7). To assess right ventricular systolic function, systolic movements of the tricuspid annular plane systolic excursion (TAPSE) were measured. TAPSE <15 mm was considered to indicate the presence of right ventricular systolic dysfunction (8).

Measurement of Arterial Stiffness
Arterial stiffness was examined by carotid–femoral PWV measured using a Pulse Trace PWV (MicroMedical Pulse Trace) device. After the patients had a resting period of 10 min prior to the measurement, their brachial blood pressure, length, and weight were measured. The measurements were performed after the patients had waited for at least 5 min in a lying position at a room temperature of approximately 23°C–24°C. For measuring carotid–femoral PWV, electrocardiography leads of the device were first connected to the patients. For measurement settings of the device, distance between the carotid and femoral measurement points was measured with an elastic meter in addition to the patient information. For distance measurement, the carotid to femoral distance was used. The values obtained were recorded in the device in mm. The accuracy of the values obtained by measurements is provided by the device along with a certain standard deviation (SD), and the SD values <5 (high-quality records) are accepted as correct by the device. In the present study, the SD average of the three measurements <5 was recorded as analysis value.

Procedure of Closing ASD
All patients gave informed consent prior to the procedure. All procedures were performed under general anesthesia and using TOE. All patients underwent the process of selecting the appropriate ASD closing device prior (ASO) to the procedure with the assistance of TOE and fluoroscopy. For patients with ASD rims of equal size of the defect diameter or borderline ASD rims, ASO 1–2 mm bigger was preferred. ASO was inserted under TOE and fluoroscopy. Following the procedure, it was checked whether there was shunt and whether there was narrowing in the vena cava superior, vena cava inferior, pulmonary veins, coronary sinuses, and mitral and tricuspid valves using TOE. Furthermore, the device was checked to determine if it was stable on its site with the Minnesota maneuver made by very slow forward and backward movements of the carrier catheter. On the controls using TOE and fluoroscopy, the carrier guide on the device was freed by rotating counterclockwise after observing that the device was inserted appropriately, there was no leakage, or there was leakage of minor degree (9).

Statistical Analysis
Statistical analyzes were conducted using SPSS software v.15.0 (SPSS Inc., Chicago, IL, USA). Compatibility of the countable variables with normal distribution was checked by Kolmogorov–Smirnov test. Non-parametric tests were applied to the variables without normal distribution after logarithmic transformation, and parametric tests were applied to those with normal distribution. Values not compatible with normal distribution were expressed as
RESULTS

The present study included a total of 54 volunteer patients who were diagnosed with secundum type ASD in the cardiology department and 40 healthy volunteers. There was no significant difference between the two groups in baseline characteristics (Table 1). Furthermore, there was no significant difference between the two groups with respect to hemodynamic parameters of cardiac rate, systolic blood pressure, and diastolic blood pressure. There was no significant difference between the two groups with respect to echocardiography parameters of LVEF, left ventricular end-systolic diameter, and LVEDD (Table 1). However, systolic pulmonary artery pressure (sPAP) and right ventricular diameter (RVD) were significantly higher in patients with ASD than in healthy subjects (Table 1). For patients with ASD, the measured mean sPAP value was 46.3±9.6 mm Hg, whereas the mean RVD value was 4.4±0.5 cm (p<0.001). When both groups were compared, the PWV values were significantly higher in patients with ASD than in healthy subjects. The mean PWV values were 7.5±1.2 m/s in the ASD group and 6.1±1.0 m/s in healthy subjects (p<0.001) (Figure 1).

In patients with ASD, a significant difference was found between sPAP values measured prior to and 1 month after the closing procedure (p<0.001). The mean sPAP value was measured as 46.3±9.9 mmHg before the closure of the defect, whereas the mean sPAP value measured 1 month after the closing procedure was 29.2±6.6 mmHg. The sPAP values of patients with ASD measured at 1 month of follow-up were lower than those measured in healthy subjects, and the difference was observed to disappear (p=0.168). There was a significant difference between the RVD values of patients with ASD measured prior to and 1 month after the procedure of closing the defect by the transcatheter route (p<0.001). The mean RVD values were 4.4±0.5 cm prior to the procedure and 3.6±0.2 cm 1 month after the procedure. On follow-up 1 month after closing the defect by the transcatheter route, right ventricular defect was seen to reduce the level of that seen in healthy subjects (p=0.232). There was a significant difference in patients with ASD between LVEF value measured prior to and 1 month after the closing procedure (p<0.001). There was a significant difference in patients with ASD between LVEDD value measured prior to and 1 month after the procedure (p<0.002). On follow-up, it was found that LVEDD values were higher 1 month after the closing procedure than prior to the procedure. There was a significant difference in patients with ASD between TAPSE value, which was a marker of right ventricular systolic function, measured prior to and 1 month after the procedure (p<0.001). The TAPSE value was measured as 29.2±6.6 mmHg before the closure of the defect, whereas the mean TAPSE value measured 1 month after the closing procedure was 22.2±6.6 mmHg. There was a significant difference in patients with ASD between PWV value measured prior to and 1 month after the closing procedure (p<0.001). There was a significant difference in patients with ASD between PWV value measured prior to and 1 month after the procedure (p<0.001). When both groups were compared, the PWV values were significantly higher in patients with ASD than in healthy subjects. The mean PWV values were 7.5±1.2 m/s in the ASD group and 6.1±1.0 m/s in healthy subjects (p<0.001) (Figure 1).

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was detected, whereas a negative correlation was observed with TAPSE (PWV and Qp/Qs, sPAP, RV, and TAPSE correlations, respectively: r=0.515 (medium), r=0.510 (medium), r=0.521 (medium), and r=–0.489 (medium)) (Figure 3).

DISCUSSION

The present study showed that PVW, a marker of endothelial function, was significantly higher in patients with ASD than in healthy subjects. When the values obtained at the first month of follow-up after the closing procedure were compared with those before the procedures and those obtained from healthy subjects, sPAP, RVD, and PWV values were observed to decrease significantly relative to baseline. Additionally, correlation analysis revealed that the PWV value in patients with ASD showed a significant positive relationship with sPAP, RVD, and the Qp/Qs ratio and a significant negative relationship with TAPSE, which was a marker of right ventricular systolic function.

PHT is the most serious complication of ASD and the most significant cause of early mortality and reduced functional capacity in these patients (10, 11). Previous studies showed that patients with PHT had endothelial dysfunction independent of its cause (12, 13). In view of this, we considered that PHT would develop, and thus PWV might be elevated in patients with ASD.
Measurement of arterial stiffness has been a prominent diagnostic tool in assessing endothelial function in recent years. Arterial stiffness indicates the elasticity and dispensability properties of the arterial wall (5). Recently, it has been demonstrated that increased arterial stiffness is a risk factor for diseases with high mortality and morbidity, such as myocardial infarction and stroke, and a predictor of end-organ damage independent of other risk factors (14). As a consequence of closing ASD by ASO, the volume load of the right heart is reduced. Thus, reduction in PAP and downsizing in the right cardiac chambers occur, and right ventricular systolic function improves. With the defect being closed, all disorders are reversible (15). One may consider that improvements in left ventricular function and hemodynamic parameters would positively affect endothelial function and would correct PWV values that are an important marker of endothelial function.

In our study, the increase in PWV in the ASD group compared with the control group was an example of endothelial dysfunction due to ASD. There is little information in the literature on the direct relationship of ASD with systemic endothelial dysfunction in patients with ASD. Nonetheless, it is possible that endothelial dysfunction may occur secondarily to PHT due to left-to-right shunt in these patients. In our study, because we had a high proportion of patients with PHT, we built our hypothesis based on this. Previous studies showed that patients with PHT had endothelial dysfunction independent of its cause (12). Impaired endothelial function due to PHT leads to a decrease in the production of vasodilator agents, such as 5-lipoxygenase, nitric oxide (NO), and prostacyclin, and increased production of vasoconstrictor mediators, such as endothelin and thromboxane A2 (3). In our study, this may be the reason why PWV values change before and after the procedure. Another study that supports our study showed that the plasma level of asymmetric dimethylarginine, which was a marker of endothelial function, was higher in patients with congenital heart disease with PHT than in patients with congenital heart disease with normal PAP and in the control group (16).

Several studies demonstrated that patients with PHT were found to have significantly higher levels of endothelin 1 (ET-1) in the peripheral and arterial blood than the control group (17, 18). Lu et al. also found that patients with systolic PAP at 30 mm Hg have significantly lower NO levels than the control group, whereas plasma ET-1 levels are significantly higher in patients with congenital heart disease with PHT than in patients with congenital heart disease with normal PAP and in the control group (19). Pirincicglu et al. found that levels of inflammatory cytokines, such as fibrinogen, interleukin-6, tumor necrosis factor-alpha, and high-sensitivity C-reactive protein (hsCRP), and some oxidative stress markers are significantly higher in children with congenital heart disease, including ASD, than in the control group (20). Quark et al., in their study of patients with PHT, found hsCRP levels to be higher than normal and found a significant decrease in hsCRP levels by decreasing pulmonary pressure by treatment of PHT. Considering that hsCRP is one of the markers of endothelial functions, it can be concluded that endothelial functions are impaired by an increase in pulmonary artery pressure (21). Another reason suggesting that there might be endothelial dysfunction in patients with PHT is that blood level of reactive oxygen species and some oxidative stress markers are shown to increase in these patients (22, 23, 24). Increased oxidative stress is viewed as one of the main mechanisms in the pathogenesis of endothelial dysfunction and a common result of impacts of the risk factors on endothelial dysfunction (25).

Overall, all these findings suggest that endothelial function in patients with ASD may be impaired secondary to PHT due to increased pulmonary arterial blood flow.

In keeping with findings, PWV value was significantly higher in patients with ASD who developed PHT; in addition, PWV significantly decreased as a result of closing the ASD by the percutaneous route, and PAP was reduced. In this finding, we support our hypothesis. There was no significant difference between PWV values measured after closing the defect and those measured in healthy volunteers. The reason for the decrease in PWV value measured after closing the ASD by the transcatheter route may be the positive hemodynamic effects on the left heart and disappearance of mechanisms considered to lead to endothelial dysfunction in patients with PHT mentioned beforehand as a result of reduced PAP.

Pascotto et al. investigated the changes in cardiac re-modeling after closing the defect by the transcatheter route and found that approximately 50% of the changes in the cardiac re-modeling occur within the first 24 h, and that 90% of the changes occur within the first month (2). Similar to the results of other studies, most of our parameters have been corrected in the first month.

The main limitation of the present study was that changes in the endothelial function could have been monitored more comprehensively by hemodynamic and biochemical parameters. Another limitation was that the follow-up time for changes in endothelial function in our patients was short.

In conclusion, we found in our study that there was a significant relationship between PWV values and TAPSE, indicating right ventricular systolic function, systolic PAP, Qp/Qs ratio, and RVD. Additionally, PWV value was shown to improve as a result of the disappearance of the negative effects caused by ASD in the right heart and pulmonary vasculature. PHT secondary to ASD may the other cause of endothelial dysfunctions and reversible after closure. More comprehensive long-term studies are needed on the role of PWV in the diagnosis, treatment, and prognosis of patients with ASD.

Ethics Committee Approval: The present study was approved by the ethics committee of Erciyes University (approval date 2011/174).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – DE, ŞK, MFB; Design – DE, ŞK, AT; Supervision – DE, AD, AO, NK; Materials – DE, SK, ZÇ, RT; Data Collection and/or Processing – ŞK, DE, AT; Analysis and/or Interpretation – DE, ŞK, AD; Literature Search – DE, ZÇ, MTI; Writing – DE, ŞK, NK; Critical Reviews – DE, RT, AO.

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