Predictors for Regression of Large Secundum Atrial Septal Defects Diagnosed in Infancy

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Purpose: To determine predictive factors of spontaneous closure or size reduction in large secundum-type atrial septal defects (ASD) diagnosed in infancy prior to catheterization or surgical intervention.

Methods: From June 2003 to October 2009, 59 infants diagnosed with secundum-type ASDs measuring ≥ 8 mm in the first year of life were retrospectively enrolled. We reviewed medical records, as well as electrocardiography and echocardiography findings. Patients were divided into 2 groups according to the last ASD size: group A (n = 23), ASD reduction in size to < 5 mm or spontaneous closure; group B (n = 36), size of ASD remained ≥ 5 mm.

Results: The ASDs spontaneously closed in 10 (17%) patients at a median age of 26.0 ± 5.1 months (range, 15-58 months), or decreased to < 5 mm in 13 (22%) (range, 6-27 months) patients. There was a significant difference in age at diagnosis between the 2 groups (p = 0.014). Patients in group A were younger than those in group B at the time of diagnosis. Changes in ASD size (p < 0.001) and body weight percentile (p = 0.01) were also significantly different from the 6-month follow-up. ASD diameter of ≥ 10 mm was a negative predictive factor for size reduction (p = 0.017).

Conclusions: Spontaneous closure or size reduction of large ASDs was not uncommon in patients diagnosed during infancy. Patients with initial ASD sizes between 8 and 10 mm who were younger at the time of diagnosis and showed better weight gain were more likely to have favorable outcomes.

Key Words: Infancy • Large secundum atrial septal defect • Natural course • Spontaneous closure

INTRODUCTION

Most secundum atrial septal defects (ASDs) are well-tolerated in infancy. Small ASDs, defined as those with diameters of less than 5 mm, have stable hemodynamics and high rates of spontaneous closure during infancy.1 Large ASDs are defined as those with diameters of > 8 mm. A series of studies showed that these ASDs rarely decreased in diameter or closed spontaneously because of large left-to-right shunting.1,2 A large ASD should be closed surgically or through interventional catheterization to prevent progression of pulmonary hypertension, atrial arrhythmia, or heart failure. It is recommended that the optimum period during which to close ASDs through interventional catheterization is when certain signs and symptoms are observed, such as large ASDs with right heart volume overload or pulmonary-to-systemic flow ratio is above 1.5. This window of opportunity typically arises when children are between two and four years of age, but they may be even older.3

Before intervention, clinicians should evaluate ASD size, patient growth, body weight gain, and signs of heart failure. Echocardiography and electrocardiography
(ECG) should be performed regularly to monitor ASD size and to detect evidence of right heart dilatation or pulmonary hypertension. Information about the natural course of large ASDs is useful for decisions regarding clinical management. The aim of the present study was to analyze predictive factors of spontaneous closure or regression in size of large ASDs in infants.

MATERIALS AND METHODS

From June 2003 to October 2009, 59 infants (18 boys and 41 girls) less than 1 year of age, with large secundum-type ASD (defined as ASDs with diameters of ≥ 8 mm) were enrolled in our study. The nature of our study was retrospective, and data collection was approved by the Institutional Review Board of Chang Gung Memorial Hospital. Exclusion criteria included the presence of multiple ASDs, and then combined with other congenital heart diseases, observation time less than 24 months before closure of ASDs, or failure to attend follow-up visits.

We followed-up patients regularly, according to their clinical indications. Reduction in ASD size was defined as a decrease to less than 5 mm, as measured on 2 separate occasions. All 59 patients were divided into 2 groups, as determined by the ASD size at the last patient visit. Patients in group A showed significant reductions in ASD size to < 5 mm or spontaneous closure. Among group B patients, ASDs remained at ≥ 5 mm in size.

Medical records were reviewed, including chest radiography, ECG, echocardiography, and cardiac catheterization. These medical records also included information on age at diagnosis, gender, body weight, and weight percentile according to the World Health Organization (WHO) Child Growth Standards database, clinical symptoms, medication used (digoxin and/or furosemide), and whether device closure was performed. ECG was recorded as rhythm, conduction, and right ventricular hypertrophy (RVH) by age-related interpretation.

Complete echocardiography examination was performed using the Philips SONOS 7500 system (Philips, Andover, MA, USA). Data were collected using 2-dimensional images, M-mode transducer, pulse wave/continuous wave, and color flow Doppler. The maximal diameter of ASDs obtained by 2-dimensional imaging was measured in the subcostal coronal and sagittal views during the cardiac cycle, to avoid the risk of overestimating the ASD diameter on color Doppler images. RVH was diagnosed when we observed paradoxical motion of the interventricular septum on the M-mode study and/or the presence of larger right ventricular volume than left ventricular volume on the apical four-chamber view. Additionally, echocardiographic evaluations were reviewed by 2 cardiologists.

Transcatheter closure of ASD with the Amplatzer Septal Occluder (ASO; AGA Medical Corp., Golden Valley, MN, USA) was performed for patients who fulfilled the closure criteria, including age of more than 2 years, body weight over 10 kilograms, ratio of pulmonary blood flow to systemic blood flow (Qp/Qs ratio) ≥ 1.5, and/or presence of RVH.

Groups A and B were compared in terms of gender, gestational age at birth, age at diagnosis, initial minimal heart rate, presence of RVH, medical therapy, and associated cardiac anomalies. ASD diameter and weight percentile were recorded during the 3-, 6-, 12- and 24-month follow-up visits. The timing of the last follow-up visit varied with patient age and time of follow-up.

Statistical analysis

The statistical analysis was performed with the Statistical Package for the Social Sciences version 19 (SPSS, Chicago, IL, USA). The non-parametric data were expressed as mean ± standard error or median (range). Clinical parameters as categorical variables between 2 groups were compared by chi-square test or Fisher’s exact test, as appropriate. Quantitative variables as comparisons of serial ASD size and body weight percentile were performed using the Mann-Whitney U test. A Kaplan-Meier survival function was used to predict ASD closure as a function of time, and the log-rank test was used for comparison of two curves. A p value of < 0.05 was considered significant.

RESULTS

The median age at diagnosis was 4.0 months (range, 5 days to 11 months), and the median ASD diameter upon diagnosis was 9.4 ± 0.3 mm (range, 8.1-19.0 mm). The median duration of follow-up was 33.5 ± 2.1 months.
The clinical symptoms at the time of diagnosis included heart murmur (90%), respiratory distress (8%), and arrhythmia (2%).

There were 23 patients in group A and 36 patients in group B; their clinical characteristics are shown in Table 1. There were no statistically significant differences between the groups with respect to gender, right heart dilatation, initial weight percentile, or gestational age at birth. Patients in group A were significantly younger at the time of diagnosis than were patients in group B (3.0 ± 0.6 months vs. 5.1 ± 0.5 months, respectively; p = 0.014).

Beginning at the 6-month follow-up visit, changes in ASD diameter sizes in the 2 groups were significantly different (-2.83 ± 0.54 mm vs. 0.54 ± 0.45 mm, p = 0.001; Figure 1). Overall, 13 patients (22%) showed reduced ASD sizes of < 5 mm at the median age of 13.0 ± 1.6 months (range, 6-27 months). Ten patients (17%) had spontaneously closed ASD at the median age of 26.0 ± 5.1 months (range, 15-58 months). Thirty patients (51%) underwent transcatheter closure of ASD at a median age of 40 months (range, 25-114 months). The median diameter of ASDs treated with transcatheter closure was 13.2 ± 0.9 mm (range, 8.2-26 mm), as measured by transthoracic echocardiography (TTE) before intervention.

Growth was evaluated by body weight gain. The weight percentiles were not significantly different between group A and group B at the time of diagnosis (37 ± 6 percentile vs. 31 ± 4 percentile; p = 0.448). During follow-up at the 6 and 12 month visits, the weight percentile was significantly higher in group A than in group B (at the 6th month: 54 ± 7 percentile vs. 30 ± 4 percentile, p = 0.005; at the 12th month: 55 ± 6 percentile vs. 35 ± 5 percentile, p = 0.012; Figure 2). It also happened at the time of decreasing ASD size. Our finding suggests that good body weight gain contributes to size reduction in ASD.

The likelihood of ASDs reaching sizes of < 5 mm is described by a Kaplan-Meier survival curve (Figure 3). Patients with ASDs of initial diameters 8-10 mm had a significantly greater likelihood of reduction to < 5 mm than those with ASD initial diameter of > 10 mm (p = 0.017). These data suggest the initial size is an important predictor of size reduction, even in large ASDs.

**DISCUSSION**

The natural courses of ASDs were predicted by ASD

**Table 1.** Clinical characteristics of patients with large atrial septal defect

<table>
<thead>
<tr>
<th></th>
<th>Group A (N = 23)</th>
<th>Group B (N = 36)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>6/17</td>
<td>12/24</td>
<td>0.773</td>
</tr>
<tr>
<td>Prematurity†</td>
<td>4</td>
<td>2</td>
<td>0.196</td>
</tr>
<tr>
<td>Age at diagnosis (month)</td>
<td>3.0 ± 0.6</td>
<td>5.1 ± 0.5</td>
<td>0.014*</td>
</tr>
<tr>
<td>Initial BW percentile (th)</td>
<td>37 ± 6</td>
<td>31 ± 4</td>
<td>0.448</td>
</tr>
<tr>
<td>ASD size (mm)</td>
<td>9.0 ± 0.3</td>
<td>10.4 ± 0.4</td>
<td>0.081</td>
</tr>
<tr>
<td>Presence of RVH</td>
<td>16</td>
<td>30</td>
<td>0.213</td>
</tr>
<tr>
<td>Medication (digoxin and/or furosemide)</td>
<td>6</td>
<td>20</td>
<td>0.026*</td>
</tr>
</tbody>
</table>

* Significant difference was defined as p < 0.05; † Prematurity: defined as less than 37 weeks’ gestational age.

Group A, reductions in ASD size of < 5 mm or spontaneous closure; Group B, ASDs remained at ≥ 5 mm in size.

ASD, atrial septal defect; BW percentile, body weight percentile; RVH, right ventricular hypertrophy.
sizes and patient age in earlier studies. Small ASDs were defined as those with a diameter of 3-5 mm because of stable hemodynamics with small left-to-right shunting. Small ASDs had a high spontaneous rate of closure (87%) in infancy. ASDs with diameters between 5 and 8 mm were defined as a moderate size. However, medical follow-up is suggested because these ASDs may decrease or increase in size. ASDs with diameters of > 8 mm were called large ASD. In previous studies, these ASDs rarely show spontaneous decrease in diameter or closure because of their large left-to-right shunting.

Previous studies have shown that spontaneous closure of large ASDs occurs in 0-8% of cases among different age groups. Different sample sizes and variable ages of diagnosis may account for the discrepancy of this study and previous studies. It is of clinical importance to establish some guidelines about the incidence of spontaneous closure or size regression in ASDs among infants aged less than 2 years. However, this study cannot rule out the possibility that, before diagnosis, some patients with large ASDs had reduced their sizes or even spontaneously closed prior to the age of 1 year.

Age at diagnosis and ASD diameter were commonly associated with the incidence of spontaneous closure in the natural course of ASD. For ASDs with the same size, the incidence of spontaneous closures varied according to age at the time of diagnosis. Radzik et al. analyzed ASD patients who were diagnosed before 3 months of age. The overall rate of spontaneous closure was 87%, but no patient had spontaneous closure in the subgroup of large ASD (diameter ≥ 8 mm). Hanslik et al. reviewed the natural course of ASDs in children, and the patients were divided into groups according to ASD size (4-5 mm, 6-7 mm, 8-10 mm or > 10 mm). Spontaneous closure occurred in 12% of patients with ASDs of 8-10 mm in diameter, and in no patients with ASDs of >10 mm in diameter. Twenty-four percent of patients with 8-10 mm ASDs and 9% of those with ASDs > 10 mm experienced regression of ASDs to ≤ 5 mm. Furthermore, children less than 1 year of age at the time of ASD diagnosis experienced higher rates of ASD closure. In this study, we focused on patients with large defects (over 8 mm), who were diagnosed within the first year of life. The overall rate of spontaneous closure was 17%, and the rate of size regression to ≤ 5 mm was 22%. Both of these ratios were higher than those reported in previous studies. For those with ASDs of > 10 mm, there were higher rates of spontaneous closure (9%) and size reduction (14%) among the 22 patients. However, there was less likelihood of regression in size or spontaneous closure among patients with larger ASDs with a size of > 10 mm than those with 8-10 mm ASDs. An ASD diameter of > 10 mm was a negative predictor for spontaneous closure of ASD.
The mechanism responsible for spontaneous ASD closure is unclear. Bostan et al.\textsuperscript{12} reported that the type of interatrial communication was a predictive factor, and that the incidence of spontaneous closure of valve-like openings was higher. Another common theory involves formation of an atrial septal aneurysm (ASA). Brand et al.\textsuperscript{13} suggested that an ASA may play a role in spontaneous closure of the associated ASD. Recently, Demir et al.\textsuperscript{14} examined 9 patients with ASAs and ASDs measuring > 7 mm. All showed decreases in size over time. Defects spontaneously closed in 3 patients. In our group A patients, valve-like openings were detected during serial follow-up in 8 patients. These may be related to anatomic changes and pressure gradients between the 2 atria.\textsuperscript{11,15} Further evaluation was limited because our patients were followed-up by transthoracic echocardiography only, without direct measurement of atrial pressures.

Failure to thrive was common in patients with congenital heart disease.\textsuperscript{16-18} Growth was generally better among patients in group A. Patient body weight percentiles were significantly higher in group A than in group B, and the difference was noted at the time of ASD diameter with rapid reduction at 6-12 months follow-up. There was a good correlation with the rate of size reduction and weight gain in the first year of follow-up. It was further shown that better weight gain was a good predictor of ASD size reduction in this study.

However, these data should be verified in larger patient studies and over longer follow-up periods. In addition, the change in ASD diameter was significantly different between the 2 groups in our study since the 6-12 month follow-up. Therefore, close medical follow-up of infants with ASD is recommended from the time of diagnosis.\textsuperscript{19}

We excluded large ASDs associated with left-side cardiac anomaly in this study. In our experience, of 5 patients with coarctation of the aorta (CoA) or patent ductus arteriosus (PDA), ASDs spontaneously closed in 4 patients after resolution of these left-side problems. Yeager et al.\textsuperscript{20} reported 9 cases with ASD and coarctation, including 4 defects measuring > 8 mm; these ASDs either closed or decreased in diameter after resolution of coarctation. According to Riggs et al.,\textsuperscript{21} large PDA may cause elevated left atrial pressure, resulting in dilation of the edges of the ASDs. We suggest that resolution of the left-side anomaly could promote spontaneous closure or reduction of ASD, even in large defects.

Finally, measurement of the size of secundum ASDs was a limitation of our study because measurement of the maximal diameter may have been hampered by the oval shape of defects and cardiac cycle. For the median size of ASDs in the neonates or young infants, an ASD diameter between 5-8 mm could be relatively large when comparing this to intact interatrial septal length. Besides the evaluation of an absolute diameter of ASDs, we could record the area of ASDs, the ratio of ASD diameter to body surface area or the ratio of ASD diameter to interatrial septal length to predict the defect size for further studies. The factors influencing closure of ASDs may be related to defect shape, ratio of pulmonary to systemic blood flow, or right heart volume overload. Given the limitations of transthoracic echocardiography and the invasiveness of transesophageal echocardiography, transthoracic 3-dimensional echocardiography may provide accurate measurements of the maximal diameters and rims of ASDs.\textsuperscript{22,23}

**CONCLUSION**

In our study, we focused on the early diagnosis of large ASDs with diameters > 8 mm in infancy. Compared with previous studies, the present study showed an elevated possibility of spontaneous reduction in size or closure for large ASDs diagnosed in infancy, especially those measuring between 8 and 10 mm in diameter. Additionally, it was observed that younger age at diagnosis and better weight gain were positive predictors. However, an ASD diameter of > 10 mm was still a negative predictor.

**REFERENCES**