Influence of Left Ventricular Stiffness on Hemodynamics in Patients With Untreated Atrial Septal Defects

Clara Kurishima, MD; Ryo Inuzuka, MD, PhD; Seiko Kuwata, MD; Yoichi Iwamoto, MD, PhD; Masaya Sugimoto, MD, PhD; Hirofumi Saiki, MD, PhD; Hirotaka Ishido, MD, PhD; Satoshi Masutani, MD, PhD; Hideaki Senzaki, MD, PhD

**Background:** Although left ventricular (LV) stiffening with age is believed to increase left-to-right shunting in patients with atrial septal defects (ASD), clinical data have not confirmed this. We sought determinants of the pulmonary-to-systemic flow ratio (Qp/Qs) in patients with untreated ASD.

**Methods and Results:** We retrospectively studied 180 patients with ASD who underwent percutaneous ASD closure between 2007 and 2011. Qp/Qs and LV stiffness were measured before ASD closure. The median age of the subjects was 18 years, and 117 (65.0%) were female. The mean ASD size adjusted for square root of body surface area (BSA) was $14.4\pm4.2\text{mm/m}$, and the Qp/Qs was $2.28\pm0.74$. Adjusted ASD size most strongly related to Qp/Qs ($r=0.74$, $P<0.0001$). Multivariate analysis revealed that LV stiffness was a significant predictor of Qp/Qs, independently of adjusted ASD size and vascular resistance ($P=0.0015$). Based on the multivariate model that accounts for the effects of LV stiffness and vascular resistance, the minimal adjusted diameter that can cause a Qp/Qs of 2.0 was predicted to be 7.3 mm/m.

**Conclusions:** Qp/Qs in ASD can change significantly depending on LV stiffness, suggesting that it would increase with age. An ASD >7.3 mm/m in diameter has the potential to cause significant left-to-right shunting, and may require closure regardless of hemodynamic status at the time of assessment. (*Circ J* 2015; 79: 1823 – 1827)

**Key Words:** Cardiac catheterization; Congenital heart defects; Vascular resistance

Atrial septal defects (ASD) are the third most common type of congenital heart disease and more patients with asymptomatic ASD are being diagnosed because of improved recognition of clinically silent defects by echocardiography. When an ASD is left untreated, heart failure, arrhythmias, pulmonary hypertension, and sometimes, paradoxical thromboembolism, can develop. Thus, an ASD with a significant left-to-right shunt is an indication for surgical or percutaneous closure. However, it is often difficult to define a “significant shunt” in an ASD based on a single assessment, because the magnitude of the shunt is determined not only by the size of the defect but also by the relative atrial pressures, and thus may change with time. In this sense, left ventricular (LV) diastolic stiffening, which often accompanies aging, would result in higher left atrial pressure, leading to increased left-to-right shunting. However, whether or not LV stiffness affects the magnitude of the shunt has never been tested. Therefore, we sought determinants of the pulmonary-to-systemic flow ratio (Qp/Qs) in patients with an untreated ASD and investigated whether or not LV stiffness has clinical relevance in terms of hemodynamic burden.

**Methods**
We retrospectively reviewed the clinical charts of 184 consecutive patients with an ostium secundum ASD who had undergone device closure between July 2007 and December 2011. Those with other congenital heart diseases, such as patent ductus arteriosus, ventricular septal defect and valvular diseases, were not included. We excluded 4 patients who were on oxygen during hemodynamic evaluations from the study to eliminate the acute effect of oxygen administration on Qp/Qs, so a total of 180 patients were studied. This study was approved by the local ethics committee at Saitama Medical University (No. 11-143).

**Procedures**
Hemodynamic evaluation, angiography, and device closure of
the ASD using an Amplatzer septal occluder (AGA Medical, Plymouth, MN, USA) were performed under general anesthesia. The size of the device was determined using transesophageal echocardiography and a sizing balloon. The device was deployed and released under fluoroscopic and ultrasound guidance. ASD size was defined as the size of the finally deployed and released under fluoroscopic and ultrasound guidance. The size of the device was determined using transesophageal echocardiography and a sizing balloon. The device was placed device rather than the diameter as measured using transesophageal echocardiography, because the shape of the defect was not always round. An adjustment for body surface area (BSA) was made as follows:

\[
\text{Adjusted ASD size (mm/m)} = \frac{\text{device size (mm)}}{\sqrt{\text{BSA}(m^2)}}
\]

We assumed a linear relation between ASD diameter (mm) and the square root of BSA (m), because, in normal children, vascular and valve diameters are reported to relate linearly to the square root of BSA. Pulmonary and systemic blood flows were determined using the Fick method based on assumed systemic flow/heart rate. Active stiffness of the LV was defined as follows:

\[
\text{LV stiffness (mmHg·ml}^{-1}·m^2) = \frac{\text{LVEDP(mmHg)} - \text{LVminP(mmHg)} × \text{BSA(m})^2)}{\text{LV stroke volume (ml)}} × \text{BSA(m}^2),
\]

where LVEDP and LVminP were LV end-diastolic pressure and LV minimum pressure, respectively.11-13

**Statistical Analysis**

Categorical variables were expressed as a percentage of the total, and comparisons between groups were performed using Fisher’s exact test. Numerical values were expressed as mean±standard deviation or median (interquartile range) as appropriate.

Univariate and multivariate linear regression analyses were used to assess the relationship between Qp/Qs and variables. For linear regression analysis, logarithmic transformation of age was performed due to the positively skewed distribution of the parameter. Variables for multivariate modeling were selected from univariate predictors in a stepwise forward manner based on Akaike information criterion (criteria for entry and retention were set at P<0.05). Homoscedasticity of the errors and normality of the error distribution was checked using the Breusch-Pagan test and normal probability plot. A P-value <0.05 was considered indicative of statistical significance. Analyses were performed using R version 3.0.1 (http://cran.r-project.org/).14

### Results

#### Baseline Clinical Data

The baseline clinical data of the 180 patients are presented in Table 1. The median age was 18 years (range 4-78), and 117 (65.0%) were female. Size of the ASD measured based on the placed device was 14.4±4.2 mm/m after adjustment for BSA (7-34 mm in absolute diameter). Larger adjusted ASD size was associated with older age in the study cohort (r=0.28, P=0.0001). No migration or erosion of the ASD device occurred in this study cohort, suggesting that the placed device was not under- or oversized.

#### Hemodynamic Data

Table 2 summarizes the hemodynamic data. The mean Qp/Qs was 2.27±0.74. Only 2 patients had a mean pulmonary arterial pressure >25 mmHg. The ratio between the pulmonary and systemic resistance (Rp/Rs) ranged from 0.0069 to 0.18 (median 0.05). Rp/Rs was related to ASD size (r=−0.17, P=0.02), but not to age or sex (P=0.97 and 0.08, respectively). LV diastolic stiffness was 0.30±0.12 mmHg·ml<sup>−1</sup>·m<sup>2</sup> and was not related to age, sex, or ASD size (P=0.33, 0.27, and 0.59, respectively).

#### Determinants of Pulmonary-to-Systemic Flow Ratio

Adjusted ASD size strongly related to Qp/Qs (r=0.74, P<0.0001, Figure 1). Other univariate predictors for higher Qp/Qs included older age (r=0.22, P=0.003), lower Rp/Rs (r=−0.50, P<0.0001), and higher LV stiffness (r=0.22, P=0.003). Sex and heart rate were not related to Qp/Qs (P=0.09 and 0.30, respectively). After inclusion of age, adjusted ASD size, LV stiffness and Rp/Rs in the multivariate stepwise regression analysis, only adjusted ASD size (P<0.0001), Rp/Rs (P<0.0001), and LV stiffness (P=0.0015) remained in the final model (Table 3). Age was not an independent predictor of Qp/Qs on multivariate analysis. The sum of squared residuals reduced by 64% (from 0.45 to 0.29), compared with that observed with a univariate prediction based on ASD size alone. Based on the multivariate model, variations of Qp/Qs corresponding to the actual variations in vascular resistance and LV diastolic stiffness were estimated to be ±0.60 (Figure 2). The mean adjusted ASD diameter leading to a Qp/Qs of 2.0 was 12.1 mm/m (16.1 mm for BSA of 1.75 m<sup>2</sup>), and an adjusted diameter as small as 7.3 mm/m (9.6 mm for BSA of 1.75 m<sup>2</sup>) was predicted to cause a Qp/Qs of 2.0 with low Rp/Rs and high LV stiffness.

### Table 1. Baseline Clinical Data of the Study Patients With ASD

<table>
<thead>
<tr>
<th>n</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR), years</td>
<td>18.0 (10.8-42.0)</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.39±0.37</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>117 (65.0)</td>
</tr>
<tr>
<td>Adjusted ASD diameter, mm/m</td>
<td>14.4±4.2</td>
</tr>
</tbody>
</table>

ASD, atrial septal defect; IQR, interquartile range.

### Table 2. Hemodynamic Data of the Study Patients With ASD

<table>
<thead>
<tr>
<th>n</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>74±15</td>
</tr>
<tr>
<td>Cardiac index, L·min&lt;sup&gt;−1&lt;/sup&gt;·m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2.67±1.03</td>
</tr>
<tr>
<td>Systemic vascular resistance, Wood units/m²</td>
<td>25.4±8.83</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, Wood units/m²</td>
<td>1.28±0.58</td>
</tr>
<tr>
<td>Pulmonary-to-systemic resistance ratio</td>
<td>0.05±0.025</td>
</tr>
<tr>
<td>LV systolic pressure, mmHg</td>
<td>92.5±10.9</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mmHg</td>
<td>12.1±2.8</td>
</tr>
<tr>
<td>LV stiffness, mmHg·ml&lt;sup&gt;−1&lt;/sup&gt;·m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.30±0.12</td>
</tr>
<tr>
<td>RV systolic pressure, mmHg</td>
<td>26.5±5.03</td>
</tr>
<tr>
<td>RV end-diastolic pressure, mmHg</td>
<td>9.1±2.5</td>
</tr>
<tr>
<td>Pulmonary-to-systemic flow ratio</td>
<td>2.28±0.74</td>
</tr>
</tbody>
</table>

Data are mean±standard deviation. ASD, atrial septal defect; LV, left ventricular; RV, right ventricular.
Discussion

The present study demonstrates that LV stiffness is indeed a significant determinant of Qp/Qs in patients with ASD, independent of ASD size and vascular resistance. This supports the validity of a generally accepted assumption that Qp/Qs in patients with ASD would increase with age, because of LV stiffening. Moreover, the variation of Qp/Qs attributed to changes in LV stiffness and vascular resistance in patients with the same ASD size was estimated to be ±0.60, which needs to be taken into account when deciding on surgical or percutaneous closure for ASD, especially in borderline cases.

Although the influence of ventricular stiffness on hemodynamics in patients with ASD has already been assumed, its clinical relevance has been unclear. In fact, few studies have investigated the determinants of Qp/Qs in patients with ASD.Fuse et al found a strong correlation between Qp/Qs and defect size, as measured using 2D transthoracic echocardiography. In that study, defect area (mm²) divided by BSA (m²) was used to compare Qp/Qs among patients with different body sizes.
In the present study, we used the adjusted diameter (mm/m) rather than the adjusted defect area (mm$^2$/m$^2$), as clinicians normally consider ASD size as a diameter. Both indices are non-dimensional and equivalent in terms of adjustment. In the study by Fuse et al., a Qp/Qs of 2.0 corresponded to a corrected defect area of 150 mm$^2$/m$^2$ (13.8 mm/m), which was similar to the result of our study in which the mean adjusted diameter was 12.1 mm/m for a Qp/Qs of 2.0 (Figure 2). Importantly, our study clearly shows that significant variations are present in the magnitude of left-to-right shunting in patients with ASD of the same size (Figure 1A), which can be partly explained by variations in LV stiffness. Owing to the cross-sectional design and relatively young study cohort, we were unable to directly demonstrate whether LV stiffness increased with age in patients with ASD. In the present study, age was related to Qp/Qs, as observed from the univariate analysis. This was because older patients had a larger ASD size in our dataset. However, LV stiffening with age is likely to be a universal phenomenon, occurring even in patients with ASD. Therefore, the effect of LV stiffness on Qp/Qs, as noted in the present study, suggests that the magnitude of the shunt in patients with ASD would increase with age.

Pulmonary vascular disease occurs in approximately 5–10% patients with untreated ASD. The pathogenesis of pulmonary arterial hypertension in such patients is unknown. In our study cohort, relative pulmonary vascular resistance was related to ASD size and inversely related to Qp/Qs. Pulmonary hypertension is known to decrease left-to-right shunting in ASD. Conversely, oxygen administration decreases pulmonary vascular resistance and increases pulmonary blood flow in patients with ASD and reversible pulmonary vascular disease. The results of the present study were consistent with such data. However, the precise mechanisms underlying vascular resistance affecting the magnitude of left-to-right shunting remain unclear. Because of the observational nature of our study, we were unable to conclude whether a correlation between relative pulmonary vascular resistance and the magnitude of the shunt represents a cause-effect relationship. This needs to be investigated further in future studies (eg, simulation studies).

The Canadian Consensus Conference on Adult Congenital Heart Disease previously stated that a significant left-to-right shunt with a Qp/Qs >2.0 is an indication for ASD closure, even without pulmonary hypertension. More recent guidelines similarly recommend ASD closure for those with significant left-to-right shunting. However, they define a significant shunt as right ventricular volume overload, rather than Qp/Qs >2.0, reflecting that the magnitude of the shunt can change with time. To quantify possible changes in the magnitude of the shunt, we calculated variations in Qp/Qs corresponding to those in vascular resistance and LV stiffness (Figure 2). The minimal adjusted diameter that can result in a Qp/Qs of 2.0 was predicted to be 9.6 mm/m for a Qp/Qs of 2.0. It has been considered from clinical experience that an ASD must be at least 10 mm in diameter to create a significant left-to-right shunt in an adult. The results of the present study support such clinical experience. Although decisions on ASD closure should not be based solely on the size of the ASD, an ASD >9.6 mm in diameter (7.3 mm/m) may cause significant left-to-right shunting and may need to be closed, regardless of the hemodynamic status at the time of assessment.

Study Limitations
We studied only those who had undergone percutaneous ASD closure and did not include surgically treated patients. More-
over, this was a single-center study including a limited number of patients and age distribution might be different from that of untreated ASD patients in the community. Although this selection bias could have affected demographic data, it is unlikely to have influenced the relationship between ventricular stiffness and Qp/Qs, the main subject of the study. However, external validation would be necessary in further investigations regarding whether or not a longitudinal change in ventricular stiffness in the same individual affects Qp/Qs, as this cross-sectional study only demonstrated that interindividual difference in ventricular stiffness contributed to Qp/Qs. Second, active stiffness was used to assess LV elastic stiffness. Compared with passive stiffness, active stiffness is known to be more susceptible to a change in preload. However, in the present study, the differences in LV stiffness among individuals were not related to ASD size, suggesting that the correlation between LV stiffness and Qp/Qs was not confounded by ASD size (ie, preload). Moreover, ASD size in the present study referred to the device size at placement (ie, stretched size). This method can slightly overestimate the actual ASD size, and this needs to be taken into account when interpreting the results of the study. Finally, in the present study, age-dependent change in BSA-adjusted ASD size was not modeled. In fact, spontaneous closure of ASD is reported in children. In contrast, the size of the ASD may grow with advancing age in the elderly, along with enlargement of atrial size. Although we did not assume that adjusted ASD size is constant during life in the analysis, adjusted ASD size needs to be interpreted together with age. For example, the suggested value for closure in the present study (ie, 7.3 mm/m) should not be applied to asymptomatic small children, in whom spontaneous closure may be expected. Similarly, the suggested value for closure may not be applicable to those with very advanced age, in whom little room for further ventricular stiffening is expected.

**Conclusions**

Qp/Qs in ASD patients can change significantly depending on LV stiffness, suggesting that it would increase with age. Although further longitudinal studies are warranted, an ASD >9.6 mm in diameter (7.3 mm/m) may cause significant left-to-right shunting and may deserve consideration for closure regardless of the hemodynamic status at the time of assessment.

**Acknowledgments**

We thank our colleagues at the International Medical Center at Saitama Medical University who performed cardiac catheterization.

**Conflict of Interest**

None.

**References**