Improvement in Exercise Capacity in Asymptomatic and Mildly Symptomatic Adults After Atrial Septal Defect Percutaneous Closure

Marie-Claude Brochu, MD; Jean-François Baril, MD; Annie Dore, MD; Martin Juneau, MD; Pierre De Guise, MD; Lise-Andrée Mercier, MD

Background—Controversy exists as to whether secundum atrial septal defects (ASDs) in asymptomatic or mildly symptomatic New York Heart Association (NYHA) class I or II adult patients should be closed.

Methods and Results—Thirty-seven patients (24 females; mean age 49.4 years, range 19 to 76) with a mean pulmonary to systemic flow ratio (Qp:Qs) of 2.1 (1.2 to 3.4) had a maximal oxygen uptake (VO\textsubscript{2max}) determination and echocardiographic measurement of right ventricular dimensions before and 6 months after elective percutaneous closure of ASD. At baseline, mean VO\textsubscript{2max} was 23.5±6.4 mL/kg per minute and was higher in the 15 NYHA I patients than in the 22 NYHA II patients (27±6.9 versus 20.8±4.6 mL/kg per minute; P=0.0015). VO\textsubscript{2max} increased significantly at 6 months (23.5±6.4 to 26.9±6.9 mL/kg per minute; P<0.0001). Improvement was as marked in NYHA I (+22%; P<0.0001) as in NYHA II patients (+12%; P<0.0001), in patients with Qp:Qs 1.2 to 2.0 (+16%; P<0.0001) as in those with Qp:Qs >2 (+12%; P<0.0001), and in patients ≥40 years of age (+14%; P<0.0001) as in those <40 years of age (+16%; P<0.0001). Compared with 15 of 37 patients before closure, 35 of 37 patients were in NYHA I at 6 months. Right ventricular dimensions decreased significantly (P<0.0001).

Conclusions—Adult ASD patients significantly increase their functional capacity after percutaneous defect closure. This is observed even in patients classified as asymptomatic, in those with lesser shunts, and in older patients. These findings suggest that ASD closure in an adult population should be considered even in the absence of symptoms. (Circulation. 2002;106:1821-1826.)

Key Words: atrial septal defect □ closure □ exercise capacity

Secundum-type atrial septal defect (ASD) is a common congenital heart defect occurring, often as an isolated lesion, in >3 of 10 000 live births.\textsuperscript{1} Infants may present with poor growth, recurrent lower respiratory tract infection, and heart failure, and older children with fatigue and dyspnea. Many children with moderate left-to-right shunt are asymptomatic, and the condition is detected during routine evaluation of a heart murmur. In the pediatric population, it has long been accepted that elective surgical repair is the treatment of choice for an ASD with significant pulmonary to systemic flow ratio (Qp:Qs ratio of >1.5:1), even if the patient has few or no symptoms.\textsuperscript{1} This choice of treatment is supported by the following observations: (1) Although patients with uncorrected secundum ASD can survive to an advanced age,\textsuperscript{2} their overall life expectancy is shortened; (2) the mortality and morbidity for surgical closure nowadays is <1%\textsuperscript{3} and even less for percutaneous closure; and (3) survival after surgical closure has been shown to be similar to an age-matched control population.\textsuperscript{4}

Despite these conclusions in the pediatric population, a consensus does not yet exist for adult patients with ASD. These patients often come to the attention of the medical profession because of an abnormal ECG or chest x-ray or the discovery of a heart murmur, sometimes in the setting of pregnancy. They usually deny any symptoms despite a significant left-to-right shunt. The aim of our study was therefore to determine if there were any short-term beneficial effects to elective percutaneous ASD closure in asymptomatic or mildly symptomatic adults by evaluating exercise capacity and right ventricular dilatation before and 6 months after the procedure.

Methods

Study Population
All patients referred for percutaneous closure of a secundum ASD at the Montreal Heart Institute between May 1, 2000, and July 1, 2001, and accepted for an elective procedure after transesophageal echocardiographic (TEE) examination were evaluated for inclusion in this study. To be eligible, patients had to be 18 years or older, asymptomatic or minimally symptomatic, New York Heart Association (NYHA) class I or II, and without any other hemodynamically significant structural cardiac anomaly. Patients unable to exercise or
with psychological or psychiatric problems were excluded. The study protocol consisted of a clinical assessment of the functional capacity according to the NYHA functional class criteria, cardiopulmonary exercise testing, and a complete 2D and Doppler transesophageal examination, just before and 6 months after ASD closure. Patients also had a complete hemodynamic evaluation just before closure.

Fifty-five patients were initially evaluated. Three patients did not meet inclusion criteria; 1 with class IV with biventricular heart failure, 1 with an associated patent ductus arteriosus with a significant left-to-right shunt, and 1 with a history of corrected tetralogy of Fallot with mild residual infundibular stenosis and mild pulmonary insufficiency. Two patients were additionally excluded because of an inability to exercise. Two patients declined to participate, and closure was differenced indefinitely by 1 patient, so that 47 patients were enrolled in the study.

Cardiopulmonary Testing
Several days before ASD closure, patients underwent symptom-limited treadmill (Marquette, Case 16) exercise testing using a ramp protocol. Exercise tests were always performed at the same period of the day after at least 2 hours of fasting for each patient. Gas exchange was evaluated during the exercise test with a computerized metabolic cart (Oxycon Alpha, Jaeger). Gas was sampled through a Rudolph mask. Maximal oxygen uptake (VO$_2_{\text{max}}$) was defined as the highest value recorded during the last minute of exercise. The VO$_2$ at the gas exchange anaerobic threshold was determined with the V-slope method. Patients were encouraged to exercise to exhaustion or to a respiratory exchange ratio $\geq$1.09. VO$_2$ at peak exercise was expressed both as mL/kg per minute and as a percentage of the predicted VO$_2_{\text{max}}$ (percent predicted VO$_2_{\text{max}}$) according to age, sex, weight, and height.$^6$ Cardiopulmonary exercise testing was repeated 6 months after successful transcatheter closure.

Echocardiographic Evaluation
All patients had 2D color Doppler echocardiography, shortly before and 6 months after successful defect closure using an Agilent Sonos 5500 ultrasound system. The right ventricle (RV) was qualitatively described as normal, mildly dilated, or severely dilated using the visual integration of 2D parasternal long-axis, short-axis, apical 4 chamber, and subcostal views. Because of the crescent shape of the RV and the fact that no standard method is available to evaluate its volume adequately, quantitative evaluation was limited to 2D measurements. Three measurements of the RV were obtained in the apical 4-chamber view, as follows: (1) the maximal long-axis dimension (LAX), defined as the distance between the RV apex and the midpoint of the tricuspid valve annulus; (2) the short-axis dimension (SAX), defined as the maximal dimension from the right septal surface to the free wall perpendicular to the long axis; and (3) the right ventricular inflow tract dimension (RVIT), also perpendicular to the long axis but measured at the proximal third of the distance between the tricuspid valve annulus and the apex.$^7$ The RV function was qualitatively described as normal, mildly hypokinetic, or severely hypokinetic. Pulmonary artery pressure was estimated using a previously described technique.$^8$ Residual shunting at the atrial level was evaluated at 6 months using 2D color Doppler. Every measurement was done at least 3 times and was averaged to obtain mean values. All patients were in sinus rhythm at the time of their echocardiographic examinations.

Hemodynamic Study
Hemodynamic evaluation and percutaneous closure were performed under general anesthesia with continuous TEE monitoring. Size, localization, and relationship of the defect with the right upper pulmonary vein, mitral and tricuspid valves, inferior and superior vena cava, and posterior wall of the atrium were assessed by TEE. A minimum margin of 5 mm between these structures and the ASD had to be present for the procedure to be initiated.$^9$ The pulmonary artery, RV, and right and left atrial pressures were obtained with standard fluid-filled catheters. With oxygen uptake measured at rest, the Qp:Qs flow ratio was calculated by oxymetry using the Fick principle. Coronary angiography was performed in patients in whom coronary artery disease was suspected. A septal Amplatzer device occluder was then implanted using previously reported techniques.$^{10}$ Absence of residual shunt or obstruction created by the prosthesis was confirmed by TEE. The prosthesis was then released and a final TEE was done to exclude an increase in atrioventricular valve regurgitation or presence of pericardial fluid. Patients were put on enteric-coated aspirin and advised to use antiplatelet prophylaxis for 6 months after the procedure.

Statistical Analysis
All variables are expressed as mean±SD. Continuous variables measured before and 6 months after closure were compared by use of a 2-tailed, paired Student’s t test. Two-way repeated-measures ANOVA was used to compare differences between baseline and 6 months in mean values among subgroups (NYHA, age, and Qp:Qs ratio).

Comparison of the percentage of NYHA I and II functional class at baseline and 6 months after closure was done by a McNemar test. The same test was used to compare preclosure and postclosure RV function. The Bowker test was used to compare qualitative RV dimensions at baseline and 6 months after closure. $P<0.05$ was considered statistically significant.

Results
Percutaneous closure was successful in 37 of the 47 enrolled patients. Mean prosthesis diameter used was 24 mm (range, 14 to 34). The deployment of the prosthesis was not attempted in 3 patients, 2 because of the presence of 2 or more ASDs with margins not amenable to closure by a single device and 1 with a large ASD and significant 2-vessel coronary artery disease requiring surgery. The procedure was unsuccessful in 3 others. These 6 patients were referred for surgical closure. The remaining 4 patients were rescheduled for a repeat procedure using larger size prostheses or new delivery catheters. Procedural complications included small pericardial effusion requiring no specific intervention (2 patients), femoral A-V fistula (2 patients; 1 requiring surgical closure), and migraines (5 patients). Therefore, the study

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Clinical and Hemodynamic Data</th>
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<tr>
<td>No. of Patients (%)</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>&lt;40</td>
</tr>
<tr>
<td>≥40</td>
</tr>
<tr>
<td>Functional status</td>
</tr>
<tr>
<td>NYHA I</td>
</tr>
<tr>
<td>NYHA II</td>
</tr>
<tr>
<td>Atrial arrhythmias</td>
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<tr>
<td>Past</td>
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<tr>
<td>At baseline</td>
</tr>
<tr>
<td>Associated lesions</td>
</tr>
<tr>
<td>CAD (lesion 50%)</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Qp:Qs ≤2:1</td>
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<tr>
<td>&gt;2:1</td>
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<td>Missing</td>
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CAD indicates coronary artery disease.
population consisted of 37 patients (24 women) with mean age of 49.4 years (range, 19 to 76). Mean Qp:Qs overall was 2.1±0.6 (1.2 to 3.4), and the mean systolic pulmonary artery pressure was 36 mm Hg (25 to 66). Additional baseline clinical and hemodynamic data are summarized in Table 1.

No patient was lost to clinical follow-up. After 6 months of follow-up, 35 of the 37 patients had a repeat echocardiogram and 29 underwent reevaluation of VO2max (3 refusals, 1 bursitis of both hips, and 4 studies limited to a standard exercise test). Twenty-nine patients therefore completed the protocol. Mean interval from the hemodynamic procedure to the follow-up VO2max was 6.6 months (5.4 to 13.2 months).

Clinical and Hemodynamic Assessment
At baseline, 15 patients (41%) were in NYHA I and 22 patients (59%) were in NYHA II. NYHA I patients had a significantly lower Qp:Qs than NYHA II patients (1.9±0.4 versus 2.3±0.7; \( P=0.0246 \)).

At 6 months, no patient reported clinical deterioration. Thirty-five patients (95%) were in NYHA I and only 2 patients (5%) were in NYHA II (\( P<0.0001 \)) (Figure 1).

Cardiopulmonary Exercise Testing
At baseline (Table 2), the NYHA I patients had a significantly higher VO2max than the NYHA II patients (27±6.9 versus 20.8±4.6; \( P=0.0015 \)). This represented 89% of the predicted VO2max in NYHA I patients and 77% in NYHA II patients (Figure 2). There were no significant differences in baseline VO2max between patients with a Qp:Qs of 1.2 to 2 and those with a Qp:Qs >2 or between patients <40 years compared with those 40 years and older.

At 6 months, VO2max increased overall by 15% (23.5±6.4 to 26.9±6.9; \( P<0.0001 \)) (Figure 3). This increase was as significant in NYHA I patients (+22%; \( P<0.001 \)) as in NYHA II patients (+12%; \( P<0.0001 \)) (Figure 4). Similar degrees of improvement were observed in patients irrespective of baseline shunt (Qp:Qs =2, +16%; \( P<0.0001 \); Qp:Qs >2, +12%; \( P<0.0001 \)) and age (\( \geq 40\) years, +14%; \( P<0.0001 \); <40 years, +16%; \( P<0.0001 \)) (Figure 5). In NYHA I patients, the percent predicted VO2max returned to normal (89% to 101%; \( P<0.0001 \)), and NYHA II patients significantly improved their performance (77% to 88%; \( P<0.0001 \)). Anaerobic threshold values were similarly higher in class I than in class II patients (22.1±5.7 versus 16.8±4.0; \( P=0.006 \)) and also increased significantly at 6 months (class I +12%; \( P=0.004 \), class II +16%; \( P=0.004 \)).

Only 5 patients did not increase their VO2max at 6 months (1 class I patient, 4 class II patients). Of these, 1 patient had recently been diagnosed with hyperthyroidism and another had had an abdominal hysterectomy 5 weeks before her 6-month evaluation. No distinguishing factors were noted in the other 3 patients. Six patients had a normal VO2max value at baseline (3 class I patients, 3 class II patients). Five of them nevertheless had an increase in exercise capacity at 6 months (+13%; range, 6% to 21%).

**Table 2.** VO2max at Baseline and 6 Months After ASD Closure Overall and for Different Subgroups

<table>
<thead>
<tr>
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<th>Baseline VO2 max</th>
<th>6-Month VO2 max</th>
<th>( P )</th>
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<tbody>
<tr>
<td>Overall</td>
<td>23.5±6.4 (14.0–40.0)</td>
<td>26.9±6.9 (17.0–44.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NYHA I</td>
<td>27.0±6.9 (15.2–40.0)</td>
<td>32.9±5.9 (24.9–44.5)</td>
<td>&lt;0.0001</td>
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<tr>
<td>NYHA II</td>
<td>20.8±4.6 (14.0–31.0)</td>
<td>23.3±4.6 (17.0–34.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Qp:Qs ≤2</td>
<td>23.8±7.3 (15.2–40.0)</td>
<td>27.6±8.3 (17.0–44.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Qp:Qs &gt;2</td>
<td>23.5±5.9 (14.0–36.8)</td>
<td>26.3±6.1 (17.3–38.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age &lt;40 y</td>
<td>25.4±6.6 (16.2–36.8)</td>
<td>29.5±6.4 (19.8–38.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age ≥40 y</td>
<td>22.5±6.3 (14.0–40.0)</td>
<td>25.6±7.0 (17.0–44.5)</td>
<td>&lt;0.0001</td>
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Values are mean±SD (range).
Echocardiographic Evaluation

At baseline (Table 3), 2 patients had a normal size RV, 14 were mildly dilated, and 21 were severely dilated. RV enlargement (qualitative and quantitative) was not correlated with lower functional class, higher Qp:Qs, or increasing age. RV function was normal in 22 patients, and mild hypokinesia was present in 15 patients.

At 6 months, 17 patients had a normal size RV, 17 were mildly dilated, and 1 was severely dilated. This decrease in dimension was significant \( P<0.0001 \) and was congruent with lower functional class, higher Qp:Qs, or increasing age. RV function was normal in 34 patients, and mild hypokinesia was present in 15 patients.

Discussion

Our study shows that a significant improvement in exercise capacity and decrease in RV size occur rapidly after percutaneous ASD closure in adults considered asymptomatic or mildly symptomatic. This benefit is observed irrespective of age or magnitude of shunt and raises questions as to whether the conservative approach often favored for these patients should be revised.

Almost 50 years after the first repair of an ASD was performed, controversy still exists as to whether adult patients, especially if they are asymptomatic or mildly symptomatic, benefit from surgery. This is attributable in part to the absence of updated medical literature on the natural history of unoperated patients and the retrospective and unrandomized nature of the surgical series dealing predominately with symptomatic patients.

As early as 1970, Campbell observed how increasingly difficult it was to determine the natural history of ASD because of the growing number of patients having surgery in infancy. Using necropsy reports and reported patients, he noted that although mortality rate was low in the first 2 decades, it increased significantly thereafter, with half of the patients being alive at age 36 years and only 10% by age 60 years. It is now accepted that his and other series underestimated the life expectancy of patients with ASD.

With the advent of echocardiography to accurately diagnose asymptomatic children and adults with heart murmurs and the practice of prophylactically closing ASDs with significant shunts in early childhood, we are now dealing with a new population of unoperated adult patients who, by definition, have a less severe form of the disease and should have a better prognosis.

Because of the invasive nature of the surgical procedure, most studies have dealt mostly with symptomatic patients (NYHA III to IV) and, when a control group was used, the deciding factor for surgery was either not specified or cited as physician preference. Clinical status before and after operation was based solely on symptoms sometimes reevaluated by written questionnaires or phone interviews as well.
as objective end points such as death, occurrence of arrhythmias, or stroke without any evaluation of functional capacity. Murphy et al\textsuperscript{17} reported on 123 operated adult patients, 75\% of whom were symptomatic, with 76\% of patients over 41 years of age taking digoxin and 48\% taking diuretics. Survival, although longer than historical controls, was significantly shorter than for the normal population.

Jemelietty et al\textsuperscript{17} in a retrospective analysis of 76 patients aged 40 to 62 years at surgery and followed for 6.9 years, found a significant improvement in functional class with 61.8\% patients in NYHA III or IV before surgery compared with 82.4\% in NYHA I or II after surgery.

The same observations were made by Konstantinides et al\textsuperscript{15} in older symptomatic patients. This retrospective nonrandomized study of surgical versus medical therapy demonstrated a considerable reduction in the risk of functional deterioration in the surgical group without any beneficial effect on the incidence of arrhythmia and stroke. Although sometimes lacking in scientific rigor by contemporary standards, these studies suggest that ASD closure benefits many or most symptomatic patients over the age of 40 years.

At the other spectrum of life, asymptomatic as well as symptomatic children are now routinely operated on in early childhood, because it has been shown that they will afterward have a normal life expectancy.\textsuperscript{4}

That the same benefit of ASD closure could be anticipated in asymptomatic or mildly symptomatic adult patients has been questioned by some authors. Shah et al\textsuperscript{14} came to this conclusion after following 82 NYHA I and II patients for 25 years. They found no difference in survival or symptoms between the medical and surgical groups. The same conclusions were reached by Favilli et al\textsuperscript{18} after a shorter follow-up of 72 patients with a mean age of 48 years. More recently, a randomized study to either medical treatment or surgical ASD closure for NYHA I or II patients >40 years old demonstrated that surgical closure decreased the occurrence of long-term major cardiovascular events, primarily because of a decrease in the incidence of recurrent pneumonia.\textsuperscript{19}

Our results confirm the limitations of clinical evaluation of functional class in a chronic disease. Rostagno et al\textsuperscript{20} showed in his study of chronic heart failure patients that concordance between NYHA classification and levels of performance using cardiopulmonary exercise testing was <50\%. Our study shows that subjective evaluation of functional class underestimates the cardiovascular burden of the left-to-right shunt. Patients who considered themselves asymptomatic had a VO\textsubscript{2max} 11\% less than their predicted value, and a subnormal VO\textsubscript{2max} (83\%) was present even in patients with modest left-to-right shunting (QP:Qs 1.2 to 2.0).

Improvement in exercise capacity occurred early after the procedure. This is in contrast to the study by Helber et al\textsuperscript{21} who reported no change in VO\textsubscript{2max} 4 months after surgery but a normalization in the predicted VO\textsubscript{2max} at 10 years; the authors commented that this delay could be explained by the trauma of operation, a situation avoided in our population by the use of a percutaneous device. Because there was no mention of the functional class in the 22 patients who completed the 10-year evaluation, it could not be inferred, however, that the benefit in exercise capacity was present in asymptomatic and mildly symptomatic patients. In our study, the improvement in VO\textsubscript{2max} was significant for the whole group as well as subgroups according to age, functional class, and magnitude of shunt and was comparable to that observed with a standard exercise training program.\textsuperscript{22}

The common observation that patients with congenital disease adapt to their limitations and tend to minimize their symptoms was again verified in our group, because only 6 patients had normal VO\textsubscript{2max} values. Because 5 of 6 patients with normal values nevertheless had an increase in exercise capacity, VO\textsubscript{2max} determination, as well as RV dimensions and functional class, does not seem to be able to predict the patients who will ultimately benefit from the procedure.

None of our patients had established atrial arrhythmias at the time of ASD closure or at follow-up, whereas most studies, even when dealing with NYHA I or II patients, report a 20\% to 25\% incidence of atrial arrhythmias.\textsuperscript{14} Also, Gatzoulis et al\textsuperscript{23} showed that the risk of atrial flutter or fibrillation after surgery is related to the age at the time of surgical repair. These observations, coupled with the short-term benefits of quality of life we have observed, could warrant as aggressive an option in asymptomatic older patients as we have adopted in asymptomatic young children.

**Study Limitations**

Because of the short observation period, the present study was not designed to evaluate the impact of the procedure on the incidence of complications usually associated with long-standing RV volume overload, such as atrial arrhythmias and the associated risk of stroke, heart failure, and death.

**Conclusions**

Based on our results, percutaneous ASD closure in asymptomatic or mildly symptomatic adult patients results in significant rapid improvement of functional capacity and regression of RV dilatation. Because this improvement seems to be present irrespective of age, functional class, RV enlargement, or baseline exercise capacity, the present practice of limiting prophylactic closure of ASD to asymptomatic children should be reevaluated with additional long-term studies.

**References**


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