Table 1. Patient Clinical Characteristics

Variables	
Age (years)	54.5 ± 10.9
Female (%)	70
Smoking (%)	25
Lung disease (%)	15
Hypertension (%)	25
Diabetes mellitus (%)	10
Stroke (%)	5
Atrial septal defect diameter (mm)	17.8 ± 4.3
Device size (mm)	21.7 ± 4.7
Pulmonary to systemic flow ratio	2.6 ± 0.6
Mean pulmonary artery pressure (mmHg)	14.5 ± 4.0
Vital capacity (l)	2.9 ± 0.6
Forced expiratory volume in 1 second (l/second)	2.3 ± 0.6

Data are presented as mean ± standard deviation or percentage.

systemic flow ratio was 2.6 ± 0.6, and mean pulmonary artery pressure under general anesthesia was 14.5 ± 4.0 mmHg. Transcatheter closure of ASD was performed successfully in all patients using an AMPLATZER septal occluder device. All patients were followed up for a mean period of 25.2 ± 10.5 months (range, 12.0–40.8 months). There were no complications including thromboembolic events in the procedural and follow-up period.

Cardiac Remodeling and Exercise Capacity. Time courses of data obtained by transthoracic echocardiography and cardiopulmonary exercise testing at baseline and after the procedure are summarized in Table 2. At baseline, RV enlargement (RV end-diastolic diameter >30 mm) was present in 18 patients (90%). After the procedure, a significant decrease in RV end-diastolic diameter was observed at 1 month, and it was maintained during the follow-up period. Eleven of 18 patients with RV enlargement (61%) achieved a normal RV size (RV end-diastolic diameter <30 mm). In addition, LV end-diastolic diameter increased significantly. Therefore, cardiac remodeling resulted in a decrease in RV/LV end-diastolic diameter ratio at 1 month (Fig. 1). LV ejection fraction and LV end-systolic diameter did not change from baseline. At baseline, 13 patients (65%) had a moderate reduction in cardiopulmonary function and 7 patients (35%) had a severe reduction. After the procedure, predicted peak VO_2 did not change at 1 month and 3 months, but it improved significantly after 6 months (Fig. 2). Predicted peak VO_2 increased overall by 15%, and 16 of the 20 patients (80%), including 10 of the 13 patients with a moderate reduction in cardiopulmonary function and 6 of the 7 patients with a severe reduction in cardiopulmonary function, showed improved predicted peak VO_2 in the follow-up period. In addition, a

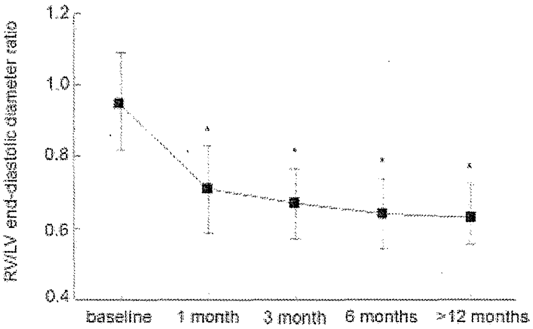

Figure 1. Time course of data on RV/LV end-diastolic diameter after transcatheter closure of atrial septal defect. *P < 0.001 versus baseline. RV = right ventricular; LV = left ventricular.

Table 2. Transthoracic Echocardiography and Cardiopulmonary Exercise Testing at Baseline and After Transcatheter Closure of Atrial Septal Defect

Variables	Baseline	1 month	3 months	6 months	>12 months
LV end-diastolic diameter (mm)	40.7 ± 5.0	45.7 ± 5.3**	46.1 ± 4.7**	46.5 ± 5.3**	46.6 ± 5.2***
LV end-systolic diameter (mm)	24.4 ± 3.9	26.9 ± 3.7	26.2 ± 3.1	26.8 ± 3.9	26.8 ± 3.6
LV ejection fraction (%)	71.2 ± 5.2	72.3 ± 4.0	74.0 ± 4.4	73.4 ± 5.4	73.6 ± 4.7
RV end-diastolic diameter (mm)	38.2 ± 4.4	31.9 ± 4.4***	30.5 ± 3.5***	29.6 ± 3.2***	29.3 ± 2.9***
RV/LV end-diastolic diameter ratio	0.95 ± 0.17	0.71 ± 0.13***	0.67 ± 0.10***	0.64 ± 0.10***	0.63 ± 0.08***
Predicted peak oxygen uptake (%)	53.6 ± 6.5	55.8 ± 11.5	56.8 ± 9.7	62.1 ± 12.6**	61.8 ± 9.7**
Peak oxygen uptake (ml/min/kg)	15.4 ± 2.3	16.3 ± 3.7	16.0 ± 2.9	17.6 ± 3.9*	17.5 ± 3.5*
Oxygen uptake to work rate ratio	7.3 ± 1.8	6.9 ± 1.6	7.9 ± 1.6	8.1 ± 1.7	8.3 ± 1.4*

Data are presented as mean ± standard deviation.
*P < 0.05 versus baseline, ** P < 0.01 versus baseline, *** P < 0.001 versus baseline.
LV = left ventricular; RV = right ventricular.

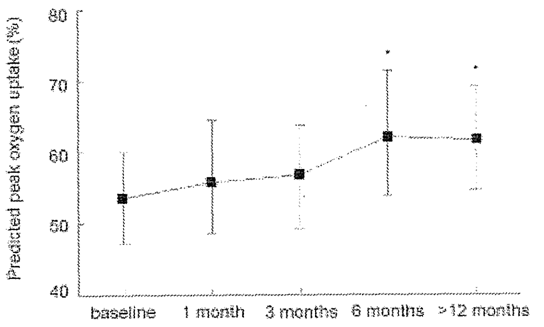

Figure 2. Time course of data on predicted peak oxygen uptake after transcatheter closure of atrial septal defect. *P < 0.01 versus baseline.

significant improvement in $\Delta VO_2/\Delta WR$ was observed at > 12 months after the procedure.

Discussion

In this study, we evaluated long-term functional benefits of transcatheter closure of ASD in middle-aged and elderly patients with a marked reduction in cardiopulmonary function, and we found significant improvements in cardiac remodeling and exercise capacity. Decrease or even normalization of RV size and RV/LV end-diastolic diameter ratio occurred early after the procedure, and they were maintained during the long-term period. Exercise capacity measured by cardiopulmonary exercise testing did not change early, but it improved during the long-term period. We also found the time delay of improvement in exercise capacity compared with cardiac remodeling in those patients. The severity of functional limitation increases with advancing age in the majority of patients with ASD.[1,2] The clinical courses and long-term results after surgery depend mainly on the patient's preoperative clinical status. In the past, controversy existed as to whether middle-aged and elderly patients benefit from surgery. Murphy et al.[11] proved that symptomatic patients who undergo surgery after the age of 40 years were at increased risk for postoperative cardiovascular complications, whereas young adults had an excellent prognosis. However, several studies have demonstrated long-term benefits of surgical ASD closure in middle-aged and elderly symptomatic patients.[3–6] Konstantinides et al.[3] showed that surgical ASD closure in symptomatic patients over the age of 40 years increased long-term survival and prevented deterioration of New York Heart Association (NYHA) functional class during a follow-up period of 8.9 years. Jemielity et al.[4], in patients aged 40–62 years and followed for 6.9 years, also found a significant improvement in functional class with 61.8% patients in NYHA functional class III and IV before surgery compared with 82.4% in NYHA functional class I and II after surgery. These studies indicated that surgical ASD closure benefits many or most middle-aged and elderly symptomatic patients in the long-term period and therefore it is widely recommended for those patients. Recently, transcatheter closure of ASD has been performed safely and effectively, and it has become an alternative to surgical ASD closure.[7,8] Similar to surgical repair, several studies have demonstrated functional benefits of transcatheter closure of ASD in adult patients.[12–15] Giardini et al.[12] evaluated long-term impacts of transcatheter closure of ASD on RV remodeling and exercise capacity in asymptomatic patients, and they found a significant decrease in RV diameter and a significant improvement in peak VO_2. In comparison with this study, their study population was younger and had less severe cardiopulmonary function at the time of the procedure. Our study population consisted of only patients ≥ 40 years of age with a marked reduction in cardiopulmonary function to investigate patients considered at higher risk for functional recovery after the procedure. Regarding middle-aged and elderly patients, Brochu et al.[9] investigated results in asymptomatic or mildly symptomatic patients over the age of 40 years, and they showed that peak VO_2 was increased significantly at 6 months after the procedure. Jategaonkar et al.[10] reported a significant decrease in RV end-diastolic diameter and significant improvements of NYHA functional class and peak VO_2 at 3 months after the procedure even in patients over the age of 60 years. However, little is known about long-term results in those patients. Furthermore, although impaired exercise capacity is a predictive parameter in terms of mortality in congenital heart disease,[16,17] limited information is available for long-term extent of functional improvement in middle-aged and elderly patients with markedly reduced cardiopulmonary function. The recently published study of Khan et al.[18] showed significant improvements in cardiac remodeling and 6-min walk test at 12 months after the procedure in patients over the age of 40 years. Our results are similar to their findings. However, we also evaluated the time course of functional improvements, and we revealed that an improvement in exercise capacity was delayed compared with cardiac remodeling in middle-aged and elderly patients with a marked reduction in cardiopulmonary function. The mechanism leading to improved exercise capacity after the procedure has been clarified. ASD closure with abolishment of left-to-right shunt leads to augmented LV filling by increased preload and therefore to improved stroke volume.[14] The rise in cardiac output may explain the increase of exercise capacity. In this study, we found the time delay of improvement in exercise capacity compared with cardiac remodeling. In addition, even if RV size was normalized in more than half of all patients, mean exercise capacity continued to be at least moderately reduced. Exercise capacity is influenced by several factors, not only cardiac output but also noncardiac factors such as pulmonary function and skeletal muscle function. We speculated that the delay of improvement in exercise capacity could be related to the time needed for the recover of skeletal muscle function after transcatheter closure of ASD in middle-aged and elderly patients with a marked reduction in cardiopulmonary function, but not the time needed for the recover of cardiac function. Similar to our results, Helber et al.[19] showed the lack of improvement in exercise capacity early after surgical ASD closure in patients over the age of 40 years, and they suggested that the improvement in exercise capacity took place after 1–2 years after the procedure. Thus, exercise training after the procedure may be needed to recover the pulmonary function and skeletal muscle function early in those patients.

Study Limitations. This study had some limitations. First, the current findings need confirmation in large studies because this study included only 20 patients from a single center. Second, exercise capacity is also influenced by noncardiac factors, but measurements of those factors are lacking. Finally, the evaluation of RV function using two-dimensional strain echocardiography, three-dimensional echocardiography, or tricuspid annular plane systolic excursion should be preferable to demonstrate RV remodeling after transcatheter closure of ASD.

Conclusion

Transcatheter closure of ASD in patients $\geq$ 40 years of age with markedly reduced cardiopulmonary function resulted in significant long-term improvements of cardiac remodeling and functional capacity. There were differences in the time course of improvement between cardiac remodeling and exercise capacity after the procedure in those patients.

References

1. Fredriksen PM, Veldtman G, Hechter S, et al. Aerobic capacity in adults with various congenital heart disease. Am J Cardiol 2001;87:310–314.
2. Markmann P, Howitt G, Wade EG. Atrial septal defect in the middle-aged and elderly. Quant J Med 1965;34:409–426.
3. Konstantinides S, Geibel A, Olschewski M, et al. A comparison of surgical and medical therapy for atrial septal defect in adults. N Engl J Med 1995;333:469–473.
4. Jemielity M, Dyszkiewicz W, Paluszkiewicz L, et al. Do patients over 40 years of age benefit from surgical closure of atrial septal defects? Heart 2001;85:300–303.
5. Nasrallah AT, Hall RJ, Garcia E, et al. Surgical repair of atrial septal defect in patients over 60 years of age. Long-term results. Circulation 1976;53:329–331.
6. Sutton MG, Tajik AJ, McGoon DC. Atrial septal defect in patients aged 60 years or older: Results and long-term postoperative follow-up. Circulation 1981;64:402–409.
7. Masura J, Gavora P, Formanek A, et al. Transcatheter closure of secundum atrial septal defects using the new self-centering amplatzer septal occluder: Initial human experience. Cathet Cardiovasc Diagn 1997;42:388–393.
8. Masura J, Gavora P, Podnar T. Long-term outcome of transcatheter secundum-type atrial septal defect closure using Amplatzer septal occluders. J Am Coll Cardiol 2005;45:505–507.
9. Brochu MC, Baril JF, Dore A, et al. Improvement in exercise capacity in asymptomatic and mildly symptomatic adults after atrial septal defect percutaneous closure. Circulation 2002;106:1821–1826.
10. Jategaonkar S, Scholtz W, Schmidt H, et al. Percutaneous closure of atrial septal defects: Echocardiographic and functional results in patients older than 60 years. Circ Cardiovasc Interv 2009;2:85–89.
11. Murphy JG, Gersh BJ, McGoon MD, et al. Long term outcome after surgery repair of isolated atrial septal defects. Follow-up at 27 to 32 years. N Engl J Med 1990;323:1645–1650.
12. Giardini A, Donti A, Specchia S, et al. Long-term impact of transcatheter atrial septal defect closure in adults on cardiac function and exercise capacity. Int J Cardiol 2008;124:179–182.
13. Veldtman GR, Razack V, Siu S, et al. Right ventricular form and function after percutaneous atrial septal defect device closure. J Am Coll Cardiol 2001;37:2108–2113.
14. Giardini A, Donti A, Formigari R, et al. Determinants of cardiopulmonary function improvement after transcatheter atrial septal defect closure in asymptomatic adults. J Am Coll Cardiol 2004;43:1886–1891.
15. Schoen SP, Kittner T, Bohl S, et al. Transcatheter closure of atrial septal defects improves right ventricular volume, mass, function, pulmonary pressure, and functional class: A magnetic resonance imaging study. Heart 2006;92:821–826.
16. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: Comparative severity, correlates, and prognostic implication. Circulation 2005;112:828–835.
17. Giardini A, Specchia S, Berton E, et al. Strong and independent prognostic value of peak circulatory power in adults with congenital heart disease. Heart 2007;154:441–447.
18. Khan AA, Tan JL, Li W, et al. The impact of transcatheter atrial septal defect closure in the older population: A prospective study. JACC Cardiovasc Interv 2010;3:276–281.
19. Helber U, Baumann R, Seboldt H, et al. Atrial septal defect in adults: Cardiopulmonary exercise capacity before and 4 months and 10 years after defect closure. J Am Coll Cardiol 1997;29:1345–1350.