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Determinants of Cardiopulmonary Functional Improvement After Transcatheter Atrial Septal Defect Closure in Asymptomatic Adults

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OBJECTIVES We sought to evaluate the course of cardiopulmonary function after transcatheter atrial septal defect (ASD) closure and to identify the physiopathologic mechanisms leading to this change.

BACKGROUND Conflicting reports exist on cardiopulmonary functional improvement in asymptomatic adults after transcatheter closure of a secundum ASD.

METHODS Thirty-two consecutive adults (13 males; age 42.6 ± 16.7 years) underwent maximal cardiopulmonary exercise testing and transthoracic echocardiography both on the day before and six months after transcatheter ASD closure. Mean pulmonary artery pressure, pulmonary to systemic flow ratio (Qp/Qs), and ASD diameter were measured before closure.

RESULTS Peak oxygen uptake (V_{O_2}) ($p < 0.001$), peak oxygen pulse ($p = 0.0027$), and vital capacity ($p = 0.0086$) improved after ASD closure, although peak heart rate did not. A significant correlation was found between peak V_{O_2} improvements and Qp/Qs ($p = 0.0013$). Left ventricular ejection fraction (LVEF) ($p < 0.0001$) and left ventricular end-diastolic diameter (LVEDD) ($p < 0.0001$) significantly increased after six months, although left ventricular end-systolic diameter did not. Right ventricular long- and short-axis dimensions decreased (both $p < 0.0001$). Peak V_{O_2} and of peak oxygen pulse improvements correlated to both LVEF ($p = 0.0009$ and 0.0019, respectively) and LVEDD ($p < 0.0001$ and 0.032, respectively) increments. The decrease of both long- and short-axis right ventricular dimensions positively correlated to both LVEF and LVEDD improvements. The improvement in LVEF correlated to Qp/Qs ($p = 0.0026$).

CONCLUSIONS Transcatheter ASD closure leads to a significant improvement in cardiopulmonary function within six months, via an increase in peak oxygen pulse. An increase in both left ventricular stroke volume and cardiac output due to a positive ventricular interaction is the mechanism leading to improved peak V_{O_2}. (J Am Coll Cardiol 2004;43:1886–91) © 2004 by the American College of Cardiology Foundation

The secundum atrial septal defect (ASD) is a common form of congenital heart disease accounting for approximately 10% of all congenital cardiac defects (1). In children, it has long been accepted that elective surgical repair is the treatment of choice if there is a considerable left-to-right shunt, even in patients with few or no symptoms (2). On the other hand, no consensus exists for adults with an ASD who

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appear to be largely asymptomatic. Even though many adults with an ASD claim to be asymptomatic or refer to only mild symptoms at rest, exercise capacity may be decreased (3) and symptoms can develop during exercise.

Surgical closure of an ASD has been practiced for more than 45 years and, until recently, was considered the standard treatment for adult patients with an ASD (4,5). Transcatheter ASD closure has been increasingly used in recent years with high success rates (6,7) and with complication rates that compare rather favorably with surgical repair (8,9), even in terms of a residual shunt (7) and normalization of right ventricular (RV) dimensions (10,11). Despite these remarkable results, only sparse and contrasting data are available on improvement of cardiopulmonary function after elective percutaneous ASD closure (12,13). Furthermore, the physiopathologic mechanisms that intervene in determining cardiopulmonary function improvement after transcatheter ASD occlusion remain to be identified.

To search for factors and mechanisms that lead to an improved exercise capacity, we investigated the impact of percutaneous ASD closure on exercise capacity in a group of asymptomatic adults, along with the role of the left ventricle (LV) in exercise capacity improvement.

METHODS

Patients and study design. Between June 2001 and September 2002, a total of 32 consecutive "asymptomatic"

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Abbreviations and Acronyms

ASD = atrial septal defect
FEV_1 = forced expiratory volume in 1 s
LV = left ventricle/ventricular
LVEDD = left ventricular end-diastolic diameter
LVEF = left ventricular ejection fraction
LVESD = left ventricular end-systolic diameter
NYHA = New York Heart Association
Qp/Qs = pulmonary to systemic flow ratio
RV = right ventricle/ventricular
TEE = transesophageal echocardiography
TTE = transthoracic echocardiography
VC = vital capacity
V_{O_2} = oxygen uptake

adults underwent cardiopulmonary exercise testing and transthoracic echocardiography (TTE), both on the day before and six months after transcatheter ASD closure (mean age at closure: 42.6 ± 16.7 years). Patient characteristics are shown in Table 1, along with baseline transesophageal echocardiographic (TEE) and right heart catheterization findings. The study protocol consisted of a clinical assessment of functional capacity, according to the New York Heart Association (NYHA) functional class criteria, and cardiopulmonary exercise testing and TTE, both on the day before and six months after the procedure. Patients also had a complete hemodynamic evaluation via cardiac catheterization just before closure of the defect. None of the patients had additional coronary artery disease, valvular heart disease, pulmonary disease, or an inability to exercise.

Cardiopulmonary exercise test. Maximal cardiopulmonary testing was performed on an ergometer cycle (Sensor-Medics, Yorba Linda, California). Peak oxygen uptake (V_{O_2}), carbon dioxide production, and minute ventilation were measured with a computerized breath-by-breath analyzer (V-MAX 29, Sensor-Medics). Patients performed a maximal exercise test using a 1-min incremental bicycle protocol with a work rate increment of 10 W/min. Criteria for test ending were considered patient exhaustion or a respiratory exchange ratio ≥1.09. A 12-lead electrocardiogram was also monitored throughout the study, and cuff blood pressure was determined manually every 2 min. Before exertion, a spirometric measurement was performed to assess forced vital capacity (VC) and forced expiratory volume in 1 s (FEV_1). Standard equations were used to generate predicted values for baseline spirometric and peak exercise parameters (14).

Table 1. Demographic, Echocardiographic, and Right Heart Catheterization Data (n = 32)

Age at closure (yrs)	42.6 ± 16.7 (18–77)
Male gender	13 (40%)
ASD diameter at TEE (mm)	23.6 ± 4.7 (12–32)
Device size (mm) median (range)	26 (18–34)*
Qp/Qs ratio	2.04 ± 0.5 (1.3–3.3)
Mean pulmonary artery pressure (mm Hg)	15.8 ± 4.2 (9–25)
NYHA functional class I	27 (84%)

Data are presented as the mean value ± SD (range), number (%) of patients, or *median value (range).

ASD = atrial septal defect; NYHA = New York Heart Association; Qp/Qs = pulmonary to systemic flow ratio; TTE = transthoracic echocardiography.

Transthoracic echocardiography. All 32 patients had two-dimensional color Doppler TTE on the day before and six months after ASD closure, using a Sonos 5500 ultrasound system (Agilent Technologies, Palo Alto, California). The examination focused on the measurement of left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular ejection fraction (LVEF) (calculated according to the Teicholz method), and left atrial diameter from the long-axis parasternal view. Two measurements of the RV were made in the apical four-chamber view: maximal RV long-axis dimension, defined as the distance between the RV apex and the mid-point of the tricuspid valve; and RV short-axis dimension, defined as the maximal dimension from the right septal surface to the free wall perpendicular to the long axis. The parasternal long-axis view was used to evaluate the presence of a paradoxical movement of the interventricular septum. Every measurement was done at least three times and averaged to obtain mean values. All patients were in sinus rhythm at the time of their echocardiographic examinations.

Hemodynamic study. Hemodynamic study and percutaneous closure were performed under general anesthesia with continuous TEE monitoring. The size, location, and relationship of the defect to the surrounding structures were assessed by TEE. A margin of ≥5 mm between these structures and the ASD had to be present for the procedure to be initiated. Pulmonary arterial and right and left atrial pressures were obtained with standard fluid-filled catheters. With V_{O_2} measured at rest, the pulmonary to systemic flow ratio (Qp/Qs) was calculated by oximetry, using the Fick principle.

ASD closure and follow-up. Closure of an ASD was achieved in all patients with an Amplatzer (AGA Medical Corp., Golden Valley, Minnesota) device (median device size 26 mm [range 18 to 34 mm]). Angiography and TEE performed immediately after device deployment showed an absence of a residual shunt in 31 (96%) of 32 patients (the patient with a periprocedural shunt was included in the study group, as no residual shunt was noted on TTE after one month since closure). In two patients (ages 77 and 58 years), pulmonary venous congestion developed a few hours after transcatheter closure and resolved within 24 h after high doses of diuretics. At TTE performed after six months, no residual shunt was noted in the entire study group. Patients received six-month aspirin therapy and were advised to use antibiotic prophylaxis for endocarditis for six months after the procedure.

Statistical analysis. The Wilcoxon matched-pairs test was used to compare pre- versus post-ASD closure exercise test and TTE variables. Correlation coefficients were calculated between the variation (percent change from baseline) of

Table 2. Mean Cardiopulmonary Test and Echocardiographic Values Before and Six Months After Transcatheter Closure of Atrial Septal Defect

	Baseline	6 Months	p Value*
VC (l)	3.44 ± 1.0	3.72 ± 0.9	0.0086
FEV_1 (l/s)	2.79 ± 0.83	2.98 ± 0.86	0.088
Peak V_{O_2} (ml O_2/kg/min)	21.9 ± 10.3	25.6 ± 9.9	<0.0001
Peak O_2 pulse (ml O_2/kg/beat)	8.9 ± 2.81	10.2 ± 3.7	0.0004
Peak heart rate (beats/min)	155.8 ± 21.7	157.4 ± 19.1	0.086
LVEDD (cm)	4.8 ± 0.4	5.1 ± 0.4	<0.0001
LVESD (cm)	3.0 ± 0.4	3.1 ± 0.4	0.19
LVEF (%)	73.8 ± 6.8	77.6 ± 5.3	<0.0001
LA diameter (mm)	28.9 ± 3.5	31.3 ± 3.8	<0.0001
RVLA dimension (mm)	75.5 ± 11.6	67.6 ± 9.6	<0.0001
RVSA dimension (mm)	36.2 ± 6.3	30.5 ± 6.0	<0.0001

*Compared by the Wilcoxon matched-pairs test. Data are presented as the mean value ± SD.

ASD = atrial septal defect; FEV_1 = forced expired volume in 1 s; LA = left atrial; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; RVLA = right ventricular long-axis; RVSA = right ventricular short-axis; VC = vital capacity; V_{O_2} = oxygen uptake.

cardiopulmonary test variables and hemodynamic, echocardiographic, and clinical variables. A value of $p = 0.05$ was considered significant.

RESULTS

Cardiopulmonary exercise test. Data on the cardiopulmonary test and TTE, both before and six months after ASD closure, are shown in Table 2. Before the intervention, peak V_{O_2} was moderately reduced with respect to the predicted values (61.6 ± 17.4%), and 6 (18%) of 32 patients had a severe reduction in peak V_{O_2} (<14 ml O_2/kg/min; mean 41% of predicted values).

Overall, a significant improvement in peak V_{O_2} ($p < 0.0001$) was noted six months after the procedure. In particular, as shown in Figure 1, 29 patients (91%) showed improved peak V_{O_2} values after percutaneous closure. It is noteworthy that two of the three patients who did not improve had almost normal peak V_{O_2} at baseline (77% and 104% of predicted values, respectively). Peak oxygen pulse had improved ($p = 0.0004$) at six months after closure. Peak V_{O_2} improvement (Δ% from baseline) correlated to Qp/Qs magnitude ($r^2 = 0.30$, $p = 0.0013$) (Fig. 2), whereas no relation was noted with age at closure ($r^2 = 0.0002$, $p = 0.92$), mean pulmonary artery pressure ($r^2 = 0.0022$, $p = 0.80$), or ASD diameter measured at TEE ($r^2 = 0.026$, $p = 0.37$). A nonsignificant increase in heart rate was recorded at six months after the procedure ($p = 0.08$). No patient showed evidence of chronotropic impairment (<85% of maximal reference heart rate) or arrhythmias during follow-up.

Comparison between subgroups. A Qp/Qs ratio <2 was found in 15 patients (47%) (median age at closure: 45.9 years [range 20 to 70 years]; male/female ratio 0.6; median Qp/Qs 1.5 [range 1.3 to 1.9]). The increase in peak V_{O_2} (Table 3) was significant both in patients ≤40 and >40 years of age at percutaneous closure (+19% and +27%, respectively), as well as in those with a Qp/Qs ratio <2 or ≥2 (+22% and +26%, respectively).

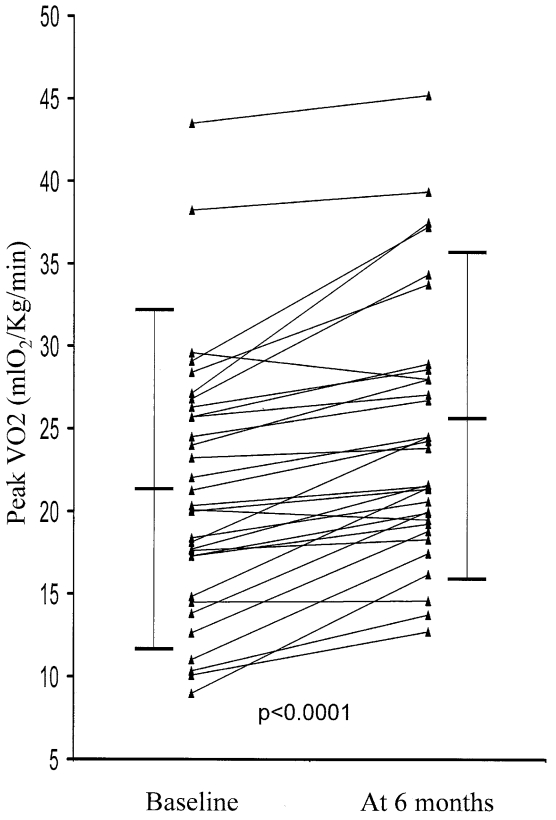

Figure 1. Peak oxygen uptake (V_{O_2}) at baseline and six months after the procedure.

Functional status. Before closure, 27 (84%) of 32 patients were self-perceived as being in NYHA functional class I, despite a moderate reduction in cardiopulmonary function, whereas the remaining five were in NYHA class II. At six months from closure, no patient reported a change in NYHA functional class.

Spirometric test. Before the intervention, the mean values for VC and FEV_1 at rest were still within the normal range (85.8 ± 10.5% and 90.9 ± 9.7%, respectively). Six months after transcatheter ASD closure, a significant improvement

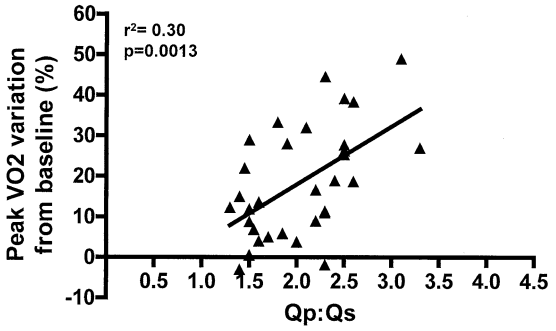

Figure 2. Correlation between the change in peak oxygen uptake (V_{O_2}) and magnitude of pulmonary to systemic flow ratio (Qp/Qs). A significant correlation exists between Qp/Qs magnitude and cardiopulmonary functional improvement after transcatheter atrial septal defect closure.

Table 3. Peak Oxygen Uptake at Baseline and Six Months After Atrial Septal Defect Closure for Different Subgroups

	Baseline Peak V_{O_2} (ml O_2/kg/min)	6-Month Peak V_{O_2} (ml O_2/kg/min)	p Value*
Age <40 yrs	29.0 ± 12.1	33.1 ± 11.4	0.0029
Age ≥40 yrs	17.6 ± 5.8	21.0 ± 5.4	0.0003
Qp/Qs ratio <2	18.8 ± 5.7	22.1 ± 5.7	0.0002
Qp/Qs ratio ≥2	25.2 ± 13.0	29.4 ± 12.2	0.0006

*Compared by the Wilcoxon matched-pairs test. Data are presented as the mean value ± SD.
Abbreviations as in Tables 1 and 2.

was observed for VC ($p = 0.0086$) but not for FEV_1 ($p = 0.08$).

Transthoracic echocardiography. As shown in Table 2, at six months after transcatheter ASD closure, significant increases in LVEF ($p < 0.0001$) and LVEDD ($p < 0.0001$) were noted in the overall population, whereas LVESD had not changed significantly from baseline ($p = 0.19$). Peak V_{O_2} increments (Δ%), with respect to baseline values, correlated to both LVEF ($r^2 = 0.31$, $p = 0.0009$) and LVEDD ($r^2 = 0.49$, $p < 0.0001$) increments from baseline (Fig. 3), but not with LVESD variation ($r^2 = 0.027$, $p = 0.43$). Similarly, pulse oxygen variation (Δ%) from baseline correlated to LVEF ($r^2 = 0.28$, $p = 0.0019$) and, in a barely significant fashion, with LVEDD ($r^2 = 0.14$, $p = 0.032$) variations (Fig. 3), but not with LVESD variation ($r^2 = 0.0021$, $p = 0.8$). A correlation ($r^2 = 0.26$, $p = 0.0026$) was noted between improvement in LVEF achieved at six months from transcatheter ASD closure and the magnitude of a left-to-right shunt (Fig. 4). The left atrial diameter was significantly increased at six months after the intervention ($p < 0.0001$) (Table 2).

The RV long- and short-axis dimensions significantly decreased six months after closure ($p < 0.0001$ and $p < 0.0001$, respectively) (Table 2). Moreover, the percent decrease in both RV long- and short-axis dimensions noted after closure correlated to both LVEF improvement ($r^2 = 0.53$, $p < 0.0001$ and $r^2 = 0.40$, $p < 0.0001$, respectively) and LVEDD increase ($r^2 = 0.35$, $p = 0.0004$ and $r^2 = 0.59$, $p < 0.0001$, respectively). A paradoxical movement of the interventricular septum was present in 17 (53%) of 32

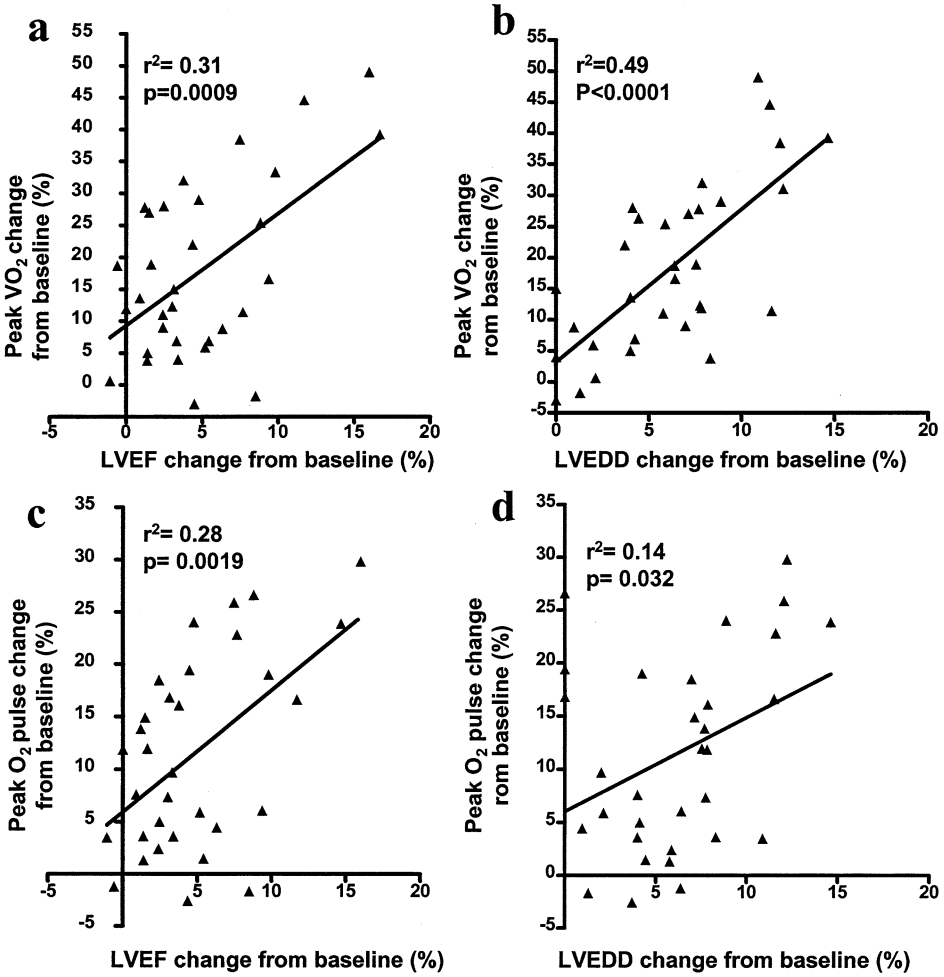

Figure 3. Correlation between transthoracic echocardiography and cardiopulmonary testing variables after transcatheter atrial septal defect closure. A significant association exists between postprocedural changes in peak oxygen uptake (V_{O_2}) and changes in left ventricular ejection fraction (LVEF) **(a)** and left ventricular end-diastolic diameter (LVEDD) **(b)**. A similar significant correlation was found between LVEF **(c)** and LVEDD **(d)** changes and peak oxygen (O_2) pulse variations from baseline.

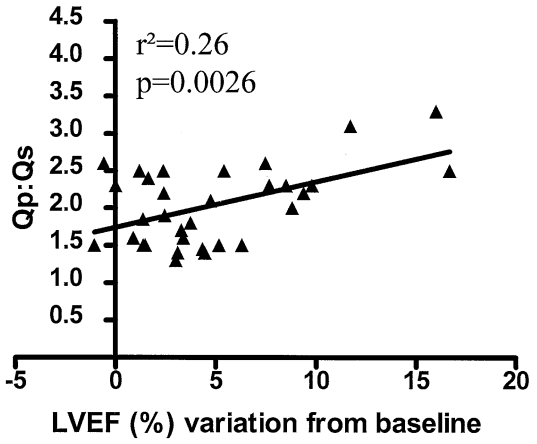

Figure 4. Correlation between magnitude of pulmonary to systemic flow ratio (Qp/Qs) and left ventricular ejection fraction (LVEF) improvement after transcatheter atrial septal defect closure.

patients at baseline and in 3 (9%) of 32 patients at six months after closure ($p = 0.0003$ by the Fisher exact test).

DISCUSSION

This prospective study provides strong evidence that in "asymptomatic" adults, transcatheter ASD closure leads to a significant increase in peak V_{O_2} within six months. Moreover, the correlation found between the extent of peak V_{O_2} improvement after transcatheter ASD closure and Qp/Qs magnitude (Fig. 2) suggests that patients with larger left-to-right shunts stand to gain the greatest benefits from transcatheter closure. Our data also suggest that the improvement of peak V_{O_2} after closure is probably a consequence of increased LV stroke volume and cardiac output.

Our TTE findings, showing significantly increased LVEDD and LVEF and unchanged LVESD after the procedure, suggest that an increase in LV stroke volume occurs after transcatheter ASD closure, ultimately leading to increased systemic cardiac output. Accordingly, as no change was found in maximal heart rate, the improvement in peak V_{O_2} after transcatheter ASD closure seems to depend on a significantly increased peak oxygen pulse (Table 3), which is an indirect marker of LV stroke volume. These observations are supported by the observations of significant correlations between improvements in peak cardiopulmonary exercise test variables (V_{O_2} and oxygen pulse) and increases in both LVEF and LVEDD, which were induced by ASD closure.

On physiopathologic grounds, our data suggest that the abolishment of left-to-right shunting after ASD closure augments LV volume filling, thereby increasing LV preload, LVEDD, LVEF, and, ultimately, LV stroke volume. Hence, the rise in LV stroke volume can explain the increase in peak oxygen pulse, and—given the unchanged maximal heart rate—the increased LV cardiac output can explain the increase in peak V_{O_2}. Furthermore, the correlation noted between Qp/Qs magnitude and LVEF improvement after closure (Fig. 4) indicates that the magnitude of improvement in LV systolic function seems to depend on the entity of the left-to-right shunt. However, a limited subgroup of asymptomatic patients with a low Qp/Qs ratio (<2) showed a significant increase in cardiopulmonary function, thus suggesting that even a low-magnitude atrial shunt may have an effect on exercise capacity.

This hypothesis is in accordance with published data on the reduction of RV volume overload after shunt closure and RV volume unloading induced by ASD closure (10,11). Moreover, the acute increase in LV filling after ASD closure may explain the observation, in both the present series and other studies (15), that a minority of patients experience pulmonary edema within a few hours of transcatheter ASD closure. The majority of these patients are elderly and hypertensive and have a hypertrophied, less compliant LV that can hardly cope with an acute increase of preload. We observed a significant dilation of the left atrium ($p < 0.0001$) after defect closure, which may indicate an increase in atrial wall tension induced by an acute increase of ventricular diastolic and atrial pressures.

Our data strongly indicate that, six months after closure, long- and short-axis dimensions of the RV chamber are significantly decreased compared with baseline values ($p < 0.0001$ and $p < 0.0001$, respectively), and the magnitude of the reduction of RV dimensions after blood volume unloading both positively and significantly correlates to improvement in LVEDD and in LVEF. Furthermore, the paradoxical movement of the interventricular septum disappeared in a significant percentage of patients, possibly causing an increase in LV stroke volume. These results suggest that an improved ventricular interaction induced by shunt abolishment probably plays a central role in the improvement of peak V_{O_2} and cardiac output.

Conflicting data have recently emerged on recovery of exercise capacity, expressed by peak V_{O_2} after transcatheter ASD closure (12,13). Our results indicate that a highly significant improvement in cardiopulmonary function occurs within six months of closure in most patients, irrespective of age at closure, defect size, and mean pulmonary artery pressure. Our findings are in keeping with those of Brochu et al. (12), who recently reported a significant increase in peak V_{O_2} after ASD closure. It should be noted, however, that their study lacked a comprehensive analysis of important cardiopulmonary test variables other than peak V_{O_2}, which could have accounted for the reported improvement. In contrast, in a small group of patients, Rhodes et al. (13) were unable to find any improvement in peak V_{O_2} at two months after percutaneous ASD closure. Their negative findings might have several explanations, including the rather young age of their patients (median 13 years [range 7 to 48 years]), which could be associated with less severe cardiopulmonary functional impairment. Moreover, the almost normal preclosure peak V_{O_2} values recorded by Rhodes and associates would have made further improvement less likely. Interestingly, two patients in our study who had normal cardiopulmonary function before ASD closure did not show any improvement at six months after the intervention. A further explanation for the discrepancy might

be that the beneficial effect of transcatheter closure on cardiopulmonary function could take more than two months to become apparent.

Another major finding of the present study is that although uncomplicated ASD was well tolerated in our asymptomatic adults, despite high pulmonary blood flow and right heart volume overload, cardiopulmonary function was markedly impaired. Our patients had moderately impaired peak V_{O_2} values before closure (61.6 ± 17.4% of predicted values), despite normal pulmonary artery pressure at rest (Table 1). This finding reveals a discrepancy between self-assessed exercise tolerance in everyday life and objective cardiopulmonary function. This might be ascribed to patients' limiting their behavior according to their functional ability. Interestingly, before closure, 27 patients (84%) thought they belonged to NYHA functional class I (despite a moderate reduction in cardiopulmonary function), whereas the remaining five thought they were in class II; at six months from closure, none of the patients subjectively noted a change in NYHA functional class.

Regarding ventilatory function, the mean VC and FEV_1 values of our patients before ASD closure were in the lower part of the normal range, in keeping with reports by De Troyer et al. (16) and Helber et al. (17), who found only mildly reduced values in adults with nonrestrictive ASD. As suggested (16), these findings may be possibly due to competition for space between the intrapulmonary blood vessels and small airways, leading to narrowing of the bronchiole and increased air resistance. Nevertheless, six months after percutaneous closure, we observed a significant increase in VC, but not in FEV_1. The improvement in VC might be related to abolishment of the upstream left-to-right shunt and of pulmonary vessel overload, with a decrease in water content in the lungs (17). In contrast to previous reports (8,18), no patient experienced arrhythmias during follow-up or during the exercise test performed at six months.

Study limitations. Despite the prospective character of the study, the limited sample size (n = 32) requires further confirmation of our findings in a larger ASD patient population. Therefore, our data need to be interpreted in the light of the patients' individual characteristics (Table 1).

Conclusions. This study strongly suggests that transcatheter ASD closure leads to a significant improvement of peak V_{O_2} within six months via an increase of peak oxygen pulse. After ASD closure, LVEF and LVEDD, but not LVESD, were significantly increased, thus producing an increase in LV stroke volume, as reflected by a concomitant improvement in peak oxygen pulse. The RV end-diastolic long- and short-axis dimensions significantly decreased after defect closure, and the magnitude of this reduction positively correlated to improvement of LVEDD and LVEF. The magnitude of peak V_{O_2} and LVEF improvement is significantly correlated to the Qp/Qs ratio. Maximal heart rate was not significantly increased at six months after closure. Thus, the mechanism responsible for peak V_{O_2} improvement after ASD closure seems to be an increase of LV output due to increased volume loading of the LV, as well as to an improved ventricular interaction.

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