Atrial Septal Defect in Adults: Cardiopulmonary Exercise Capacity Before and 4 Months and 10 Years After Defect Closure

UWE HELBER, MD, REINHARD BAUMANN, MD,* HARTWIG SEBOLDT, MD,*
ULRICH REINHARD, MD, HANS MARTIN HOFFMEISTER, MD

Tübingen, Germany

Objectives. **The purpose of the study was to evaluate the cardiopulmonary exercise capacity and ventilatory function in adults with atrial septal defect (ASD) preoperatively and 4 months and 10 years postoperatively.**

Background. **Only few data are available on cardiopulmonary exercise tolerance after ASD closure, but detailed knowledge might be helpful for indication for defect closure in certain patients.**

Methods. **The study was performed in adult patients (mean [±SD] age at operation 39.9 ± 11.5 years; left–right shunt 9.6 ± 5.6 liters/min; pulmonary/systemic flow ratio 2.8 ± 1.2; mean pulmonary artery pressure 18.2 ± 6.2 mm Hg). Cardiopulmonary exercise testing was performed with a bicycle ergometer. We determined peak oxygen uptake, anaerobic threshold, performance at anaerobic threshold and maximal performance in relation to these variables in a normal group. Ventilatory function at rest was expressed by vital capacity, maximal voluntary ventilation and forced expiratory volume in 1 s.**

Results. **Preoperatively, ventilatory function at rest was only moderately reduced to ~75% to 85%. Four months postoperatively we found no significant improvement, but 10 years postoperatively ventilatory function at rest was normalized. Preoperative cardiopulmonary exercise capacity was markedly reduced to 50% to 60%; early postoperatively it was only slightly higher, but late postoperatively exercise capacity significantly improved and was completely normalized.**

Conclusions. **Although preoperative cardiopulmonary capacity in adult patients with nonrestrictive ASD was significantly decreased, some improvement was seen at 4 months postoperatively, with complete restitution to normal at 10 years after shunt closure.**

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Patients with atrial septal defect (ASD) are usually asymptomatic in early life, but there may be some physical underdevelopment and an increased tendency for respiratory infections in adults (1). Cardiopulmonary symptoms and complications occur typically in older patients (1,2). Despite significant volume overloading, many adults with ASD do not complain of limited exercise capacity (3). However, the operative closure of defects with significant left to right shunting has been widely accepted in adults (4–7), although data regarding outcomes in surgically versus medically treated adult patients in controlled follow-up studies are lacking. The recently published data of Konstantinides et al. (8) showed that ASD closure in patients >40 years old increases long-term survival and limits deterioration of function due to heart failure. The main purpose of the present study was to examine quantitatively whether ASD closure is preferrable from the standpoint of exercise tolerance. Published follow-up data after closure of an ASD consist of subjective evaluation of functional classes (6–8) and objective data, including measurement of respiration and circulatory function at rest and during exercise are lacking. Ventilatory function at rest has been reported (9,10) to be normal or borderline in many patients with uncomplicated ASD in the first decades of life. Vital capacity and forced expiratory volume in 1 s at rest decrease but not before pulmonary resistance increases in progressive stages of the disease (11,12).

The present study was undertaken to determine ventilatory function at rest and cardiopulmonary exercise capacity preoperatively and 4 months and 10 years after defect closure. We also examined whether cardiorespiratory limitations in patients with ASD are detectable earlier and more sensitively under exercise conditions and whether such possible alterations are reversible postoperatively.

Methods

Patients. We included all patients with ASD closure at our institution between March 1982 and April 1983 who gave informed consent to participate in the study. Patients with additional coronary heart disease, valvular heart disease or pulmonary disease and those unable to exercise were excluded. Catheterization of the right heart and pulmonary artery, including oximetry, was performed in all patients. All patients >40 years old with a risk constellation underwent coronary

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Address for correspondence: Dr. Uwe Helber, Medizinische Universitätsklinik, Abteilung III, Otfried-Müller-Straße 10, D-72076 Tübingen, Germany.

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Abbreviations and Acronyms

ASD = atrial septal defect
FEV_1 = forced expiratory volume in 1 s
Qp/Qs = ratio of pulmonary to systemic flow

angiography, and those with coronary heart disease (stenosis >50%) were excluded from the study cohort, leaving 31 patients for inclusion (15 women, 16 men; mean age 39.9 years, range 19 to 56). Twenty-seven patients had an ostium secundum defect; three had a sinus venosus defect; and one had an isolated ostium primum defect. The ratio of pulmonary to systemic blood flow (Qp/Qs) was 2.8 ± 1.2. Mean pulmonary artery pressure was 18.2 ± 6.2 mm Hg, and mean pulmonary vascular resistance was 0.83 ± 0.68 mm Hg × min/liter (Table 1). Twenty-nine patients had normal sinus rhythm; one had atrial fibrillation; and one with sinus venosus defect had an ectopic atrial focus preoperatively. ASD was diagnosed 2 to 4 months preoperatively, and findings at catheterization were confirmed in all patients intraoperatively. All operations were performed with standard cardiopulmonary bypass using bicaval and ascending aorta cannulation and with moderate hypothermia and Bretschneider cardioplegia. The defect was closed by direct suture, pericardial or Dacron patch. All patients were reexamined at 4 months postoperatively; at 10 years postoperatively, reevaluation of 22 patients was possible (mean age 50.3 years, range 29 to 67; 14 women, 8 men). We could not contact five of the missing nine patients: Three were from states of the former Yugoslavia; one declined to appear because of his excellent condition; and one, who lived relatively far away, declined to appear because of marked heart failure. The latter patient (Table 1, Patient 19) had had increased left atrial pressure at the time of diagnosis of ASD (14 mm Hg; mitral valve disease was excluded). A report by the patient's physician revealed global heart failure. One other patient with known severe arterial hypertension (postoperative RR values up to 230/120 mm Hg despite intensive medical treatment [Table 1,

Table 1. Preoperative Data of 31 Study Patients and Results of Heart Catheterization

Pt No./ Gender	Age (yr)	P_{PA} (mm Hg)	P_c (mm Hg)	PBF (liters/min)	SBF (liters/min)	PAR (mm Hg × min/liter)
1/M	49	21	—	16.1	7.1	0.87
2/F	30	18	—	32.0	3.9	0.25
3/F	43	11	4	6.1	4.3	1.16
4/M	48	15	8	11.2	5.1	0.55
5/M	52	20	—	11.7	5.9	1.36
6/M	19	17	11	23.1	5.0	0.26
7/F	44	17	4	7.5	3.5	1.73
8/F	51	19	11	11.7	3.2	0.68
9/F	24	15	6	17.7	4.4	0.34
10/F	19	13	8	16.9	7.4	0.30
11/M	48	15	8	9.3	4.2	0.75
12/M	45	18	5	17.8	6.3	0.73
13/F	42	22	—	14.6	6.2	1.10
14/F	56	14	—	7.7	4.1	1.30
15/M	42	17	10	18.8	7.7	0.37
16/F	51	24	—	10.6	4.4	0.94
17/F	46	13	—	13.9	6.2	0.43
18/F	41	14	—	11.8	4.6	0.51
19/M	50	31	—	19.4	7.3	0.88
20/F	18	13	—	11.1	4.8	0.72
21/F	30	15	9	8.9	3.1	0.45
22/F	28	12	—	12.9	3.5	0.47
23/M	49	22	—	16.1	6.4	0.93
24/F	42	18	—	16.4	3.5	0.85
25/M	37	20	—	16.2	6.5	0.90
26/M	52	17	—	12.4	5.0	0.89
27/M	42	14	11	27.4	6.9	0.11
28/M	19	21	—	28.1	8.9	0.50
29/M	27	14	7	15.7	6.1	0.45
30/F	46	20	—	13.6	6.6	0.95
31/M	48	43	7	9.5	5.4	3.90
Mean	39.93	18.2	7.8	15.0	5.4	0.83
±SD	±11.5	±6.2	±2.3	±6.1	±1.5	±0.68

F = female; M = male; P_c = mean capillary wedge pressure; P_{PA} = mean pulmonary artery pressure; PAR = pulmonary artery resistance; PBF = pulmonary blood flow; Pt = patient; SBF = systemic blood flow.

Patient 16]) died 10 days postoperatively; Autopsy of this patient revealed changes due to brain bleeding. Another patient died of cancer 7 years postoperatively.

Protocol. Heart catheterization was performed 2 to 4 months preoperatively, and ventilatory function at rest was determined and a cardiopulmonary exercise test performed 1 to 5 days preoperatively in all patients. Intraoperatively, small pulmonary biopsy samples were taken; 4 months and 10 years postoperatively, patients were reexamined by determination of ventilatory function at rest and a cardiopulmonary exercise test (routine postoperative examinations of patients were performed by cardiologists in their residential areas). Patients were not encouraged to engage in fitness programs during the 4-month to 10-year interval after intervention. No specific fitness activities were reported by the patients at the time of reexamination. In all cases, a persistent postoperative shunt could be excluded by echocardiography.

Diagnostic catheterization was performed preoperatively in all patients, and we measured left atrial, right atrial, pulmonary artery and pulmonary artery wedge pressures. In addition, oxygen saturation of the pulmonary artery and superior and inferior venae cavae was measured. Using these data and oxygen uptake measured at rest, we calculated pulmonary and systemic flow and the left to right shunt.

Ventilatory function at rest was determined by a body plethysmograph at constant pressure (Fa Fenyves & Gut, Basel, Switzerland). We documented respiratory airway resistance, thoracic gas volume, expiratory reserve volume, residual volume, vital capacity, total lung capacity, forced expiratory volume in 1 s (FEV_1) and maximal voluntary ventilation. Values were compared with normal data for age, gender and body mass (Rühle et al. [13], Amrein et al. [14] and EGKS European Society of Coal and Steel normal values).

Cardiopulmonary exercise test. Cardiopulmonary exercise testing was performed with a symptom-limited 1-min incremental work test protocol (computerized cardiopulmonary exercise test, FA Fenyves & Gut). We used a bicycle ergometer in the upright position (Bosch ERG 602, Stuttgart, Germany). The exercise test began with 4 min of unloaded cycling under steady state conditions at rest before the start of the actual stress test with increasing 15 W/min. The examination was performed with an open system. Gas analysis was performed for oxygen by the paramagnetic principle (Oxytest S, Fa Hartmann and Braun, Frankfurt am Main, Germany) and for carbon dioxide by the ultrared absorption method (Uras MZ, Fa Hartmann and Braun). We measured the following variables: ventilatory flow, inspiratory–expiratory oxygen concentration difference, expiratory carbon dioxide concentration. From these variables we calculated on-line the oxygen uptake, peak oxygen uptake, carbon dioxide delivery, respiratory ratio and ventilatory equivalents for oxygen and carbon dioxide. The anaerobic threshold was determined according to the criteria of Wasserman and colleagues (15,16), especially with regard to the respiratory equivalent for oxygen (17). We measured maximal performance and performance at anaerobic threshold in relation to that in a normal group. Normal values for gender

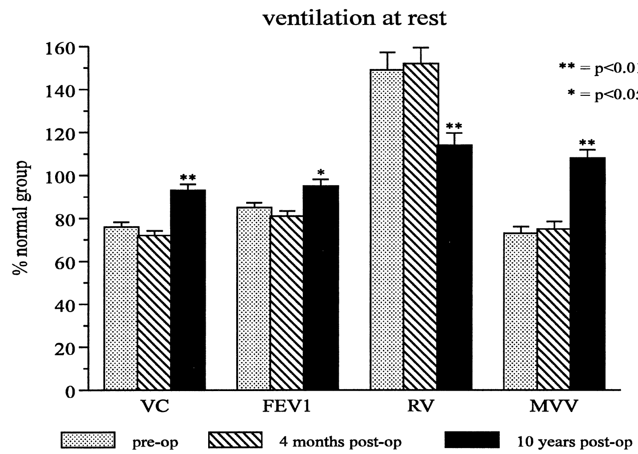


Figure 1. Ventilatory function at rest expressed as vital capacity (VC), forced expiratory volume in 1 s (FEV1), residual volume (RV) and maximal voluntary ventilation (MVV). **Columns** = mean value ± SEM. pre-op = preoperatively; post-op = postoperatively. $*p < 0.05$. $**p < 0.01$.

and age-related oxygen uptake were calculated by the predicted value of Wasserman et al. (16).

Statistics. Results are presented as mean value ± SEM. Data were analyzed by one-way analysis of variance. For multiple intergroup comparison, the Scheffé test was used as a post hoc test, according to that proposed by Wallenstein et al. (18) (statistical package JMP, SAS Institut Inc.), and $p < 0.05$ was regarded significant ($p < 0.01$ highly significant).

Results

Preoperative variables. Mean pulmonary artery pressure preoperatively was 18.2 ± 6.2 mm Hg, in the upper normal range. The results of the preoperative heart catheterization are shown in detail in Table 1. Mean pulmonary wedge pressure was 7.9 ± 2.3 mm Hg; pulmonary blood flow ranged from 6.1 to 32.0 liters/min (mean 15.0 ± 5.4 liters/min). Qp/Qs was 2.8 (range 1.4 to 8.2; all patients but three had a Qp/Qs ratio ≥2.0). Pulmonary resistance was normal (0.83 ± 0.68 mm Hg × min/liter).

Events during follow-up. At postoperative reexamination, there was no evidence for a persistent shunt by echocardiography. One patient, who had atrial fibrillation preoperatively, developed atrial tachycardia postoperatively. One additional patient developed atrial fibrillation postoperatively. One of the three patients with sinus venosus defect showed a preoperative and postoperative ectopic atrial focus with inverted P waves on leads I, II and aVF. All other patients were in sinus rhythm at 10 years postoperatively. One patient, with markedly reduced cardiopulmonary exercise capacity 10 years postoperatively, underwent coronary artery bypass graft surgery with rethoracotomy 6 years after ASD closure (this patient was included in the calculation of mean values).

Ventilatory function at rest. The results of ventilatory function at rest in a normal group are shown in Figure 1.

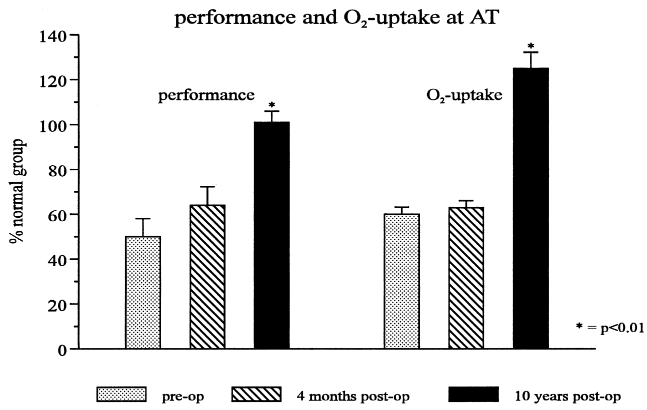
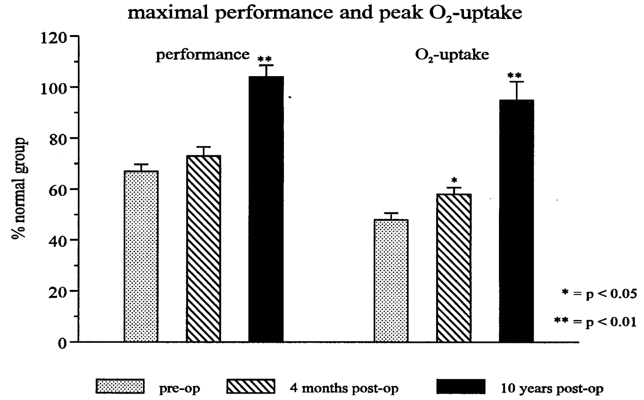


Figure 2. Cardiopulmonary exercise capacity at anaerobic threshold (AT) levels. **Columns** = mean value ± SEM. Abbreviations as in Figure 1. *$p < 0.01$.

Preoperatively the values for vital capacity, FEV_1 and maximal voluntary ventilation were slightly decreased compared with those in a group of normal subjects (75% to 85%). Residual volume was increased to ~150%. Ventilatory function at rest at 4 months postoperatively was not markedly changed in relation to the preoperative results. At 10 years postoperatively, there was a significant change, with normalization of vital capacity, FEV_1 and maximal voluntary ventilation. Residual volume was significantly decreased compared with the preoperative value and nearly normalized.

Cardiopulmonary exercise test. The results of the cardiopulmonary exercise test are shown in Figures 2 and 3. Cardiopulmonary exercise capacity, expressed as exercise capacity at anaerobic threshold, and maximal exercise capacity and oxygen uptake at these levels are reduced preoperatively to ~50% to 60%. At 4 months postoperatively, we found no significant improvement in maximal performance and peak oxygen uptake or performance and oxygen uptake at anaerobic threshold. At 10 years postoperatively, both values increased significantly and reached normal values at both levels.

Figure 3. Maximal cardiopulmonary exercise capacity expressed as peak oxygen uptake and performance in relation to normal subjects. **Columns** = mean value ± SEM. Abbreviations as in Figure 1. *$p < 0.05$. **$p < 0.01$.



The absolute value for peak oxygen uptake was markedly decreased to 13.1 ml/kg per kg body weight preoperatively, tended to increase at 4 months postoperatively to 13.6 ml/kg per kg body weight and significantly improved to 27.0 ml/kg per kg body weight at 10 years postoperatively. We found the same pattern for oxygen uptake at anaerobic threshold: 7.8, 8.5 and 16.1 ml/kg per kg body weight, respectively. Despite the patients being 10 years older at the late reexamination, exercise capacity even in absolute terms was markedly higher. This improvement was observed for both maximal performance (1.64, 1.76 and 2.07 W/kg per kg body weight, respectively) and performance at anaerobic threshold (0.53, 0.66 and 1.08 W/kg per kg body weight, respectively).

There was a negative correlation between mean pulmonary artery pressure and maximal performance (W/kg) ($r = -0.40$) and peak oxygen uptake (ml/kg per min) ($r = -0.43$) preoperatively. There was no close relation between shunt volume and cardiopulmonary exercise values.

Pulmonary biopsy samples showed only mild histologic alteration of the pulmonary arteries with no correlation to cardiopulmonary exercise test data, and additional pulmonary diseases were excluded.

Discussion

The results of the present study indicate that in adults with ASD, left to right shunt >40% of pulmonary blood flow and absence of pulmonary hypertension, ventilatory function at rest is only slightly reduced before defect closure; in contrast, cardiopulmonary exercise capacity is significantly impaired despite only minor subjective complaints.

Ten years after defect closure, ventilatory function at rest normalizes, and complete normalization of the preoperatively limited exercise capacity is possible in the long term.

Ventilatory function. Uncomplicated ASD is well tolerated long term despite high pulmonary blood flow and right heart volume overloading (1,2). Reports have documented that a few patients with an ASD have survived into their 80s (19,20). Burdzinnska et al. (10) found normal values for vital capacity and borderline decreased values for FEV_1 in children with ASD. In older patients, the lung volumes become smaller, and bronchial obstruction develops. Schofield et al. (11) and De Troyer et al. (12) found in patients with ASD a reduction of vital capacity and FEV_1, with increasing pulmonary artery pressure. With increasing pulmonary artery pressure, De Troyer et al. found an increasing pulmonary airway resistance. A possible explanation for this increasing pulmonary airway resistance is the high pulmonary blood volume (21). Hogg et al. (22) hypothesized that there is competition between the intrapulmonary blood vessels and the small airways for space, and the expansion of the small pulmonary vessels causes a narrowing of the bronchiole and an increase in airway resistance. Their data are in accordance with those of the present study, with pulmonary artery pressure in the upper normal range preoperatively and slightly reduced values for vital capacity and FEV_1 in parallel. The high residual volume may be explained by the increased airway resistance of 130%. However, the hypothesis of increased intrapulmonary blood vessel volume being the main reason for the increased resistance and residual volume might be challenged by the persistently increased resistance 4 months postoperatively despite successful defect closure.

Four months after defect closure, ventilatory function at rest did not change markedly. This lack of improvement early after defect closure may be explained by the trauma of operation. According to our data, Nolte (23) reported an impaired vital capacity of 30% in patients 14 days after thoracotomy, and Uhl (24) found that 6 to 8 weeks after thoracotomy, vital capacity decreased by ~10% (24). Ten years after defect closure, the values for ventilatory function at rest normalized in our study group, probably because of the missing pulmonary vessel overloading postoperatively and only mild histologic alteration of the pulmonary arteries.

Exercise capacity. In contrast to the only slightly reduced ventilatory function at rest in our group of patients with pulmonary artery pressure in the upper normal range, cardiopulmonary exercise capacity was significantly impaired despite only minor subjective complaints. The complaints of the patients are difficult to quantify in this group with significant left to right shunt but no pulmonary hypertension. Although they often denied relevant exercise limitations or had disabling symptoms only according to functional class II preoperatively, they reported improvement in exercise capacity at 10 years after defect closure; they could not have known preoperatively how well they would feel postoperatively because they had adapted to their condition. Sutton et al. (5) reported that ~60% of their patients were in functional class III or IV, but they examined patients ≥60 years old, and pulmonary artery pressure was markedly higher in their patients than in ours.

Most studies agree that the presence and severity of functional limitation among patients with ASD increases with age. Hamilton et al. (2) found that only 4% of their patients >40 years old were asymptomatic as opposed to 71% in the first decade of life (2). Markman et al. reported that 6% of their patients at the end of the fourth decade were in functional class III or IV, rising to 30% by the end of the fifth decade and to 49% by the sixth decade (1). These and other studies (4–6) are based on data influenced by subjective complaints of the patients and, because they were made before the "era of echocardiography," often represent the "bad end of the spectrum," with the resultant problem of an obvious bias. However, from this "early era" the report of Murphy et al. (25) should be mentioned, in which long-term follow-up data of patients with ASD who had been treated surgically were compared with that from an age- and gender-matched control group without ASD. They reported that the overall survival of the surgically treated patients was better than that among medically treated controls.

The present study showed by objective measurement a decreased cardiopulmonary exercise capacity to ~50% to 60%, expressed by performance (W/kg) and oxygen uptake. Many young study patients with a relative lack of symptoms had objectively decreased exercise tolerance. Cardiopulmonary exercise testing is recognized as an objective means of assessing functional capacity in patients with chronic heart failure (16,26,27). Determination of anaerobic threshold and oxygen uptake and performance at this level represents an important aspect of exercise function that is particularly relevant to the exercise tolerance of patients with cardiac disease.

Four months postoperatively, cardiopulmonary exercise capacity in our study group increased somewhat, but there was no significant improvement. This result may be explained by the trauma of operation and the lack of a training effect. Normalization of cardiopulmonary exercise capacity, expressed by all four variables (peak oxygen uptake, oxygen uptake at anaerobic threshold, maximal performance and performance at anaerobic threshold) was documented 10 years after defect closure, but it is probable that this improvement took place much earlier. The data assessed by questionnaire in the referring physicians or directly in the patients to determine functional class suggest that the improvement in the exercise capacity takes place after 1 to 2 years. Because of missing exercise tests we do not have quantitative results, and the exact time is not clear. However, long-term improvement seems to be much more important and quantitatively underscores the findings of Konstantinides et al. (8). Normalization of exercise capacity confirms the data of other investigators who report that most of their patients were symptomatically improved by at least one functional class postoperatively (5,7). In contrast, Shah et al. (3) found no improvement in the functional class after defect closure (3); however, their study group differed in that >70% of their patients were symptom free, so that no improvement could be shown. Seventy-one percent of their surgically treated patients were in functional class I and 29% in class II preoperatively, and only a few patients went from class I to class II at late reevaluation. Shah et al. did not find any benefit from operative treatment with respect to mortality, atrial fibrillation, emboli and incidence of breathlessness and cardiac failure. However, as Ward (28) discussed, the study by Shah et al. (3) was not a controlled study, and the indications for inclusion in medical or surgical groups are not clear; and by design, patients with advanced pulmonary vascular disease were not enrolled. Murphy et al. (25) reported that the overall survival of the surgically treated patients was better than that among medically treated historical control subjects (1,29–32). They found that closure of an ASD in patients ≥24 years old was associated with normal long-term survival. Closure in patients 25 to 41 years old was associated with good long-term survival but shorter than that expected in a normal population, and closure after 41 years of age was associated with significantly increased late mortality. Konstantinides et al. (8) responded to the question of whether patients >40 years old benefit from defect closure. In 1995 they published a comparison of surgical and medical therapy for ASD closure in adults and found that surgical repair in patients >40 years old increases long-term survival and limits the deterioration of function caused by heart failure. The risk of atrial arrhythmia was not reduced by closure of the defect. A limitation of the study of Konstantinides et al. was the retrospective, nonrandomized assignment of patients to the two treatment groups and the subjectively influenced functional classes; but the differences in the surgically treated group versus the medically treated patients did not indicate a more favorable prognosis for one group, especially with regarding to age, pulmonary artery resistance and Qp/Qs ratio. According to these data, Sutton et al. (5) also found an improvement in functional class in his patients >60 years old. We did not find such age-related results for cardiopulmonary exercise capacity, but our group was probably too small to see such differences in age subclasses. The mortality and morbidity rates in this small cohort are not representative enough to calculate statistics (the mortality rate at our center was $\leq$0.05% in the past decade), especially when taking into account the fact that the patient who died early postoperatively and the patient with global heart failure had severe concomitant disease.

Conclusions. From the findings of the present and previous studies, it can be concluded that even if older patients with ASD do not have a normal life expectancy after defect closure, surgical treatment is superior to medical treatment with regard long-term survival and prevention of functional limitations due to heart failure, and cardiopulmonary exercise capacity can be improved in these patients over the long term. Cardiopulmonary exercise testing is a feasible and important method for detecting functional impairment before defect closure. Adults with markedly reduced exercise tolerance often have few subjective complaints, and the finding of significant postoperative improvement may be helpful in making decisions with respect to operative management.

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