Latent pulmonary hypertension in atrial septal defect: Dynamic stress echocardiography reveals unapparent pulmonary hypertension and confirms rapid normalisation after ASD closure

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Abstract

Objective Closure of atrial septal defects (ASD) prevents pulmonary hypertension, right heart failure and thromboembolic stroke. The exact timing for ASD closure is controversial.

Methods In a prospective study to address the question whether unapparent pulmonary hypertension can be revealed prior to right ventricular (RV) remodelling, patients were investigated before and 6, 12, and 24 months after ASD closure using exercise stress echocardiography (ESE) and ergospirometry (n=24).

Results At rest, RV systolic pressure (RVSP) was normal in 58.8 %, slightly elevated in 26.5 %, and moderately elevated in 11.8 %. One patient showed severe pulmonary hypertension. During ESE, all patients with normal RVSP at rest exhibited an increase (25.7±1.2 mmHg vs. 45.3±2.3 mmHg, p<0.001). After closure the RVSP was lower, both at rest and ESE. RV diameters decreased too. Tricuspid annulus plane systolic excursion (TAPSE) at rest remained lower after closure (24.0±0.9 vs. 22.0±0.9 mm, p<0.05). TAPSE in ESE was elevated, and stayed stable after closure (30.1±1.8 mm vs. 29.3±1.6 mm). Before closure, RV systolic tissue velocities (sa) at rest were normal and decreased after closure (14.0±1.0 cm/s vs. 11.5±0.7 (6 month) vs. 10.6±0.5 cm/s (12 month), p<0.05). During ESE, sa velocity was similar before and after closure (23.0±1.3 cm/s vs. 23.3±1.9 cm/s). Maximal oxygen uptake (VO2/kg) did not differ between baseline and follow-ups.

Conclusion Latent pulmonary hypertension may become apparent in ESE. ASD closure leads to a significant reduction in this stress-induced pulmonary hypertension and to a decrease in the right heart diameters indicating reverse RV remodelling. RV functional parameters at rest did not improve. The VO2/kg did not change after ASD closure.

Keywords Pulmonary hypertension · ASD closure · Exercise stress echocardiography · Ergospirometry

Introduction

Percutaneous closure of atrial septal defects (ASD) and patent foramen ovale (PFO) has proven to be a promising therapy for ASD with apparent volume overload of the pulmonary system and in the prevention of recurrent paradoxical embolic events and cryptogenic strokes. During intervention or follow-up complications ranged from 0 to 22 %. In
some patients, thromboembolic events occur due to clotting of a device surface [1–4]. Our research group showed a very low rate of complications in PFO closure [5]. Only a few cases of partial malposition of PFO closure devices have been described [6, 7] and only a few reports about cardiac perforation caused by different PFO and ASD occluder devices [3, 8–10], which is the most serious complication known, and mild-to-moderate insufficiencies of the aortic valve [11] have been reported.

In patients with larger shunts resulting in pulmonary hypertension, ASD closure resulted in a decline in pulmonary pressures and a reduction in the right ventricular (RV) and right atrial (RA) volumes and sizes [4, 12].

Asymptomatic patients with smaller shunts without pulmonary hypertension also increased their functional capacity after ASD closure [13]. Yet patients also developed a diminution of their aerobic capacity [14]. Thus, the timing of ASD closure remains controversial.

In the present prospective study, exercise stress echocardiography (ESE) and ergospirometry were used to address the question whether unapparent pulmonary hypertension and the onset of RV remodelling leading to an impairment of RV function can be identified in asymptomatic patients in order to determine the optimal timing for ASD closure.

This study addresses the question whether, in asymptomatic patients with ASD, an early pulmonary hypertension which is unapparent at rest can become evident during stress testing and may help to identify optimal timing and need for an interventional or operative ASD closure. Furthermore, the study also addresses, in a prospective fashion, whether a subclinical worsening of RV function can be revealed during stress testing and this impairment can recover within 6 to 12 months after ASD closure.

Methods

Patients

The study included 59 patients (median age 50 years, range 17–78 years) with a haemodynamically relevant ASD. Patients with small ASD who did not have relevant alterations of the right heart diameters and function at rest, clinically all patients who did not have pulmonary hypertension at rest and during exercise, without clinical symptoms of heart failure, and without paradoxical embolism, did not receive an ASD closure in accordance to AHA guidelines [15], and were not included into this study.

Twenty-seven patients with normal to moderate pulmonary hypertension at rest received an ESE before, and 6 and 12 months after ASD closure. In addition, 24 patients with a normal to moderately elevated pulmonary pressure at rest underwent an ergospirometry before and during follow-up.

Echocardiography

Before study inclusion, each patient (n=59) underwent a transthoracic two-dimensional echocardiography, according to the guidelines of echocardiography [16] (TTE, Sonos 5500 ultrasound system, Agilent Technologies, Santa Clara, California, USA and Sonos 7000 ultrasound system, Philips, Amsterdam, the Netherlands) at rest and a transoesophageal echocardiography (TEE) (Fig. 1a, b) to characterise the ASD and to measure the maximal ASD diameter and the surrounding margin, especially the aortic rim. Echocardiography was also used to calculate: 1) the ratios of pulmonary-to-systemic flow and the shunt volume, 2) the maximal pulmonary systolic pressure, 3) the diameters of the left and right ventricle and 4) the function of the left and right heart at rest. Echocardiography parameters were chosen for semiquantification of valve regurgitation or stenosis according to AHA guidelines [15].

A total of 27 patients with normal to moderately elevated pulmonary pressure at rest had a bicycle stress test in a half-sitting position (30°–45°) with a left incline of 45° (Ergometrics 900, Ergoline, Bitz, Germany). The stress testing was based on a modified Bruce protocol [17]: the ergometric load started at 25 W and increased by 25 W every 3 min. Before and during exercise (within the third minute), we measured blood pressure and heart rate. Echocardiography was used simultaneously to measure E wave velocity and deceleration time, tricuspid annulus plane excursion (TAPSE) of the right ventricle, and the RV systolic pressure (RVSP).

Incompetence of the mitral and tricuspid valves was also assessed during ESE.

Finally, the tissue Doppler imaging (TDI) values of the lateral tricuspid valve annulus were collected [18].

Ergospirometry

Patients (n=24) with a normal to moderately elevated pulmonary pressure at rest and who were in a sufficient physical condition underwent ergometric bicycle testing (eBike bicycle ergometer, GE) with a ramp protocol starting at 20 W for warm-up for the first 2 min. The workload was then increased by 20 W every 2 min until patients reached their individual performance limitation. The recovery period lasted at least 3 min. Breath-to-breath measurements of expired gas values were analysed every 30 s (Oxycon Pro; Jaeger/Viasys; Höchberg, Germany). Heart rate, blood pressure, and ventilation were recorded continuously during ergospirometry. The VO2 at the gas exchange anaerobic threshold was determined with the V-slope method. An ECG to analyse ST-segment deviations or rhythm disturbance was recorded continuously during the exercise and recovery period.
Invasive procedures and percutaneous atrial defect closure

Patients with ASD received a complete cardiac catheterisation of the left and right heart to determine pulmonary systolic pressure, pulmonary resistance, and the Qp/Qs ratio (calculated oxymetrically using the Fick principle). The coronary angiography was also performed to investigate coronary vessel disease or coronary anomalies.

ASD closure was accomplished in patients with a pulmonary to systemic flow ratio Qp/Qs>1.5, in the presence of one or more of the following conditions: a) RV volume overload, b) impairment of RV function, c) pulmonary hypertension, d) clinically symptomatic dyspnoea (NYHA degree II or greater).

Percutaneous closure was performed under local anaesthesia (lidocaine 2 %) and sedation with midazolam (2–5 mg i.v.). The interventional closure procedure was guided by TEE. Balloon sizing was performed for exact determination of the ASD size (Fig. 1c).

All patients were anticoagulated at the time of the procedure with 10,000 IE heparin. They all received amoxycillin (1.2 g) and atropine (0.5–1.0 mg) intravenously to prevent thromboembolic events, endocarditis and catheter-induced coronary spasm. Post-intervention all patients received double platelet inhibition with clopidogrel 75 mg/day and acetylsalicylic acid 100 mg/day to prevent thrombus formation on the device. After 6 months the clopidogrel was stopped.

Statistics

Data are means ± standard error of means (SEM). Student’s t-test for paired samples was used to test for differences between the individual parameters before ASD closure and during follow-up. A probability value of less than 0.05 was considered to be statistically significant. The statistic analysis was performed with SPPS 11.5.
Fifty-nine patients with ASD were enrolled prospectively: 36 were female (61 %) and the median age at the time of ASD closure was 50 (17–78) years. The mean body mass index was 26.2±0.6 kg/m².

There were 46 patients (78 %) with ASD II, 11 patients (19 %) with ASD II and PFO, 1 patient (2 %) with ASD I, and one patient (2 %) with ASD I and PFO.

Sinus rhythm was present in 74.6 % and atrial fibrillation in 25.4 %. Three patients had a history of minor stroke and ten patients had a history of major stroke. The prevalence of cardiovascular and metabolic risk factors was as follows: 27 (45.8%) arterial hypertension, 20 (33.9 %) hyperlipoproteinaemia, and 12 (20.3 %) diabetes mellitus.

Cardiac catheterisation

A haemodynamically relevant coronary heart disease was found in one patient (occlusion of the right coronary artery (RCA) after previous percutaneous coronary intervention). Three patients had a coronary anomaly (single and atypical origin of the left anterior descending artery, an atypical origin of the circumflex, and an atypical origin of the RCA). The invasively determined averaged systolic PAP and pulmonary resistance were in the upper normal range (PAP 29.0±1.5 mmHg, pulmonary vascular resistance 122.3±10.6 dyn*s*cm$^{-5}$). The pulmonary flow to systemic flow ratio was 1.69±0.09, and the mean value for the left to right shunt was 36.6±1.0 % (Table 1).

Percutaneous ASD closure was performed and successful in 49 patients. We used 41 Amplatz Septal Occluders (AGA Medical Corporation, Plymouth, Massachusetts, USA), and 8 Cardia Star ASD Devices (CARDIA, Eagan, Minnesota, USA) (Fig. 1d). Eight patients received a surgical ASD closure due to a small aortic rim, and one patient had a secondary surgical ASD closure with Amplatz Septal Occluder after an intervventional procedure because of an ASD relapse. In one patient, a percutaneous ASD closure with a Cardia Star Device was required after minimal surgical ASD patch implantation because of a haemodynamically relevant residual shunt volume.

Echocardiography

The mean ASD size measured by TEE was only 13.6±0.9 mm (SEM). The calculated mean left-to-right shunt was 37.7±3.4 %, which was in good agreement with the invasively determined shunt volume. The left ventricular ejection fraction was in the normal range (64.2±0.8 %), and the degree of mitral and tricuspid valve insufficiency were also mild (Table 2).

The diastolic value of the left heart, e.g. maximal early velocity (E-Vmax) and deceleration time (DT), did not

| Table 1 | Angiography parameters before ASD closure |
|---------|------------------------------------------|
|         | mean ± SEM  | 95 % CI       |
| Qp: Qs  | 1.69±0.09   | (1.50–1.87)   |
| Left right shunt | %  | 36.6±1.0 | (34.6–38.7) |
| Right ventricular systolic pressure | mmHg | 29.0±1.5 | (26.0–32.0) |
| Right ventricular mean pressure | mmHg | 16.8±1.0 | (14.7–18.8) |
| Pulmonary vascular resistance | dyn*s*cm$^{-5}$ | 122.3±10.6 | (101.0–143.6) |

| Table 2 | Echocardiography (TTE and TEE) Parameters before ASD Closure |
|---------|-------------------------------------------------------------|
| ASD size | mm | 13.6±0.9 | (11.8–15.4) |
| LV ejection fraction | % | 64.2±0.8 | (62.7–65.8) |
| Left right shunt | % | 37.7±3.4 | (30.6–44.7) |
| Tricuspid valve insufficiency | degree | 1.35±0.08 | (1.19–1.51) |
| Mitral valve insufficiency | degree | 0.89±0.09 | (0.72–1.07) |
| Aortic valve insufficiency | degree | 0.39±0.09 | (0.21–0.56) |
| Pulmonary valve insufficiency | degree | 0.31±0.07 | (0.17–0.45) |
| E velocity max. | cm/s | 91.1±4.3 | (82.4–99.8) |
| Deceleration time | ms | 197.1±7.5 | (182.1–212.2) |
change significantly during follow-up, neither at rest nor during exercise (Table 3).

The RVSP before closure was in the normal range at rest (<35 mmHg) in 27 patients (55.1%). There was mild

**Table 3** Diastolic inflow parameters of the left heart at Rest and at Peak Exercise

|                      | Before ASD closure | Month 6  | Month 12 |
|----------------------|--------------------|----------|----------|
|                      | Rest               |          |          |
| E Vmax [cm/s]        | 88.7±7.0           | 79.3±9.0 | 71.1±11.3|
| n                    | 21                 | 8        | 7        |
| P*                   | (95%CI 74.0–103.4) | 0.61     | 0.42     |
| Exercise             | 126.6±6.7          | 141.3±11.6| 124.5±11.8|
| n                    | 20                 | 6        | 6        |
| P*                   | (95%CI 112.6–140.6)| 0.13     | 0.34     |
| DT [ms]              | Rest               |          |          |
|                      | 206.3±10.7         | 213.9±19.7| 236.6±28.1|
| n                    | 22                 | 8        | 8        |
| P*                   | (95%CI 184.0–228.7)| 0.96     | 0.358    |
| Exercise             | 156.1±7.1          | 144.4±6.1| 165.7±7.9|
| n                    | 20                 | 7        | 6        |
| P*                   | (95%CI 141.3–170.8)| 0.24     | 0.47     |

*paired comparisons with baseline data before ASD closure

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Fig. 2  a. Normal RVSP at rest increased significantly during exercise. b. Mild elevated RVSP at rest increased significantly during exercise. c. Moderate to severe RVSP at rest increased during exercise.
pulmonary hypertension at rest (35–49 mmHg) in 16 patients (32.7 %), moderate pulmonary hypertension (50–69 mmHg) in 5 patients (10.2 %), and severe pulmonary hypertension at rest (≥70 mmHg) in 1 patient (2.0 %).

During ESE, most of the patients with normal RVSP at rest exhibited a significant increase in the RVSP (25.7±1.2 mmHg up to 45.3±2.3 mmHg; p<0.001); only three patients remained in the normal range. The incline of the RVSP reached pulmonary hypertension of at least a moderate degree in eight patients. In detail, patients with mild pulmonary hypertension developed a moderately elevated PAP. In three patients the RVSP increased even beyond 60 mmHg (from 40.2±1.8 mmHg up to 65.7±3.6 mmHg; p<0.001). Five patients with moderate to severe pulmonary hypertension before ASD closure had an increase of RVSP during exercise from 56.3±2.2 mmHg up to 76.5±7.5 mmHg (p=0.062) (Fig. 2a–c).

During follow-up the RVSP decreased significantly in all patients at rest and also during exercise. This reduction reached significance at month 6 at rest and at month 12 in ESE (Figs. 3a–c and 4a–c). RVSP results at rest and during exercise are summarised in Table 4.

The diameters of the right atrium and right ventricle declined soon after ASD closure.

TAPSE and TDI Doppler s	extsubscript{a} [18, 19]: The mean ± SEM (95 % CI) TAPSE at rest before ASD closure was 24.0±0.9 (95 % CI: 22.1–25.9), thus within the normal range. During exercise, TAPSE increased 30.1±1.8 mm (95 % CI: 26.4–33.8). After ASD closure, TAPSE at rest decreased significantly, but TAPSE measured during exercise did not change significantly. In contrast, these values were lower than equally determined peak values in healthy volunteers (TAPSE up to 33.7±1.1 mm) (unpublished data).

Another parameter of RV function was systolic TDI velocities at the lateral tricuspid annulus (s	extsubscript{a}) [18]. Before closure, TDI s	extsubscript{a} values at rest were in the normal range (14.0±1.0 cm/s (95 % CI: 12.0–16.1) and decreased significantly after ASD closure.

During ESE the TDI s	extsubscript{a} values increased to 23.0±1.3 cm/s (95 % CI: 20.2–25.8) before ASD closure. These peak exercise values remained stable during follow-ups. In comparison, TDI s	extsubscript{a} values in healthy volunteers increased to

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**Fig. 3** a. RVSP at rest decreased significantly after ASD closure at month 6. b. RVSP at rest before and 12 months after ASD closure. c. RVSP at rest before and 24 months after ASD closure.
25.2±0.7 cm/s (unpublished data). Right heart values and functional parameters are summarised in Table 5.

Ergospirometry

Comparison of the maximal oxygen uptake (VO$_2$ max, VO$_2$/kg) before and after ASD closure did not differ significantly between baseline values and follow-up. Only the measured oxygen uptake at the anaerobic threshold (VO$_2$-AT) at month 6 was significantly decreased, but rose again during further follow-up. The nominal oxygen capacity before closure was nearly 95 %, but it did not change significantly after ASD closure.

The peak ventilation (VE) was elevated during follow-up, significantly so by the end of the follow-up period.

Breathing equivalents of CO$_2$ at the anaerobic threshold increased slightly but significantly at months 12 and 24. Breathing equivalents of O$_2$ at the anaerobic threshold were increased significantly at months 12 and 24 but the magnitude of increase was not clinically meaningful. Only the mean breathing equivalents for CO$_2$ at month 24 were out of the normal range (30.8±0.9).

Table 4 Right ventricular systolic pressure at rest and peak exercise before ASD closure

|                | Normal <35 mmHg | Mild hypertension 35–49 mmHg | Moderate hypertension 50–69 mmHg | Severe hypertension ≥70 mmHg |
|----------------|-----------------|------------------------------|---------------------------------|-----------------------------|
| RVSP at rest   | 26.6±5.1        | 40.4±4.5                     | 57.0±4.1                        | 74                          |
| n              | 27              | 16                           | 5                               | 1                           |
| RVSP during exercise | 28.0±7.2       | 42.4±3.9                     | 56.2±4.8                        | 78.0±8.1                    |
| n              | 3               | 9                            | 14                              | 8                           |
The oxygen pulse, a parameter that correlates with stroke volume, did not change significantly.

Ergospirometry results are summarised in Table 6.

### Discussion

The salient findings of the present prospective study are that:

1. Clinically asymptomatic patients with ASD yet with normal baseline pulmonary pressures at rest may reveal significantly elevated pulmonary pressures during stress test and that

2. The elevated pulmonary pressures may be rapidly normalised after interventional or operative ASD closure.

The increase in pulmonary pressure during exercise was not unexpected [20] yet the association with clinically completely asymptomatic patients has not been shown previously to this extent. Moreover, the rapidity of the recovery of the stress-induced increase of pulmonary pressure after successful ASD closure in asymptomatic patients has not been shown before.

The right heart diameters declined soon after ASD closure. These data confirm previously published data [4, 12, 13, 20, 21]. In previous studies, the magnitude and time course of cardiac remodelling did not differ significantly between age groups, but the right ventricle remained larger in older patients [20–24].

Hence our interest focused on RV functional parameters: The M-mode measurement of the TAPSE was used in an attempt to evaluate the quality of right heart contraction. TAPSE seems to be a powerful parameter for reflecting RV function in pulmonary arterial hypertension [25]. In the present study, TAPSE was reduced during follow-up in contrast to expectation. Previous studies have described TAPSE at rest but have also shown attenuation in patients with right and/or left heart failure [19, 26]. In the present study TAPSE was within the normal range at baseline and as expected significantly increased during the stress test. In contrast to expectation, TAPSE at rest significantly decreased after ASD closure. Considering the observation that ASD closure even improved pulmonary pressures under stress, it seems unlikely that the reduction of TAPSE after ASD closure reflects an impairment of RV function. Potentially, the geometric changes after device implantation or surgical ASD closure alter basal excursion of the right ventricle. Consequently the parameter TAPSE may be an inadequate parameter to estimate RV function in these patients. This notion is supported by the observation that RV volumes have normalised after ASD closure suggesting haemodynamic improvement of these patients. A normalisation of RV volumes has been shown before after ASD closure [24].

| Table 5 Right heart diameters and functional parameters |
|---------------------------------------------------------|
| Before ASD closure | Month 3 | Month 6 | Month 12 | Month 24 | Month 36 |
|---------------------|---------|---------|---------|---------|---------|
| **Right atrium** [mm] | 45.2±0.9 | 40.5±0.6 | 40.8±1.0 | 39.7±1.1 | 41.5±1.3 | 41.2±3.4 |
| n                   | 50      | 39      | 33      | 29      | 18      | 6       |
| p*                  | <0.001  | <0.001  | <0.001  | <0.05   | 0.58    |
| **Right ventricle** [mm] | 36.2±0.8 | 33.6±1.1 | 32.2±0.9 | 32.1±1.1 | 32.8±1.2 | 31±1.6 |
| n                   | 50      | 39      | 33      | 29      | 18      | 6       |
| p*                  | <0.05   | <0.001  | <0.01   | <0.05   | 0.33    |
| **TAPSE at rest** [cm] | 24.0±0.9 | 23.2±0.9 | 22.0±1.0 | 22.0±0.9 | 23.2±1.7 |
| n                   | 37      | 23      | 19      | 19      | 5       |
| p*                  | 0.443   | 0.05    | 0.05    | 0.315   |
| **TAPSE at peak exercise** [cm] | 30.1±1.8 | 26.1±1.8 | 29.3±1.6 | 23.2±1.7 |
| n                   | 25      | 9       | 12      | 5       |
| p*                  | 0.075   | 0.8     | 0.315   |
| **S4 velocity at rest** [cm/s] | 14.02±0.98 | 11.49±0.68 | 10.63±0.45 |
| (95 %CI 11.98–16.05) | 9       | 6       |
| n                   | 21      | 9       | 6       |
| p*                  | <0.05   | 0.01    |
| **S4 velocity at peak exercise** [cm/s] | 23.00±1.33 | 20.63±1.82 | 23.3±1.91 |
| (95 %CI 20.22-25.78) | 9       | 5       |
| n                   | 20      | 9       | 5       |
| p*                  | 0.179   | 0.664   |

* paired comparisons with baseline data before ASD closure
Measurement of the TDI strain velocities of the right ventricle wall was used as another attempt to characterise the RV function. An animal study in dogs provided evidence of a strong correlation between systolic TDI velocities (sa) and RV contractility [27]. A limited study in patients presented a good correlation between tissue displacement and strain and RV stroke volume index measured by the method of Fick or by thermodilution [28]. In recent studies in patients after ASD closure, it was reported that ASD closure resulted in a decrease in TDI regional peak strain of the right ventricle [29–31].

Congruently, we found that peak strain velocities in the lateral tricuspid annulus area were significantly reduced after ASD closure and were in a lower but normal range compared with healthy volunteers. Our results agree partially with a study that showed a transient deterioration of the RV function after ASD closure, as ascertained by RV Tei index [24]. In contrast, a study exhibited an improvement of RV function after transcatheter closure of ASD [32]. However, in this study the time interval between ASD closure and echocardiographic examination was in the wide range of 8 to 270 days and could not be used as a valid comparison with our data.

In addition, we found that this peak systolic strain increased significantly during exercise, without important differences in the exercise tests before vs. after ASD closure. This observation could be an indication of the preserved RV functional capacity in these patients. Future studies will point out the significance of the peak systolic strain value during exercise in the decision regarding ASD closure in patients with clinically relevant impaired RV function. However, in our study there were no patients with symptoms of severe right heart failure.

A significant decrease in maximal oxygen consumption with ageing has been found in various congenital heart diseases, especially in tetralogy of Fallot, Ebstein’s anomaly and of course in atrial septal defects [14]. The preoperatively reduced cardiopulmonary exercise capacity in adults with ASD improved slightly 4 months after ASD closure and normalised 10 years after surgical shunt closure [33]. In addition, patients with percutaneous ASD closure presented a significant improvement in

| Table 6 Ergospirometry parameters | Before ASD closure | Month 6 | Month 12 | Month 24 |
|-----------------------------------|-------------------|--------|---------|---------|
| Oxygen (VO2) Max [ml/min]         | 1656.9±134.5      | 1677±205.3 | 1723.1±199.2 | 1800.8±142.4 |
| n                                 | 24                | 12     | 13      | 6       |
| p*                                | 0.57              | 0.50   | 0.18    | 0.18    |
| Anaerobic threshold [ml/min]      | 1032.8±66.1       | 954.6±88.4 | 1085±120.5 | 1101.8±147.6 |
| n                                 | 22                | 11     | 11      | 6       |
| p*                                | <0.05             | 0.27   | 0.43    | 0.43    |
| Nominal [%]                       | 94.7±5.5          | 93.0±6.9 | 96.1±9.4 | 94.3±5.8 |
| n                                 | 21                | 12     | 12      | 6       |
| p*                                | 0.63              | 0.38   | 0.25    | 0.25    |
| Per body weight [ml/min/kg]       | 23.6±2.1          | 24.3±2.9 | 24.8±3.1 | 23.2±2.3 |
| n                                 | 24                | 12     | 13      | 6       |
| p*                                | 0.12              | 0.52   | <0.01   | <0.01   |
| Peak ventilation Mean [l/min]     | 32.6±2.1          | 53.7±5.6 | 49.67±5.8 | 62.8±4.3 |
| n                                 | 23                | 11     | 10      | 6       |
| p*                                | 0.12              | 0.52   | <0.01   | <0.01   |
| Breathing equivalents Eq CO2 anaerobic threshold | 26.6±1.6 | 24.3±2.6 | 26.2±2.4 | 30.8±0.9 |
| n                                 | 22                | 11     | 9       | 6       |
| p*                                | 0.27              | <0.05  | <0.01   | <0.01   |
| Eq O2 anaerobic threshold         | 21.6±1.1          | 21.1±2.3 | 24.0±2.0 | 26.6±0.7 |
| n                                 | 22                | 11     | 11      | 6       |
| p*                                | 0.65              | <0.01  | <0.01   | <0.01   |
| Peak oxygen pulse Peak exercise [ml] | 11.6±0.7 | 12.0±1.3 | 12.7±1.0 | 12.1±1.2 |
| n                                 | 23                | 11     | 12      | 6       |
| p*                                | 0.77              | 0.48   | 0.35    | 0.35    |

*paired comparisons with baseline data before ASD closure
their exercise capacity at month 6 [13] and month 12, respectively [32]. This improvement was observed even in patients classified as asymptomatic, in those with lesser shunts (Qp:Qs ≤ 2.0), and in older patients [13]. Patients, who did not achieve a normal exercise capacity after 3 years from closure had a severely depressed pre-closure peak oxygen uptake [22].

In our study, ergospirometry before ASD closure and during follow-up showed no relevant changes in the maximum individual oxygen capacity or the oxygen pulse, before vs. after ASD closure. Nonetheless, the oxygen uptake at the anaerobic threshold at month 6 was significantly reduced but was increased at later follow-ups. Our patients also showed an increase of peak ventilation after ASD closure. The sensitive but unspecific breathing equivalents for CO2 and O2 rose slightly after the closing procedure but remained in the normal range (except VE/CO2 at month 24). These findings might contrast with previously reported data from various study groups [13, 20, 22, 29, 34]. Potentially, the patients in the present study were healthier than the patients in those earlier studies. In the present study nearly normal (95%) nominal oxygen capacity before closure could be documented. However, in previous studies the pre-closure peak oxygen consumption was 50 to 63 % [20, 33, 35]. In comparison with previous studies, our patients had lower right ventricle systolic pressure before ASD closure and a lower pulmonary to systemic flow ratio. Abnormal RVSP at rest was established as the exclusive parameter affecting cardiopulmonary exercise capacity in patients with ASD. Patients with higher RVSP reached significantly earlier the anaerobic threshold [20, 25].

Two major limitations of the study should be discussed. First, some patients missed their follow-ups or were unwilling to have exercise tests before and/or during follow-up, especially at month 24 or 36 after ASD closure. However, a paired comparison permitted a statistically valid analysis. Second, the number of patients in our study was not sufficient to perform subgroup analysis on which patients benefited most from ASD closure.

**Conclusion**

Pulmonary hypertension is the most important complication in patients with haemodynamically relevant ASD, and severe pulmonary hypertension predicts shortened life expectancy. Patients with ASD often have latent pulmonary hypertension that becomes apparent during exercise. ASD closure, especially by ASD septal occluder systems, led to a significant reduction in pulmonary hypertension at rest and also during exercise and also to a distinct decrease in the right heart volumes and diameters. In contrast, functional parameters of the right ventricle at rest did not improve after ASD closure, and the maximum individual oxygen capacity did not change after ASD closure.

However our findings, especially the reduced pulmonary pressure during exercise stress, should help physicians in their decision regarding early ASD closure in this kind of patients.

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