Impaired exercise capacity following atrial septal defect closure: an invasive study of the right heart and pulmonary circulation

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Abstract: Patients with early repair of an isolated atrial septal defect (ASD) are expected to have unremarkable right ventricular (RV) and pulmonary circulation physiology. Some studies, however, suggest persistent functional impairment. We aimed to examine the role of abnormal RV and pulmonary vascular response to exercise in patients who had undergone ASD closure. Using a previously published data set, we reviewed invasive exercise cardiopulmonary testing with right-sided hemodynamic data for 12 asymptomatic patients who had undergone ASD closure. The 5 (42%) patients with impaired maximal oxygen uptake ($\dot{V}o_{2max}$) were older and exhibited a lower peak cardiac index (5.6 ± 0.8 vs. 9.0 ± 1.2 L/min/m^2; P = .005) because of abnormal stroke volume augmentation (+3.2 ± 3.9 vs. +17.4 ± 10.2 mL/m^2; P = .02). While all resting hemodynamic variables were similar, patients with low $\dot{V}o_{2max}$ tended to have abnormal total pulmonary vascular resistance change during exercise (+11% ± 41% vs. −28% ± 26%; P = .06) and had a steeper relation between mean pulmonary arterial pressure and cardiac index (5.8 ± 0.6 vs. 2.2 ± 0.1 L/min/m^2; P = .02). The increase in peak mean RV power during exercise was also significantly lower in the impaired-$\dot{V}o_{2max}$ patients (4.7 ± 1.6 vs. 7.6 ± 2.1 J/s; P = .04). As described in the original study, despite normal resting hemodynamics, a subset of asymptomatic patients with repaired ASD had diminished exercise capacity. Our analysis allows us to conclude that this is due to a combination of abnormal pulmonary vascular response to exercise and impaired RV function.

Keywords: atrial septal defect, right ventricle, pulmonary circulation, exercise.

Pulm Circ 2014;4(4):630-637. DOI: 10.1086/678509.

INTRODUCTION

Atrial septal defect (ASD) is a common congenital heart lesion that results in additional flow through the right atrium, the right ventricle (RV), and the pulmonary circulation. This is usually well tolerated for a prolonged period of time, and the diagnosis is frequently made in adulthood. In general, it is thought that patients who undergo ASD closure early in life have normal exercise capacity and little, if any, associated risk of adverse consequences. Hemodynamically significant ASDs are, however, associated with increased morbidity and mortality if not repaired by early adulthood.[1] Complications include atrial arrhythmia, RV failure, and pulmonary arterial hypertension (PAH). Both surgical and percutaneous ASD closure are effective treatments and are associated with relatively low procedural risk.[2] The clinical course after closure is influenced by a number of factors, with age at time of repair being the most important. Patients who undergo early closure, at age 25 years or younger, are at low risk of clinical events.[1] Few data, however, are available on pulmonary vascular response to closure, with the general assumption being that most patients with normal pulmonary vascular resistance (PVR) before closure have unremarkable pulmonary vascular physiology both before and after the procedure. Similarly, when the RV is no more than moderately dilated before closure, there is little concern for persistent clinically relevant RV

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Submitted February 10, 2014; Accepted April 16, 2014; Electronically published October 28, 2014.

dysfunction. However, while most patients have resolution of RV dilation, some studies demonstrate that, in a sizable subset of patients, RV dilation may persist and maximal exercise capacity may remain impaired in long-term follow-up.[3-5] In theory, exercise impairment due to cardiovascular limitation could result from persistent, underrecognized changes in the RV and the pulmonary arterial (PA) bed. Epstein and colleagues[6] published unique invasive exercise-hemodynamics data for asymptomatic patients who had undergone ASD closure. They pointed to cardiac output as the explanation of impaired aerobic capacity. In light of contemporary concepts of pulmonary vascular physiology during exercise, we hypothesized that both residual RV and pulmonary vascular dysfunction contribute to impaired exercise capacity in patients with surgically repaired ASD. To test this hypothesis, we reanalyzed the published raw data, focusing on both the RV and pulmonary vascular performance.

METHODS

We reviewed data collected by Epstein and colleagues at the National Institutes of Health.[6] The authors studied 12 patients (9 women and 3 men) 6–15 months after surgical closure of isolated secundum ASD without clinically apparent pulmonary vascular disease. All patients were asymptomatic (New York Heart Association functional class I). Each patient underwent right heart catheterization at rest, followed by treadmill exercise with indwelling brachial and pulmonary artery (PA) catheters. Invasive hemodynamic data and oxygen uptake ($\dot{V}o_2$) were recorded at rest and during submaximal and maximal exercise. Maximal exercise was confirmed by a PA oxygen saturation of no more than 30%. Cardiac output (Qt) was estimated by the direct Fick principle. Primary data are available at http://circ.ahajournals.org/content/47/5/1065.full.pdf.[6]

Preoperative resting catheterization was performed in all 12 subjects. One patient had clinical evidence of heart failure several months before surgical closure, but this markedly improved with sodium restriction and diuretic medication. As reported in the initial series, preoperative Qp : Qs (pulmonary cardiac output : systemic cardiac output) ranged from 1.6 to 3.0, and Rp : Rs (pulmonary vascular resistance : systemic vascular resistance) ranged from 0.03 to 0.22, with only 1 subject having a ratio higher than 0.16. Right and left atrial pressure and cardiac index (CI) were normal (<8 mmHg, <11 mmHg, and >2.2 L/min/m^2, respectively) in all patients. PA systolic pressure (PASP) was normal in 7 patients, mildly elevated (40–55 mmHg) in 4 patients, and more severely elevated (90 mmHg) in 1 patient. In 7 of the 12 patients, maximal $\dot{V}o_2$ ($\dot{V}o_{2max}$) was determined both pre- and postoperatively. The $\dot{V}o_{2max}$ increased an average of 23% (from 23.2 $\pm$ 1.9 to 28.5 $\pm$ 3.4 mL/kg/min) between the preoperative and postoperative studies in that subset.

Of the 12 patients undergoing maximal exercise testing postoperatively, all asymptomatic, 5 (42%) had an impaired exercise response, compared to a group of healthy controls, despite the presence of normal resting hemodynamics. Given the absence of arrhythmia, residual shunt, or resting PAH, the authors ascribed this exercise limitation to RV dysfunction. Only 4 of the 12 patients developed a mean PA pressure (mPAP) higher than 30 mmHg at peak exercise. The physiologic mechanism of impaired Qt was not, however, further explored.

We reanalyzed these invasive hemodynamic data in the light of contemporary interest in the dynamic response of the RV and pulmonary circulation to exercise. In the original study, the exercise performance was classified by direct comparison of patients with 16 healthy subjects used as controls, whereas we categorized patients as having or not having an abnormal maximal exercise capacity by using individual $\dot{V}o_{2max}$ predicted according to the Wasserman algorithm,[7] not available at that time. A $\dot{V}o_{2max}$ less than 80% of that predicted was defined as an impaired exercise capacity. Of the 12 patients, 9 were women. We did not, however, have access to the gender of individual subjects, and we therefore applied the female predicted $\dot{V}o_2$ equations to all subjects. Although we cannot rule out the misclassification of male subjects to the normal group, given the higher proportion of women in the studied population, applying the female equation seemed the most reasonable and conservative approach, as it would tend to underestimate the presence of impaired exercise capacity. To further address the possibility that misclassification may have affected our results, we assumed that the 3 subjects with highest body surface area (BSA) were male and repeated our analyses using male equations for predicted $\dot{V}o_2$ for those 3 subjects. To investigate the mechanisms of the low CI, we evaluated chronotropic competence by calculating the percentage of the predicted maximal heart rate (HR; [(220 − age)/peak HR] × 100). To assess RV function, we calculated RV mean power, expressed in joules per second, as HR × mPAP × stroke volume (SV) × 2.22 × 10^{-6}, at rest and at maximum exercise.[8] The relationship between ΔmPAP and ΔQt was assessed both graphically and by calculating the slopes of these relationships from the 3 study points (rest and submaximal

and maximal exercise) for individual patients. We also calculated total PVR indexed to BSA (TPVRi), calculated as mPAP/CI. Neither left atrial pressure nor pulmonary capillary wedge pressure during exercise was reported. PA compliance (Cp), calculated as SV/PA pulse pressure, was determined in the 8 patients with available data.

Statistical analysis. Continuous variables are expressed as means ± SD, and categorical variables are expressed as number of subjects and proportion (*n* (%)). Comparisons between groups were performed with 2-sided parametric or nonparametric tests (unpaired or paired *t* or Wilcoxon rank-sum test), depending on the underlying distribution; the Fisher exact test was applied to compare proportions. The slope of the mPAP/Qt plot was estimated with linear regression analysis. We used analysis of covariance to compare the slopes between groups. A *P* value of less than .05 was considered significant. Statistical analysis was performed with Stata software, version 12.1 (StataCorp, College Station, TX), and SAS for Windows, version 9.3 (SAS Institute, Cary, NC).

RESULTS

Postoperative maximal aerobic capacity was reduced ($\downarrow\dot{V}o_{2max}$, i.e., $\dot{V}o_{2max}$ < 80% of that predicted by current normative predictive equations) in 5 of the 12 patients (42%). Those with $\downarrow\dot{V}o_{2max}$ were older than those with normal exercise capacity (41 ± 12 vs. 26 ± 11 years, P = .03). No other significant differences were found between groups regarding preoperative factors, including hemodynamic data (Table 1). However, preoperative resting PASP (50.4 ± 27.9 vs. 32.3 ± 8.1 mmHg, P = .19) and Rp : Rs (0.12 ± 0.07 vs. 0.06 ± 0.01 mmHg, P = .19) showed a trend toward higher values in patients with $\downarrow\dot{V}o_{2max}$. Postoperatively, no patient had residual shunting at rest or with exercise (i.e., Qp = Qs), and no patient demonstrated systemic arterial desaturation (arterial O_2 saturation > 97%). Resting postoperative hemodynamic data were similar between groups (Table 2), including CI, mPAP, TPVR, RV power, and Cp. The investigators confirmed peak aerobic effort by using PA saturation (all <30%); in addition, all subjects had peak HR higher than 85% of that predicted.

Table 1. Preoperative characteristics of ASD patients

Variable	$\downarrow\dot{V}o_{2max}$ (n = 5)	Normal $\dot{V}o_{2max}$ (n = 7)	P value
Age, years	41 ± 12	26 ± 11	.03
BMI, kg/m^2	21.1 ± 3.6	22.8 ± 3.9	.29
CI, L/min/m^2	2.7 ± 0.5	2.9 ± 0.4	.57
RA pressure, mmHg	5.0 ± 1.9	4.6 ± 2.1	.80
LA pressure, mmHg	6.4 ± 2.0	5.3 ± 2.0	.32
PASP, mmHg	50.4 ± 27.9	32.3 ± 8.1	.19
TPVRi, WU m^2	10.8 ± 5.3	7.2 ± 2.2	.43
Qp : Qs	2.4 ± 0.4	2.3 ± 0.5	.62
Rp : Rs	0.12 ± 0.07	0.06 ± 0.01	.19

Note: Data are presented as mean ± SD. ASD: atrial septal defect; BMI: body mass index; CI: cardiac index; LA: left atrium; PASP: pulmonary artery systolic pressure; Qp: pulmonary cardiac output; Qs: systemic cardiac output; RA: right atrium; Rp: pulmonary vascular resistance; Rs: systemic vascular resistance; TPVRi: total pulmonary vascular resistance, indexed to body surface area; $\dot{V}o_{2max}$: maximal oxygen uptake with exercise; $\downarrow\dot{V}o_{2max}$: $\dot{V}o_{2max}$ <80% of that predicted.

Pulmonary vascular response to exercise

Peak-exercise CI was significantly lower in the group with $\downarrow\dot{V}o_{2max}$ (5.6 ± 0.8 vs. 9.0 ± 1.2 L/min/m^2, P = .005; Table 2). At peak exercise, mPAP was slightly higher among patients with $\downarrow\dot{V}o_{2max}$ (30.4 ± 7.8 vs. 25.3 ± 5.2 mmHg, P = .26), although this difference did not reach statistical significance in the context of the small sample size. Three patients with $\downarrow\dot{V}o_{2max}$ and 1 patient with normal $\dot{V}o_{2max}$ had peak mPAP greater than 30 mmHg. There was a difference in the ΔmPAP/ΔQt slope (Fig. 1), with a steeper slope among those with $\downarrow\dot{V}o_{2max}$, compared with patients who had normal aerobic capacity (5.8 ± 0.6 vs. 2.2 ± 0.1 mmHg/L/min, P = .02). TPVRi decreased 28% from baseline to peak exercise in those with normal $\dot{V}o_{2max}$, consistent with a normal physiologic response (Table 2). Conversely, TPVRi tended to increase (+11%), on average, in the patients with reduced aerobic capacity. An exercise increase in TPVRi was observed in 2 (40%) of the 5 patients with impaired $\dot{V}o_{2max}$ and in only 1 (14%) of the 7 with normal $\dot{V}o_{2max}$. There was overlap between resting TPVRi values, but peak TPVRi decreased to less than 4 Wood units/m^2 for all 7 of the patients with normal $\dot{V}o_{2max}$ but remained above that figure for the 5 with impaired $\dot{V}o_{2max}$ (Fig. 2). Likewise, Cp declined in the impaired-$\dot{V}o_2$ group, while Cp changed little in the normal-$\dot{V}o_{2max}$ patients during exercise (−7.7 ± 5.7 vs. −1.4 ± 4.8 mL/mmHg; P = .23). While mPAP was available in all subjects, only 3 of the 5 patients in the low-$\dot{V}o_{2max}$ group and 5 of the 7 patients in the normal-$\dot{V}o_{2max}$ group had available data (systolic and diastolic PAP) to calculate Cp.

Right ventricular response to exercise

Despite equivalent resting values, peak mean RV power tended to be lower in the $\downarrow\dot{V}o_{2max}$ group than in the

Table 2. Resting and peak-exercise hemodynamic data by peak $\dot{V}o_2$ status

Variable	$\downarrow\dot{V}o_{2max}$ ($n = 5$)	Normal $\dot{V}o_{2max}$ ($n = 7$)	P value
$\dot{V}o_{2max}$, mL/Kg/min	21.9 ± 3.2	35.1 ± 7.3	.007 (by design)
$\dot{V}o_{2max}$, % of predicted	53 ± 8	112 ± 18	.005 (by design)
Resting CI, L/min/m^2	2.6 ± 0.7	2.7 ± 0.6	.68
Peak CI, L/min/m^2	5.6 ± 0.8	9.0 ± 1.2	.005
ΔCI, L/min/m^2	3.0 ± 0.5	6.3 ± 1.3	.004
Resting SVi, mL/ m^2	29.8 ± 6.6	33.1 ± 6.7	.46
Peak SVi, mL/ m^2	33.0 ± 3.0	50.6 ± 8.0	.004
ΔSVi, mL/m^2	3.2 ± 3.9	17.4 ± 10.2	.02
Peak PA O_2 saturation, %	26 ± 3	22 ± 8	.57
Resting HR, bpm	86 ± 7	82 ± 8	.34
Peak HR, bpm	171 ± 13	180 ± 10	.33
% predicted maximal HR	104 ± 5	108 ± 10	.29
Resting TPVRi, WU m^2	5.2 ± 1.7	4.3 ± 1.6	.22
Peak TPVRi, WU m^2	5.3 ± 1.2	2.8 ± 0.4	.004
ΔTPVRi, %	11 ± 41	−28 ± 26	.06
Resting Cp, mL/mmHg[a]	10.7 ± 5.5	6.4 ± 3.9	.23
Peak Cp, mL/mmHg[a]	3.0 ± 1.7	5.2 ± 2.8	.16
ΔCp, mL/mmHg[a]	−7.7 ± 5.7	−1.4 ± 4.8	.23
Resting mPAP, mmHg	12.8 ± 2.8	11.1 ± 3.0	.28
Peak mPAP, mmHg	30.4 ± 7.8	25.3 ± 5.2	.26
ΔmPAP/Δ CI, mmHg/(L/min/m^2)	5.8 ± 0.6	2.2 ± 0.1	.02
Resting μRV power, J/s	1.1 ± 0.3	1.1 ± 0.4	.81
Peak μRV power, J/s	5.9 ± 1.8	8.7 ± 2.3	.06
ΔμRV power, J/s	4.7 ± 1.6	7.6 ± 2.1	.04

Note: Data are presented as mean ± SD. CI: cardiac index; CO: cardiac output; Cp: pulmonary artery compliance; Δ: change between resting and peak-exercise values; HR: heart rate; mPAP: mean pulmonary artery pressure; μRV power: mean right ventricle power; PA: pulmonary artery; peak: at peak exercise; RV: right ventricle; SVi: indexed stroke volume; TPVRi: indexed total pulmonary vascular resistance; $\dot{V}o_{2max}$: maximal body oxygen uptake; $\downarrow\dot{V}o_{2max}$: $\dot{V}o_{2max}$ <80% of that predicted; WU: Wood units.

[a] Hemodynamic data required to calculate Cp were available from 8 of 12 patients.

normal-$\dot{V}o_{2max}$ group (5.9 ± 1.8 vs. 8.7 ± 2.3 J/s, P = .06). The RV augmented its mean energy generation per unit time 8-fold in those with normal $\dot{V}o_{2max}$ but only 5-fold in those with $\downarrow\dot{V}o_{2max}$ (Table 2).

Ventricular-arterial interaction

As shown in Figure 3, both greater negative ΔTPVRi% (r^2 = 0.32, P = .06) and higher peak mean RV power (r^2 = 0.64, P = .003) were associated with higher $\dot{V}o_{2max}$. In the univariate analysis, age was inversely associated with $\dot{V}o_{2max}$ (r^2 = 0.54, P = .007). A multivariable model including all 3 variables as predictors of $\dot{V}o_{2max}$ improved prediction of $\dot{V}o_{2max}$ (r^2 = 0.85, P = .001), and each tended to retain independent predictive capacity (ΔTPVRi%: β = −0.23, P = .11; RV power: β = +6.81, P = .01; age: β = −1.08, P = .03). Removing ΔTPVRi% from the model decreased the r^2 to 0.80.

Sensitivity analysis

Using the male predicted-$\dot{V}o_2$ equation for the 3 subjects with the highest BSA, 1 of the 3 would be reclassified from normal to low $\dot{V}o_{2max}$, and 50% (6/12) of all subjects would be classified as having low $\dot{V}o_{2max}$. This change did not substantively affect the results of our analysis, however, and only the results with peak $\dot{V}o_2$ classified assuming female predicted values are presented.

DISCUSSION

These data demonstrate the presence of distinctly abnormal RV and pulmonary vascular responses to exercise in

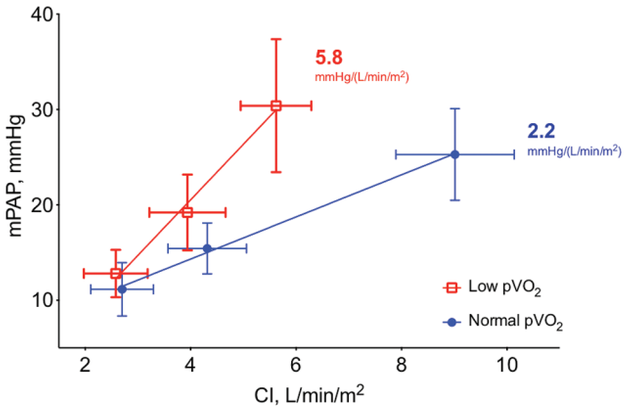

Figure 1. Relationship between mean pulmonary arterial pressure (mPAP) and cardiac index (CI): mPAP-flow plots in patients with impaired and normal $\dot{V}o_{2max}$.

a subset of patients after successful ASD closure. It is especially notable that all the patients were asymptomatic and had uniformly normal resting hemodynamics, yet the presence of isolated abnormal exercise RV and pulmonary vascular dysfunction was associated with a significantly reduced $\dot{V}o_{2max}$. The combination of blunted physiological decrease of TPVR during exercise and limited RV systolic function appears to be an important determinant of impaired exercise capacity in patients after ASD repair.

The beneficial impact of ASD closure on quality of life, functional capacity, and life expectancy is clear.[3,9] Nevertheless, studies suggest residual impaired exercise capacity after closure in a substantial fraction of patients.[3-5] Recently, Cuypers et al.[3] reported impaired exercise capacity, increased RV volumes, and mild RV dysfunction in one-third of repaired-ASD patients, using echocardiography and cardiac magnetic resonance imaging. Using similar methodology, de Koning et al.[10] documented residual RV dilatation but normal exercise capacity. Both studies reported normal resting PASPs estimated by echocardiography. Accordingly, we found no significant differences in resting mPAP between the impaired- and normal-aerobic-capacity groups. Further, patients from both groups presented similar peak mPAPs. PAP, however, is a function of both PVR and blood flow, with the latter importantly influenced by RV function. Thus, even in the presence of an increased TPVR, it is not entirely surprising that patients with impaired $\dot{V}o_{2max}$ due to a central cardiac limit presented with no differences in peak mPAP. Although TPVR at peak exercise provides some insight into pulmonary structure and function, an evaluation of the dynamic relationship between changes in mPAP and Qt consequent to exercise better defines the presence of an abnormal pulmonary vasculature. Concordantly with a previous noninvasive echocardiographic study, where the ΔmPAP/ΔQt was associated with $\dot{V}o_{2max}$ in patients with repaired and unrepaired ASD,[11] our data demonstrate that patients with impaired $\dot{V}o_{2max}$ have a steeper ΔmPAP/ΔQt relationship than those with normal $\dot{V}o_{2max}$ (Fig. 1). Age is associated with reduced PA compliance, which may explain the steeper ΔmPAP/ΔQt slope during exercise in healthy elderly.[12] Nevertheless, differences in age between groups likely do not account for the observed ΔmPAP/ΔQt slope difference, as TPVRi was independently associated with functional impairment after adjustment to age. In addition, an increased ΔmPAP/ΔQt slope has been described only for healthy people more than 50 years old, especially those more than 70 years old.[12]

Normally, with exercise there is a decrease in TPVR, mainly explained by mechanical factors such as dilation of perfused vessels and recruitment of collapsed vessels by progressive exercise-induced increase in PAP and shear forces. These changes explain why mPAP normally increases only modestly despite increases in Qt of 2–5-fold during exercise. The increase in TPVR during exercise seen in the patients with impaired $\dot{V}o_{2max}$, despite normal resting TPVR, is strikingly abnormal. This could represent decreased precapillary pulmonary vessel compliance, a smaller number of recruitable vessels, impaired flow-dependent vasodilation, or PA vasospasm.[13,14] Any such changes are presumably a consequence of chronic shunt flow during the preclosure ASD period.[15] Alternatively, increased mPAP could be due to a rise in pulmonary venous pressure; since data on left-sided pressures

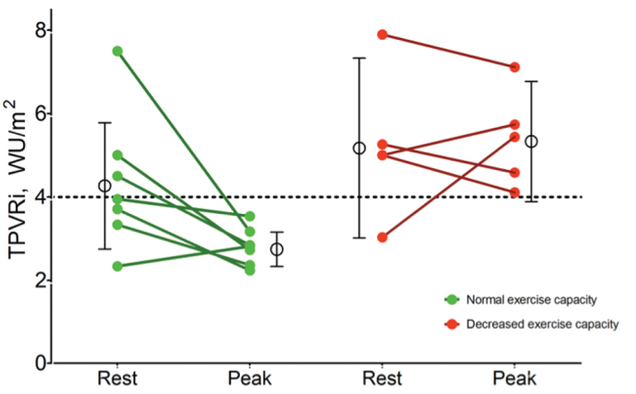

Figure 2. Total pulmonary vascular resistance (TPVR) at rest and at peak exercise. TPVRi (TPVR indexed to body surface area) for each subject at rest and at peak exercise, categorized by impaired (red) and normal (green) $\dot{V}o_{2max}$. Means and 95% confidence intervals are also provided. WU: Wood units.

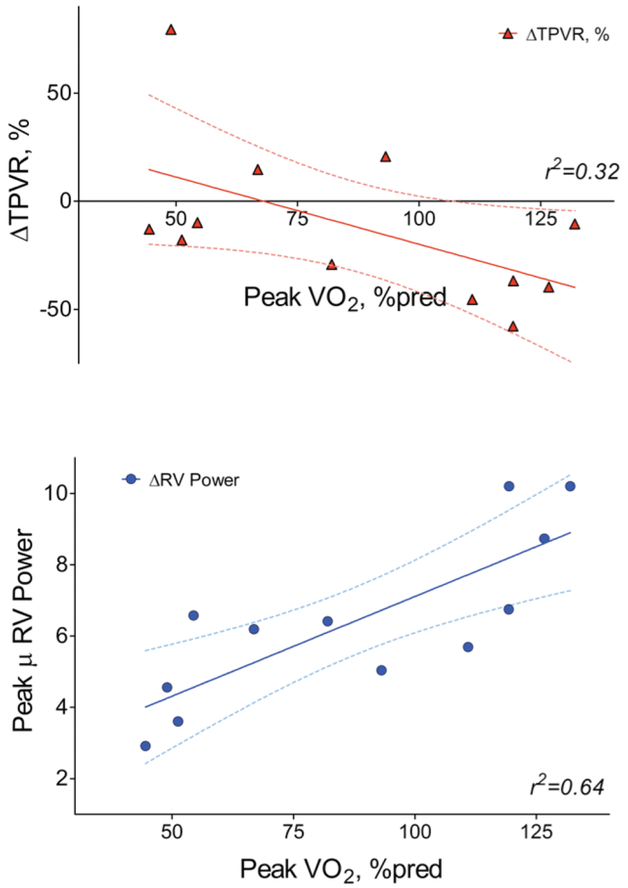

Figure 3. Relationship between $\dot{V}O_{2max}$ and variation of total pulmonary vascular resistance (TPVR) during exercise and right ventricle (RV) power at peak exercise: percentage of predicted $\dot{V}O_{2max}$ by change in TPVRi (TPVR indexed to body surface area) from rest to peak exercise ($P = .057$; *top*) and by peak mean RV (μRV) power ($P = .003$; *bottom*). Both plots show linear regression lines and 95% confidence intervals for the estimate.

with exercise were not reported, we cannot exclude the presence of left ventricular diastolic dysfunction as a cause of these findings.[16] The relatively young age (41 ± 12 years) and normal resting left atrial pressure (9.0 ± 2.2 mmHg) of impaired-$\dot{V}O_{2max}$ patients argues against this mechanism; however, the existence of normal resting data does not preclude an exaggerated exercise-related increase in left atrial pressure.

Cp measures the PA compliance and reflects the energy storage capacity of the PA system during RV ejection. Together with the PVR, Cp contributes to the hydraulic load imposed on the RV, but in distinction to PVR, it is sensitive to its pulsatile component. Resting Cp is a strong independent predictor of prognosis in PAH associated with congenital heart disease.[17] We found that, at peak exercise, patients with impaired exercise capacity demonstrated a substantially decreased Cp, compared with that at baseline, which is associated with an increase in impedance to RV ejection.

The group of patients with impaired exercise capacity showed substantially reduced RV peak cardiac power. Power is energy per unit of time, and mean RV cardiac power is the energy expended by the RV to drive the mean flow of blood through the pulmonary circulation. While this measure does not include a measure of pulsatile hydraulic power, it is nevertheless closely correlated with total RV power.[8] There are several possible explanations for the reduced RV power augmentation during exercise in the $\dot{V}O_{2max}$-impaired patients. Decreased RV contractility (e.g., related to myocardial fibrosis) has been described in others types of congenital heart disease.[18] Using echocardiography, Van De Bruaene et al.[19] reported that in repaired-ASD patients, changes in RV mean power during exercise were correlated with the RV systolic reserve. RV volume has a hyperbolic relationship with RV power.[20] Additional studies have also shown that an increase in RV volume beyond a certain value reduces RV energetic efficiency. The normal augmentation of preload with exercise may cause a decline in cardiac power at peak exercise, because of a myocardial stretch of an abnormal RV. Finally, progressive tricuspid regurgitation during exercise would result in wasted RV work and lower estimates of peak mean RV power, despite normal intrinsic RV myocardial function. Reduced RV functional reserve was recently demonstrated to be an important prognostic marker in patients with pulmonary vascular disease. Grünig et al.[21] identified pulmonary hypertension patients with high mortality risk, measuring, by echocardiography, the exercise-induced PASP increase, an RV contractile-reserve estimate. The generalizability of these findings to patients with various forms of congenital heart disease is unknown. It is inappropriate to extrapolate from this small data set of patients with an isolated repaired simple pretricuspid congenital shunt lesion to unrepaired lesions or more complex diagnoses, which may have other or multiple reasons for decreased RV power augmentation at rest and during exercise.

To the best of our knowledge, the work from which this article is derived[6] is unique in its use of invasive exercise hemodynamics before and after ASD closure. These data importantly enhance understanding of the pathophysiological mechanisms of impaired exercise capacity in this population. Our study design, by using a published historical data set in conjunction with contemporary concepts and techniques in hemodynamic eval-

uation, not only makes efficient use of an available resource but also takes on special, perhaps irreplaceable, value in an era where invasive research on asymptomatic human subjects is increasingly challenging. While several studies have used echocardiography to assess structural changes and PASP, few have measured exercise response.[11] Further, using echocardiography to assess the pulmonary vascular response to exercise is technically very challenging in this population and still requires validation with invasive gold-standard methods.

Our study has several notable limitations. The small sample size limits extensive inference. The postoperative evaluation was performed 6–15 months after repair, and exercise responses of the pulmonary vasculature and RV may improve over time. Left-sided filling pressures were not measured, and we cannot comment on the possible existence of subclinical LV diastolic dysfunction. Finally, we have no concomitant imaging data, limiting our insight into the mechanisms underlying abnormal RV function with exercise.

Conclusions. A subset of patients with repaired ASD demonstrated a markedly abnormal pulmonary vascular and right ventricular response to exercise, despite normal resting hemodynamics. While these patients reported no symptoms, the abnormal hemodynamic response to exercise was associated with considerably reduced aerobic capacity. An abnormal pulmonary vascular response to exercise, coupled with RV dysfunction, may synergistically limit exercise capacity. These data emphasize the often-overlooked role of assessing exercise response in the comprehensive clinical evaluation of patients with repaired ASD. Further studies are needed to characterize the observed abnormal pulmonary vascular response to exercise and the impaired RV systolic reserve in order to best direct postclosure evaluation and define potential therapeutic approaches. Most important, perhaps, is the need to determine the long-term clinical consequences of these medium-term postoperative abnormalities we have described.

Source of Support: MS receives funds from grant HMSP-ICJ/0013/2012, from the Portuguese Foundation for Science and Technology.

Conflict of Interest: None declared.

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