Restrictive Right Ventricular Physiology and Right Ventricular Fibrosis as Assessed by Cardiac Magnetic Resonance and Exercise Capacity After Biventricular Repair of Pulmonary Atresia and Intact Ventricular Septum

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ABSTRACT

Background: The hypertrophic myocardium, myocardial fiber disarray, and endocardial fibroelastosis in pulmonary atresia and intact ventricular septum (PAIVS) may provide anatomic substrates for restrictive filling of the right ventricle.

Hypothesis: Restrictive right ventricle (RV) physiology is related to RV fibrosis and exercise capacity in patients after biventricular repair of PAIVS.

Methods: A total of 27 patients, age 16.5 ± 5.6 years, were recruited after biventricular repair of PAIVS. Restrictive RV physiology was defined by the presence of antegrade diastolic pulmonary flow and RV fibrosis assessed by late gadolinium enhancement (LGE) cardiac magnetic resonance. Their RV function was compared with that of 27 healthy controls and related to RV LGE score and exercise capacity.

Results: Compared with controls, PAIVS patients had lower tricuspid annular systolic and early diastolic velocities, RV global longitudinal systolic strain, systolic strain rate, and early and late diastolic strain rates (all $P < 0.05$). A total of 22 (81%, 95% confidence interval: 62%–94%) PAIVS patients demonstrated restrictive RV physiology. Compared to those without restrictive RV physiology (n=5), these 22 patients had lower RV global systolic strain, lower RV systolic and early diastolic strain rates, higher RV LGE score, and a greater percent of predicted maximum oxygen consumption (all $P < 0.05$).

Conclusion: Restrictive RV physiology reflects RV diastolic dysfunction and is associated with more severe RV fibrosis but better exercise capacity in patients after biventricular repair of PAIVS.

Introduction

The evolution in management strategy has significantly improved the long-term outcomes of patients with pulmonary atresia and intact ventricular septum (PAIVS).[1–3] In the presence of a reasonably good-sized right ventricle and the absence of a right ventricular (RV)-dependent coronary circulation, RV decompression could be achieved by outflow reconstruction,[2–5] surgical pulmonary valvotomy,[2,3] and transcatheter pulmonary valvotomy with balloon valvoplasty.[6–8] Previous studies have implicated persistent RV diastolic dysfunction despite the achievement of a biventricular repair.[9,10] The hypertrophic myocardium, myocardial fiber disarray, and varying degrees of endocardial fibroelastosis in PAIVS[11–14] probably provide anatomic substrates for restrictive RV physiology defined on the basis of increased antegrade late diastolic flow in the RV outflow during atrial systole.[15] Little is known, however, of the prevalence of restrictive RV physiology, extent of RV fibrosis, and the functional implications of RV diastolic dysfunction in long-term survivors of PAIVS with biventricular circulation. In this study, we tested the hypothesis that restrictive RV physiology is prevalent and related to RV fibrosis as assessed by late gadolinium enhancement (LGE) cardiac magnetic resonance and exercise capacity in adolescents after biventricular repair of PAIVS.

Methods

Subjects

A total of 27 (16 males) patients, age 16.5 ± 5.6 years, who had undergone biventricular repair of PAIVS were consecutively recruited from the cardiac outpatient clinic. The following data were retrieved from the case records: cardiac diagnosis, coronary arterial and RV anatomy, age at interventions, types of procedure, and duration of follow-up since biventricular repair. A total of 27 healthy subjects (16 males), age 15.6 ± 3.9 years ($P = 0.49$), were recruited as controls. All of the patients underwent echocardiography, cardiac

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Clin. Cardiol. 33, 2, 104–110 (2010)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20711

Received: September 22, 2009
Accepted with revision: October 29, 2009

magnetic resonance, and treadmill exercise testing, while control subjects had only echocardiographic assessment. The institutional review board approved the study and all of the subjects gave informed consent.

Echocardiographic Assessment

Transthoracic echocardiography was performed using the Vivid 7 ultrasound system (General Electric/Vingmed Ultrasound, Horten, Norway). All echocardiographic data were analyzed off-line using EchoPAC software (General Electric/Vingmed Ultrasound, Horten, Norway). The average of 3 measurements was used for statistical analyses.

Two-dimensional images were obtained from the apical 4-chamber view for determination of RV end-diastolic and end-systolic areas. M-mode echocardiography was performed from the parasternal short-axis view for measurement of left ventricular (LV) dimensions at end-systole and end-diastole and RV end-diastolic dimension. The images were further analyzed using the 2-dimensional strain software (EchoPAC, General Electric/Vingmed Ultrasound, Horten, Norway) with calculation of RV global longitudinal systolic strain, systolic strain rate, and early and late diastolic strain rates for the entire traced contour of the right ventricle.[16,17]

Pulsed-wave Doppler assessment was performed to detect restrictive right ventricular physiology as defined by the presence of late-diastolic antegrade flow in the pulmonary artery throughout the respiratory cycle.[15] Color tissue Doppler imaging data were recorded from the apical 4-chamber view with determination of the peak tricuspid annular systolic (s), early diastolic (e), and late diastolic (a) velocities and RV isovolumic acceleration (IVA) during myocardial contraction.[18]

Cardiac Magnetic Resonance Imaging

Cardiovascular magnetic resonance was performed using a 1.5T superconducting whole-body imager (GE Signa Horizon Echospeed, General Electric Medical Systems, Milwaukee, WI) with a phase-array torso coil. Late gadolinium enhancement imaging was performed from 5 minutes after intravenous injection of gadolinium-diethylenetriamine pentaacetic acid (DTPA; 0.1 mmol/kg). To analyze the extent of right ventricular LGE, a scoring system based on division of the right ventricle into 7 segments was adopted.[19] The maximum RV LGE score was 20 (3 for 6 segments and 2 for 1 segment). For the left ventricle, a standard 17-segment model was used. Each of the LV segments was scored on a 5-point scale (0 to 4),[20] and the maximum LV LGE score was 68. To assess the interobserver variability in scoring LGE, the images of all patients were independently assessed by 2 radiologists (WWML, AKPW). The intraclass correlation coefficient was 0.98.

Exercise Testing

Treadmill exercise testing (Cardio$_2$, MedGraphics, St. Paul, MN) of patients was performed according to the Bruce protocol. Data collection included duration of exercise, peak oxygen consumption (Vo_{2max}), percent predicted (Vo_{2max}), minute ventilation (V_E), and carbon dioxide production (Vco_2) at maximal exercise. The V_E/Vco_2 slope was derived accordingly.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD). Demographic data and echocardiographic indices between patients and controls were compared using an unpaired Student *t* test and Fisher exact test where appropriate. Echocardiographic, cardiac magnetic resonance, and treadmill exercise parameters were similarly compared between patients with and those without restrictive RV physiology. Pearson correlation analysis was used to assess the relationships between RV and LV LGE scores and indices of RV function and exercise parameters. A P value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 11.5 (SPSS, Inc., Chicago, IL).

Results

Subjects

The 27 PAIVS patients underwent biventricular repair at 0.96 ± 1.48 years of age. A total of 17 patients had surgical pulmonary valvotomy as the initial intervention, 6 patients had RV outflow reconstruction, and 4 patients had transcatheter pulmonary valvotomy with balloon valvoplasty. Of the 27 patients, 21 patients required more than 1 surgical or transcatheter intervention, which included pulmonary balloon valvoplasty (n = 9), RV outflow reconstruction (n = 8), balloon valvoplasty with subsequent outflow reconstruction (n = 2), and systemic-to-pulmonary arterial shunt insertion (n = 2), to achieve biventricular circulation. None of the patients were symptomatic and none required cardiac medications. Weight (54 ± 17 kg vs 53 ± 12 kg, $P = 0.95$) and body surface area (1.5 ± 0.3 m^2 vs 1.5 ± 0.2 m^2, $P = 0.82$) were similar between patients and controls.

Echocardiographic Findings

The echocardiographic findings of PAIVS patients and controls are shown in Table 1. Compared with controls, PAIVS patients had significantly larger RV areas and end-diastolic dimensions (all $P < 0.05$), and LV systolic ($P = 0.02$) and end-diastolic ($P = 0.03$) dimensions. Right ventricular diastolic dysfunction was reflected by the significantly reduced tricuspid annular e velocity ($P < 0.001$), e/a ratio ($P < 0.001$), and global longitudinal early ($P = 0.029$) and late ($P = 0.006$) diastolic strain rates. Systolic RV dysfunction in patients was also suggested by the significantly reduced tricuspid annular s velocity ($P < 0.001$), RV IVA

Table 1. Comparison of Echocardiographic Parameters Between Patients After Biventricular Repair of PAIVS and Controls

	PAIVS Patients (n = 27)	Controls (n = 27)	P
Two-dimensional echocardiography			
RV EDA/BSA (cm^2/m^2)	12.6 ± 3.3	9.2 ± 1.8	<0.001[a]
RV ESA/BSA (cm^2/m^2)	6.5 ± 1.8	5.3 ± 1.2	0.02[a]
RV EDD (cm)	2.8 ± 0.7	2.0 ± 0.4	<0.001[a]
LV EDD (cm)	4.0 ± 0.5	4.3 ± 0.4	0.03[a]
LV ESD (cm)	2.5 ± 0.5	2.8 ± 0.4	0.03[a]
TV annulus tissue Doppler			
s (cm/s)	7.4 ± 1.4	9.3 ± 1.3	<0.001[a]
e (cm/s)	7.8 ± 1.1	11.3 ± 1.9	<0.001[a]
a (cm/s)	6.4 ± 1.9	6.2 ± 2.0	0.85
e/a ratio	1.3 ± 0.4	2.1 ± 1.0	0.004[a]
IVA (m/s^2)	1.0 ± 0.4	1.4 ± 0.4	0.003[a]
Two-dimensional strain			
RV systolic strain (%)	22.7 ± 4.6	25.8 ± 4.1	0.01[a]
RV systolic strain rate (/s)	1.2 ± 0.2	1.4 ± 0.3	0.008[a]
RV early diastolic strain rate (/s)	1.7 ± 0.5	2.0 ± 0.4	0.03[a]
RV late diastolic strain rate (/s)	0.8 ± 0.3	1.0 ± 0.2	0.006[a]

Abbreviations: a, peak tricuspid annular velocity during late diastole; BSA, body surface area; e, peak tricuspid annular velocity during early diastole; EDA, end-diastolic area; ESA, end-systolic area; EDD, end-diastolic dimension; ESD, end-systolic dimension; IVA, isovolumic acceleration; s, peak tricuspid annular velocity during systole; PAIVS, pulmonary atresia and intact ventricular septum; RV, right ventricular; TV, tricuspid valve.
[a] Statistically significant.

Table 2. Comparison of Echocardiographic Parameters Between Patients With and Those Without Restrictive Right Ventricular Physiology

	With Restrictive RV Physiology (n = 22)	Without Restrictive RV Physiology (n = 5)	P
TV annulus tissue Doppler			
s (cm/s)	7.4 ± 1.5	7.3 ± 1.6	0.92
e (cm/s)	7.9 ± 1.0	7.6 ± 1.6	0.59
a (cm/s)	6.5 ± 2.0	6.0 ± 1.1	0.60
e/a ratio	1.3 ± 0.4	1.3 ± 0.2	0.78
IVA (m/s^2)	0.9 ± 0.4	1.3 ± 0.7	0.06
Two-dimensional strain			
RV systolic strain (%)	21.5 ± 4.2	27.8 ± 2.8	0.004[a]
RV systolic strain rate (/s)	1.1 ± 0.2	1.4 ± 0.2	0.012[a]
RV early diastolic strain rate (/s)	1.6 ± 0.4	2.2 ± 0.5	0.005[a]
RV late diastolic strain rate (/s)	0.8 ± 0.3	1.0 ± 0.3	0.18

Abbreviations: a, peak tricuspid annular velocity during late diastole; e, peak tricuspid annular velocity during early diastole; IVA, isovolumic acceleration; s, peak tricuspid annular velocity during systole; RV, right ventricular; TV, tricuspid valve.
[a] Statistically significant.

($P = 0.002$), and global systolic strain ($P = 0.012$), and strain rate ($P = 0.008$).

Restrictive RV Physiology

The prevalence of restrictive RV physiology after biventricular repair of PAIVS was 81% (22/27) with a 95% confidence interval of 62% to 94%. Age ($P = 0.26$), age at achievement of biventricular circulation ($P = 0.63$), and duration of follow-up ($P = 0.26$) were similar between these 22 patients and the 5 patients without restrictive RV physiology.

Table 2 shows the echocardiographic parameters of PAIVS patients with and those without restrictive RV physiology. Compared to patients without restrictive RV physiology, patients with restrictive RV physiology had significantly lower global RV systolic strain ($P = 0.004$), systolic strain rate ($P = 0.012$), and early diastolic strain rate ($P = 0.005$).

In terms of exercise capacity, patients with restrictive RV physiology had significantly greater percent predicted Vo_{2max} (76.6% ± 9.0% vs 63.6% ± 16.0%, $P = 0.03$) and their V_E/Vco_2 slope also tended to be lower (32.0 ± 4.3 vs 36.6 ± 5.6, $P = 0.09$) compared to those without. Their exercise duration also appeared longer, but did not reach statistical significance (594 ± 163 sec vs 478 ± 152 sec, $P = 0.20$).

Cardiac Magnetic Resonance Imaging

The RV and LV LGE scores are summarized in Table 3. Examples of LGE after PAIVS repair are shown in Figure 1. In the right ventricle, the most significantly affected segments were the anterior wall, inferior wall, and RV outflow, while the distribution in the left ventricle appeared to be more scattered. There was no correlation between RV and LV LGE scores ($P = 0.24$).

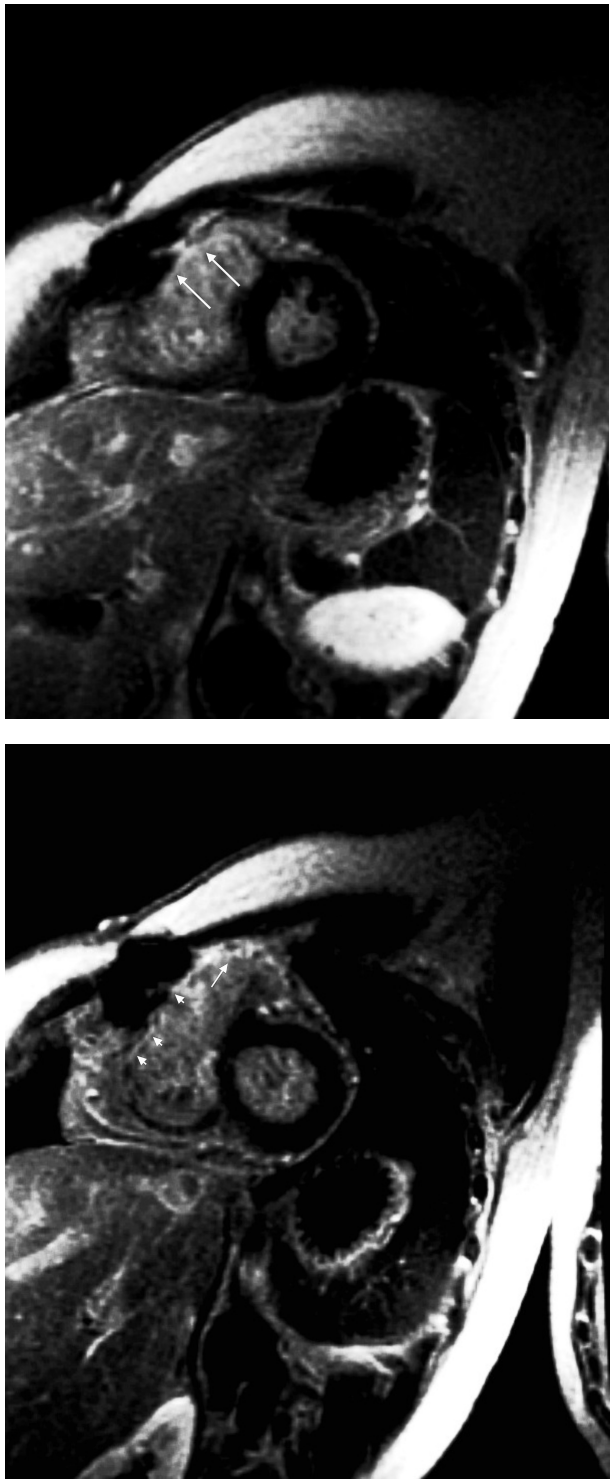

Figure 1. Late gadolinium enhancement (arrows) of the right ventricular anterior wall (upper panel) and anterior wall and infundibulum (lower panel) in 2 patients.

Table 3. Late Gadolinium Enhancement Scores of the Right and Left Ventricles in Patients

Ventricular Segment	Total Score of 27 Patients	Mean ± SD
Right ventricle		
Anterior wall of outflow	29	1.0 ± 1.0
Anterior wall	46	1.6 ± 0.9
Inferior wall	33	1.2 ± 1.1
RV surface of septum	4	0.1 ± 0.4
Membranous region	1	0.04 ± 0.2
Trabecular bands	1	0.04 ± 0.2
RV insertion points	21	0.8 ± 0.5
Left ventricle		
Basal anterior	7	0.3 ± 0.5
Basal anteroseptal	6	0.2 ± 0.6
Basal inferoseptal	15	0.5 ± 0.7
Basal inferior	3	0.1 ± 0.3
Basal inferolateral	2	0.07 ± 0.3
Basal anterolateral	4	0.1 ± 0.4
Mid anterior	4	0.1 ± 0.4
Mid anteroseptal	8	0.3 ± 0.7
Mid inferoseptal	20	0.7 ± 1.0
Mid inferior	10	0.4 ± 0.8
Mid inferolateral	0	0.0 ± 0.0
Mid anterolateral	6	0.2 ± 0.5
Apical anterior	6	0.2 ± 0.5
Apical septal	9	0.3 ± 0.8
Apical inferior	6	0.2 ± 0.6
Apical lateral	6	0.2 ± 0.6
Apex	13	0.5 ± 1.0

Abbreviations: RV, right ventricular; SD, standard deviation.

The RV LGE score was significantly greater in PAIVS patients with restrictive RV physiology than those without restrictive RV physiology (5.6 ± 2.4 vs 3.2 ± 1.9, $P = 0.042$). The RV LGE score correlated negatively with RV global longitudinal early diastolic strain rate ($r = -0.40$, $P = 0.038$; Figure 2A), and positively with age at study ($r = 0.43$, $P = 0.024$), exercise duration ($r = 0.45$, $P = 0.029$), and

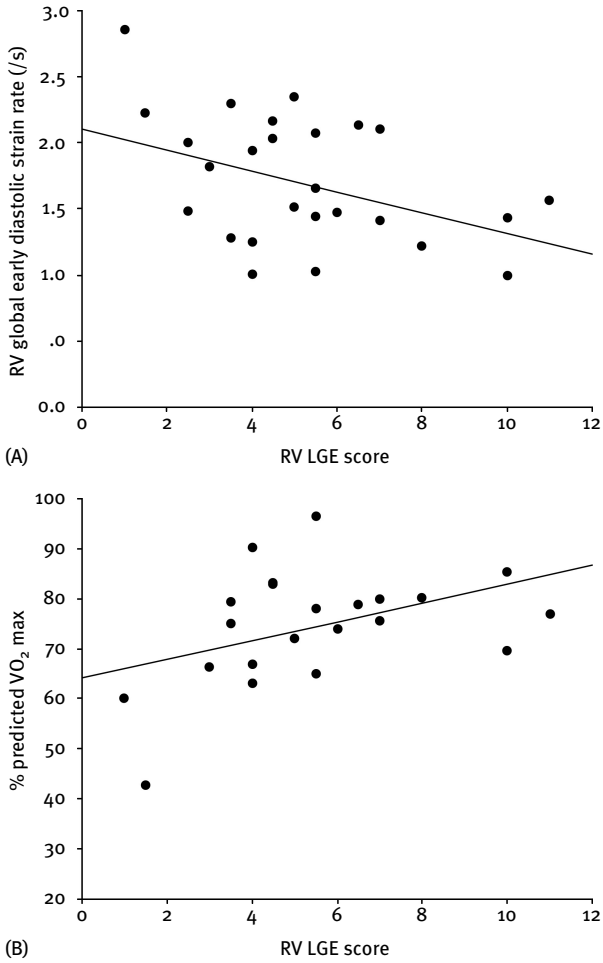

Figure 2. Scatter plots showing correlations between RV LGE scores and (A) RV global longitudinal early diastolic strain rate, and (B) percent predicted peak oxygen consumption $\%VO_{2max}$. Abbreviations: LGE, late gadolinium enhancement; RV, right ventricular.

percent predicted Vo_{2max} ($r = 0.43, P = 0.042$; Figure 2B). There were no correlations between RV LGE scores and indices of RV systolic function including RV IVA, global systolic strain, and global systolic strain rate (all $P > 0.05$).

The LV LGE scores, on the other hand, were similar between patients with and those without restrictive RV physiology (4.9 ± 4.7 vs 2.9 ± 2.4, $P = 0.36$). The LV LGE score did not correlate with age, indices of RV systolic and diastolic function, and parameters of exercise capacity (all $P > 0.05$).

In terms of cardiac magnetic resonance-derived ventricular volumes, patients with restrictive RV physiology compared to those without tended to have smaller RV end-diastolic volume (111 ± 44 mL vs 154 ± 55 mL, $P = 0.10$). larger LV end-diastolic volume (84.5 ± 18.6 mL vs 68.9 ± 14.9 mL, $P = 0.08$), and LV stroke volume (57.5 ± 11.0 mL vs 46.3 ± 12.5 mL, $P = 0.05$).

Discussion

The present study shows that restrictive RV physiology is prevalent in patients with PAIVS despite achievement of biventricular circulation. The novel findings of this study include: (1) demonstration of LGE suggestive of ventricular fibrosis and (2) unveiling of relationships between RV diastolic dysfunction, magnitude of RV fibrosis, and exercise capacity in adolescents after biventricular repair of PAIVS.

Data on RV function in patients after biventricular repair of PAIVS are limited. We have previously reported on significant impairment of longitudinal RV systolic and diastolic function, as assessed by tissue Doppler-derived strain and strain rate imaging, in these patients.[10] Results of the present study suggest stiffening of the right ventricle and corroborate those of Redington et al.[21] Additionally, we have shown that restrictive RV physiology is highly prevalent (81%) in these patients, exceeding the reported 53% prevalence in patients at 15 to 35 years after repair of tetralogy of Fallot (TOF).[22] In postoperative TOF patients, age at repair,[23] placement of a transannular patch,[15,24] and intraoperative myocardial injury with postoperative oxidative stress[25] have variably been incriminated as the cause of restrictive RV physiology. In the current era, RV decompression for PAVIS is usually achieved in young infancy and the need for open heart surgery with placement of a transannular patch has been reduced since the introduction of transcatheter interventions.[3,6–8] Additional factors likely contribute to persistent RV diastolic dysfunction in these patients.

Endocardial and myocardial abnormalities of the right ventricle are well documented in PAIVS, which include massive hypertrophy,[11] extensive myocardial fiber disarray,[12] and endocardial fibroelastosis. While growth in RV size has been shown to occur after RV decompression,[6,7] complete normalization of the histologic abnormalities seems unlikely. Late gadolinium enhancement has been regarded as a marker of myocardial fibrosis and scarring.[26,27] Our findings of RV LGE, which involves predominantly the anterior wall, inferior wall, and RV outflow, and its inverse relationship with indices of RV diastolic function support the contention that persistent myocardial abnormalities due to fibrosis or scarring contribute to persistent RV diastolic dysfunction. Furthermore, the finding of higher LGE in patients with restrictive RV physiology in this study agrees with that reported in adults after repair of TOF.[19] The increase in RV LGE with age in our patients suggests progressive RV fibrosis, although the mechanism is unclear.

Left ventricular abnormalities are also well documented in PAIVS. The influence of associated coronary abnormalities

on LV function has been reported.[28,29] Even in the absence of abnormal coronary sinusoidal communications, medial thickening of intramyocardial coronary arteries, discrete areas of fibrosis and calcification, and high levels of endomysial collagen suggestive of chronic ischemia have been documented.[30,31] Our finding of scattered areas of LGE in the left ventricle is perhaps a reflection of these discrete pathological changes.

A novel finding of the present study is the finding of better exercise capacity in PAIVS patients after biventricular repair with stiffer right ventricles. Data on exercise capacity of PAIVS patients after repair are scarce. In the only previous study that included comprehensive evaluation of exercise function in these patients, Sanghavi et alconcluded that biventricular repair may not guarantee superior exercise performance over univentricular palliation and that the retrospectively reviewed conventional Doppler echocardiographic indices and magnetic resonance imaging parameters did not predict exercise capacity in patients after biventricular repair.[32]

Our findings suggest that worsening RV diastolic function and increased RV fibrosis are associated with better exercise capacity in PAIVS patients after biventricular repair. The cardiac magnetic resonance findings can perhaps shed light on a possible explanation. It appears that stiff right ventricles with impaired diastolic filling may increase LV end-diastolic volume and LV stroke volume. Higher cardiac output may manifest as better functional performance in these patients. Our findings agree with the reported superior exercise capacity in patients with a restrictive right ventricular physiology after repair of TOF, which has been attributed to the contribution of atrial systole to forward pulmonary arterial flow and shortening of duration of pulmonary regurgitation.[22] A similar mechanism might have operated in our patients, although this remains speculative. Clinically, restrictive filling of the right ventricle may ameliorate the impact of pulmonary regurgitation on RV dilation and hence potentially reduce the need for pulmonary valve replacement.

The relatively small number of PAIVS patients with nonrestrictive RV physiology may cause concern about the power of the study. Nonetheless, this would have caused false negative rather than positive findings. Further validation of the greater LV end-diastolic volume and stroke volume is required in a larger population of patients with restrictive RV physiology. Another limitation to this study is the heterogeneous approach to RV decompression. Whether the type of initial intervention would influence long-term RV function remains uncertain. Thirdly, data on the tricuspid valve annulus or RV size at initial presentation during the neonatal period are not available. While a varying degree of RV hypoplasia is characteristic of PAIVS, our patients have probably achieved reasonable RV growth as evidenced by the echocardiographic and magnetic resonance findings. Finally, we have not systemically evaluated the LV systolic and diastolic function as the focus of the present study was on restrictive RV physiology. It remains possible that ventricular-ventricular interaction occurs in our cohort of patients. Additionally, as cardiac catheterization was not performed on our patients, data on pulmonary arterial pressure and capillary wedge pressure are unavailable. Pulmonary hypertension is nonetheless not typical in patients after biventricular repair of PAIVS.

In conclusion, restrictive RV physiology is prevalent in patients after biventricular repair of PAIVS, while the corresponding RV diastolic dysfunction is related to the magnitude of RV fibrosis and associated with better exercise capacity.

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20711

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20711