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ORIGINAL ARTICLE

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Right ventricular contractile reserve in tetralogy of Fallot patients with pulmonary regurgitation

Clotilde Kingsley MBBS[1] | Saad Ahmad MD[2] | John Pappachan MA, MB, BChir, FRCA, MBBS, PhD[1] | Sujata Khambekar MBBS, FRCP, MBBS, PhD[1] | Thomas Smith BSc, MBBS, PhD[1] | Diane Gardiner BSc, MBBS, PhD[1] | James Shambrook MBBS, FRCR[1] | Shankar Baskar MD[3] | Ryan Moore MD[3] | Gruschen Veldtman MBChB, FRCP[3]

[1]Department of Congenital Heart Disease, Southampton University Hospital, Wessex Cardiothoracic Centre, Southampton, UK

[2]Division of Cardiovascular Health and Diseases, University of Cincinnati, Cincinnati, Ohio, USA

[3]Heart Institute Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

Correspondence
Gruschen R Veldtman, Adolescent and Adult Congenital Program, Heart Institute Cincinnati Children's Hospital Medical Centre, 3333 Burnet Avenue, Cincinnati, Ohio 45229, USA.
Email: Gruschen.veldtman@cchmc.org

Abstract

Background: The right ventricular (RV) contractile reserve is a measure of the dynamic function of the RV and is a sensitive indicator of volume load. This can be measured noninvasively using the tricuspid annular plane systolic excursion (TAPSE) during exercise. We studied the RV contractile reserve of patients after tetralogy of Fallot (TOF) repair with varying degree of RV dilation and pulmonary regurgitation (PR), and compared them to a control group.

Methods: Twenty-six patients who had undergone TOF repair (mean age 29 ± 10 years) were identified and stratified into three group based on the presence and severity of RV dilation and PR. We recruited 13 age- and sex-matched controls with normal cardiac anatomy for comparison. After obtaining a baseline echocardiogram in the resting state, patients underwent exercise testing on a treadmill utilizing Bruce protocol. At maximal voluntary ability during the exercise testing, the patient was immediately laid down on an echocardiography couch, and a peak exercise echocardiogram was obtained.

Results: TOF patients, regardless of RV size and PR severity, had significantly shorter exercise duration (685 vs 802 s, $P = .02$), lower TAPSE at rest (1.7 vs 2.3 cm, $P < 0.001$) and at peak exercise (1.6 ± 0.4 vs 2.6 ± 0.5 cm $P < .001$) when compared to the control group. Patients with RV dilation were more likely to have worse RV contractile reserve but increased TAPSE and tricuspid annular acceleration at rest when compared to patients without RV dilation.

Conclusions: TOF patients with dilated RV and PR have worse RV function at rest and during exercise, compared to TOF subjects without RV dilation. Long-axis RV contractile reserve as assessed by TAPSE, was lower in TOF subjects versus controls, and was worse in those with significant RV dilation, suggesting a decline in contractile reserve with an increase in RV volume.

KEYWORDS
contractile reserve, pulmonary valve replacement, timing, tricuspid annular plane systolic excursion

ABBREVIATIONS: EF, ejection fraction; LV, left ventricle; MAPSE, mitral annular plane systolic excursion; MR, magnetic resonance; PR, pulmonary regurgitation; PVR, pulmonary valve replacement; RV, right ventricle; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVOT, right ventricular outflow tract; TAPSE, tricuspid annular plane systolic excursion; TOF, tetralogy of Fallot.

1 | INTRODUCTION

Tetralogy of Fallot (TOF) has a prevalence of 3 per 10 000 live births, accounting for 7%–10% of all congenital cardiac defects.[1] It is surgically repaired by ventricular septal defect closure, resection of muscular right ventricular (RV) outflow obstruction, and/or RV outflow augmentation with a transannular patch which inturn leads to residual pulmonary regurgitation (PR). Failure of RV outflow competence is the most common cause for late reintervention.[2] Pulmonary regurgitation increases RV preload with subsequent RV dilation and possible ventricular dysfunction and dyssynchrony.[3] This portends greater mortality risk from ventricular and atrial arrhythmia.[4] Pulmonary valve replacement (PVR) is performed electively in this setting with low operative mortality of around 1–4%[2,5,6]; however, there is often a requirement for repeat PVR following this procedure.[7] Optimal timing of both initial and subsequent PVR is crucially important. Current guidelines suggest patients with a RV end-diastolic volume (EDV) >150 cc/m^2 or RV end-systolic volume of >80 cc/m^2 require PVR, as normalization of RV volume is more likely if done at this stage.[8,9] When RVEDV exceeds 160 cc/m^2 there is low likelihood for the RV to recover.[9] We aimed to evaluate the relationship between RV volume by cardiac magnetic resonance (CMR) imaging and RV contractile reserve at rest and during exercise using echocardiography-based tricuspid annular plane systolic excursion (TAPSE).

2 | METHODS

2.1 | Participants

Ethical approval for the study was obtained from the Southampton and South West Hampshire Research Ethics Committee as well as approval from the Hospital Trust's Research and Development division. Informed consent was taken from each participant.

2.2 | Study design

This study, with a case-control design, observed exercise-related ventricular contractile response in postoperative TOF patients with varying degrees of RV dilation and PR; where the regurgitation that was unrestricted by valvar tissue was termed as free PR, classifying them into 3 separate groups.

Group 1—normal RV chamber size and trace or mild PR;

Group 2—moderate RV dilation (100 cc/m^2≥RVEDV <140cc/m^2) and moderate-severe PR,

Group 3—severe RV dilation (RVEDV > 140cc/m^2) and moderate-severe PR.

The criteria for inclusion were postoperative TOF patients aged 18 years and older identified from the Southampton University Hospital MRI database. RV volumes and PR measured by cardiac MRI were used to find TOF patients eligible for the study. These patients were sent an invitation to participate in the study. The exclusion criteria included: Left ventricular systolic dysfunction, heart failure exacerbation, known cardiac arrhythmias, age less than 18 years, pregnant women, cardiac MRI done more than 12 months prior to the study, and an inability to obtain consent.

2.3 | MRI analysis

All CMR examinations were performed on a 1.5 Tesla scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany) with body coil and phased array surface coil, using retrospective electrocardiographic gating with the patient in the supine position. Only study subjects with TOF had CMR scan. After piloting using localizers, steady-state free precession cine images (TE/TR 1.5/3.0 ms, flip angle 60°, slice thickness 6 mm, 4 mm interslice in-plane resolution 1.5 × 1.5 mm^2, temporal resolution 45 ms) were acquired in the 2, 3, and 4-chamber long axis views, a full stack of short axis views covering the both ventricles from base to apex. Pulmonary artery velocity flow and direction was performed using a velocity-encoded phase contrast sequence, sagittal and coronal localizer images were used to construct a double oblique plane perpendicular to the vessel. CMR image analysis was performed with Argus software (Siemens Medical Solutions). The short-axis orientation cine stack was used to calculate the left ventricular end-diastolic volume, end-systolic volume, stroke volume and ejection fraction (EF).[10] The axial orientation cine stack was used to calculate the RV end-diastolic volume, end-systolic volume, stroke volume and EF.[11.] All volumes were indexed for body surface area. Calculated pulmonary artery flow was expressed as antegrade and retrograde flow. Pulmonary regurgitant (PR) fraction (%) was calculated as retrograde flow/antegrade flow × 100. Based on the regurgitation fraction, PR was defined as mild (< 25%), moderate (25%-35%) and severe (> 35%).

2.4 | Echocardiography

2.4.1 | Resting echocardiography

A single experienced congenital heart disease sonographer performed all echocardiograms. All images were acquired using a Phillips iE33 echocardiography system with 1–5 MHz transducer (Philips, Andover, MA), with the subject in the left lateral decubitus position. Each view was recorded with a minimum of three sinus beats at end expiration. All the images were digitally captured using and stored in a DICOM file format for offline analysis. Annular excursion measurements of the tricuspid, and mitral valve were obtained via M-mode in the 4-chamber view by placing a marker at the junction between the valve and respective free wall for systolic excursion of the atrioventricular valves.[12,13] Standard 2D and Doppler images were acquired in the apical 4-chamber view, as well as, apical 2-chamber views of both ventricles (Supplement S1).

2.4.2 | Exercise echocardiography

Following the baseline echocardiogram, patients underwent exercise testing on a treadmill utilizing Bruce protocol. At maximal voluntary ability during the exercise testing, the patient was immediately laid down on an echocardiography couch and a peak echocardiogram was obtained.After the procedure, the participant remained monitored until vital signs returned to baseline.

2.4.3 | Offline data analysis for measuring RV contractile reserve

M-mode analysis was performed using 2DQ function on the software (Supplement S2). The tricuspid annulus was identified on the M-mode image and 2 points were selected using the cursor, one point at the baseline (end-diastole) and another at the peak of the waveform (end-systole) to measure the maximal displacement of the TAPSE during the cardiac cycle. The gradient of the initial slope was then calculated to measure mean annular descent velocity. The average of three readings was taken for each of these measurements at the tricuspid valve. This process was repeated for mitral valve annular plane excursion (MAPSE) and septal plane excursion at the crux of the heart. The difference between rest and exercise parameters was denoted as contractile reserve.

2.5 | Statistical analysis

All the data was analyzed using SPSS version 15.0 (IBM, Armonk, NY). All continuous normally distributed data was expressed as means ± standard deviation and range. Noncontinuous data was described as proportions, and percentages. A *P* value < .05 was considered to be statistically significant. A Student *t*-test was used when assessing the difference between the means of continuous variables that were normally distributed, whereas the nonparametric Mann-Whitney U test was used for nonnormally distributed parameters. A nonparametric one-way ANOVA was used when comparing the difference between the mean values of continuous data for the four subgroups (Group 1, Group 2, and Group 3) of TOF patients and the control group. A Spearman's rank correlation coefficient was calculated to evaluate the relationship between various continuous and ordinal data such as RV and LV functional parameters. For the assessment of contractile reserve determinants, factors found to be significant on univariate analysis, were entered into a multivariable model to determine independent predictors of RV contractile reserve.

3 | RESULTS

Twenty-six TOF patients (mean age 29 ± 10 years) were included for the study and grouped after single observer reanalysis of MRI determined RV volumes and PR. Group 1 (n = 9), Group 2 (n = 9), and Group 3 (n = 8). Their mean age at reparative surgery was 31 ± 24 months, 9 (35%) had such surgery during their first month of life. Fourteen patients (54%) had transannular patch at the time of the repair, while no operative data was available in 7 (26%). Four (15%) had at least 1 prior PVR procedure. Thirteen healthy age- and sex-matched volunteers were recruited for comparison from the Southampton region. There was no significant difference between the age, sex and body habitus between the patients and controls (Table 1). Results from the MRI analysis are summarized in Table 2. Although LV volumes and EF were not significantly different between the three groups, RV volume and EF showed significant difference.

TABLE 1 Characteristics of study sample

	Control group (n = 13)	Study group (n = 26)	*P* value
Age (years)	29 ± 10	30 ± 12	.818
Female	11 (42%)	6 (46%)	.464
Ht (meters)	1.7 ± 0.06	1.7 ± 0.12	.911
Wt (kg)	73 ± 17	71 ± 13	.719
BMI (m^2)	26 ± 6.3	25 ± 1.73	.524

3.1 | Exercise test

The TOF patients had a significantly shorter exercise duration (685 ± 162 vs 802 ± 108 sec., *P* = 0.02), achieved a lower maximal workload (13.07 ± 3.11 vs 15.61 ± 2.36 METS, *P* = 0.016), and had lower peak heart rates (137 ± 17 bpm vs 149 ± 16 bpm, *P* = 0.04) than the controls.

3.2 | Echocardiography at rest

TAPSE and mean annular velocity were significantly greater in the control group as compared to TOF groups (Figures 1 and 2). Within the TOF group, TAPSE and mean annular velocity were greater in those with significant RV dilation in the presence of moderate or severe PR. At rest, MAPSE was not significantly different between the control and the TOF group, or within the TOF subgroups. Mitral valve annular mean velocity was greater in the control group compared to the TOF group, (*P* = .05) but did not vary signficantly within the TOF subgroups (Figure 3).

TABLE 2 MRI parameters in the Tetralogy Study Group

	LVEDVi (cc/m^2)	LVESVi (cc/m^2)	LVEF (%)	RVEDVi (cc/m^2)	RVESVi (cc/m^2)	RVEF (%)	PR (%)
Group 1	76 ± 11	31 ± 6	58 ± 5	90 ± 11	43 ± 11	53 ± 6	1 ± 1
Group 2	69 ± 10	25 ± 8	63 ± 8	108 ± 28	43 ± 13	42 ± 7	29 ± 7
Group 3	78 ± 4	35 ± 15	61 ± 6	157 ± 18	78 ± 11	30 ± 4	40 ± 5
All TOF patients	74 ± 10	30 ± 10	61 ± 7	115 ± 34	53 ± 20	42 ± 11	22 ± 17
P value	.105	.171	.257	<.001[a]	<.001[a]	<.001[a]	<.001[a]

Abbreviations: LVEDVi, indexed left ventricular end-diastolic volume; LVESVi, indexed left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; RVEDVi, indexed right ventricular end-diastolic volume; RVESVi, indexed right ventricular end-systolic volume; RVEF, right ventricular ejection fraction; PR, pulmonary regurgitation. [a]Statistically significant.

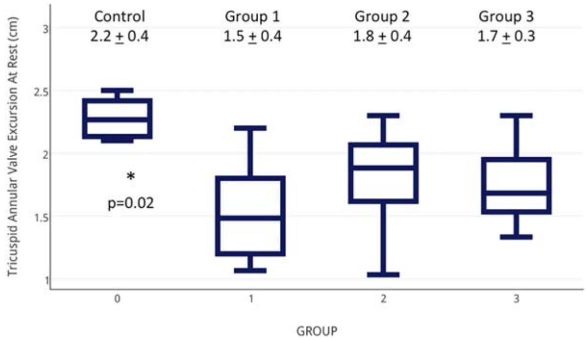

FIGURE 1 TAPSE at rest compared between control and study groups. Group 0 = control participants, Groups 1, 2, and 3 are study groups as defined in the study. Tricuspid annular excursion at rest was significantly higher in the control population when compared to the study groups ($P = .02$)

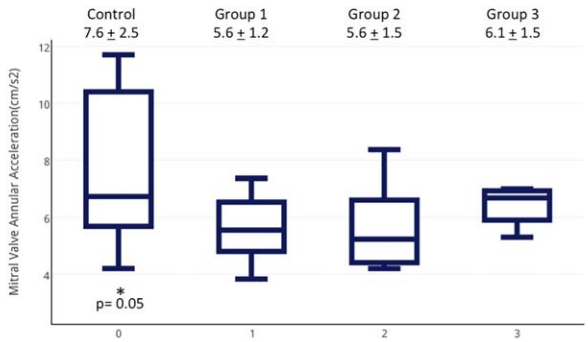

FIGURE 3 Mitral valve annular mean velocity at rest compared between control and study group. Group 0 = control participants, Groups 1, 2, and 3 are study groups as defined in the study. The mitral valve annular acceleration was significantly higher in the control at rest compared to the study groups ($P = .05$)

3.3 | Echocardiography at peak exercise (RV contractile reserve)

Twenty-four TOF patients and all the control patients had interpretable peak exercise TAPSE. At peak exercise TAPSE increased by 0.5 ± 0.3cm in the control group which was significantly greater than that observed in the study group (Figure 4). Within the TOF group, there was minimal increase and even a decline of TAPSE noted at peak exercise (Figure 4). Patients with RV dilation (RVEDV >/= 100 cc/m^2) were more likely to have increased resting tricuspid annular acceleration ($P < .003$) and decreased RV contractile reserve ($P = .036$) when compared to those without RV dilation (Table 3).

3.4 | Patients with decreased tricuspid annular excursion during exercise (negative RV contractile reserve)

Among the 23 TOF patients who had an interpretable peak exercise TAPSE, 15 patients (mean age: 31 ± 12 years) decreased their TAPSE during exercise signifying negative RV contractile reserve. Patients with a negative RV contractile reserve were more likely to have increased resting TAPSE ($P < .04$) and resting tricuspid annular acceleration ($P < .007$) when compared to those with a positive contractile reserve (Table 4).

4 | DISCUSSION

The most significant findings of this study were the documentation of diminished long-axis function at rest and during exercise, as well diminished ontractile reserve in long axis function, particularly in those with larger RV's. Furthermore, patients with RV dilation demonstrated worse RV contractile reserve but relatively preserved resting longitudinal RV function.

Current guidelines for postoperative PR in TOF patients recommend intervention after the onset of either symptoms or progressive RV dilatation. Right ventricular volume is commonly assessed using MRI and function can be quantified by deriving the EF. These measures are usually obtained at rest and provide limited insight into the ability of the RV to cope with volume overload, particularly during exertion. Right ventricular hypertrophy is a defining feature of TOF and hence right ventricular diastolic function, as well as systolic function, may be

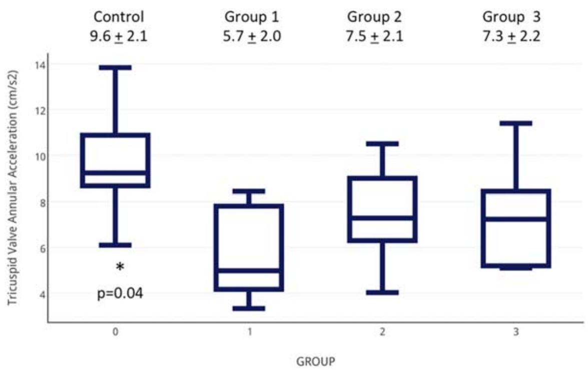

FIGURE 2 Mean tricuspid annular velocity at rest compared between control and study groups. Group 0 = control participants, Groups 1, 2, and 3 are study groups as defined in the study. Tricuspid annular acceleration at rest was significantly higher in the control group compared to the study groups ($P = .04$)

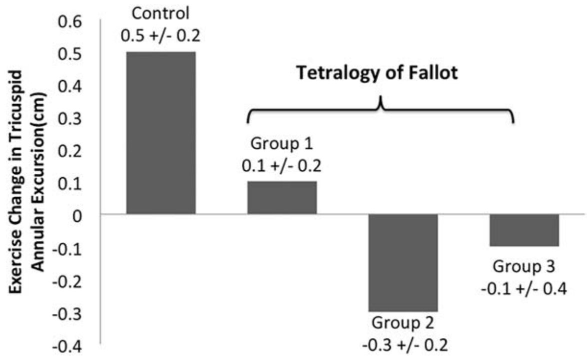

FIGURE 4 Change in TAPSE from rest to peak exercise (right ventricular contractile reserve). The control group had a significant increase in the tricuspid annular excursion at peak exercise compared to the study groups. There was decrease in the annular excursion for TOF Groups 2 and 3

TABLE 3 Comparison of tricuspid excursion characteristics between patients with and without right ventricular dilation

	No RV dilation (<100 ml/m^2) (n = 9)	RV dilation (RVEDI >= 100 ml/m^2) (n = 14)	*P* value
TCV excur diff	0.12 ± 0.38	−0.22 ± 0.24	.036
TAPSE rest	1.56 ± 0.49	1.78 ± 0.28	.31
TCVannaccRest	3.95 ± 0.69	5.13 ± 1.12	.005

Abbreviations: RV, right ventricle, TCV excus diff, tricuspid valve annular plane systolic excursion difference between rest and peak exercise; TAPSE, tricuspid annular plane systolic excursion; TCVAnnAcc, tricuspid valve annular acceleration.

impaired. As in the left ventricle, abnormal diastology may restrict ventricular dilatation in response to volume overload. While MRI provides excellent spatial resolution and image quality to provide more accurate determination of ventricular volumes, the better temporal resolution of echocardiography enables superior assessment of tissue mechanics, in particular tissue contractile function and relaxation patterns to assess diastolic function.

TAPSE is an established indicator of right ventricular longitudinal function. Previous studies confirmed its correlation with MRI derived volumes and EF in both volume and pressure loaded right ventricles in the context of congenital heart disease.[14,15] In younger patients, the correlation between TAPSE and MRI derived EF is less robust as demonstrated by Koestenberger et al. in a large cohort.[16] This is perhaps not that surprising as the right ventricle is able to accommodate increased volumes for many decades prior to the commencement of contractile compromise. Furthermore MRI derived volumes inherently measure different properties of the RV as compared to that assessed by TAPSE.

In our cohort, patients with TOF and dilated RVs in association with PR, had reduced tricuspid annular excursion and mean annular velocities of descent. Importantly they also had lower mean mitral annular velocities at rest as compared to healthy controls. These findings imply that PR and RV dilation have a negative impact on long axis function in both the right and left ventricles. Ventricular-ventricular interaction has long been recognized as an important contributor to both systolic and diastolic ventricular function. Right ventricular filling may, therefore, occur at the expense of the lower diastolic filling of the contralateral ventricle as the septum shifts toward the LV in patients with dilated RV and volume over load. The increased RV volume may also induce relative dyssynchrony of the left ventricle. Cheung et al.[17] demonstrated an inverse relationship between RV volumes and global LV circumferential strain and SR in the left ventricles of patients with TOF and PR.

4.1 | RV contractile reserve

Assessment of contractile reserve in the left ventricle is an established concept. Lee et al.[18] have showed that in asymptomatic patients with severe mitral regurgitation and normal resting LV function, a deteriorating contractile reserve on exercise predicts late LV dysfunction and morbidity postoperatively. A similar study on aortic regurgitation, showed that a decrease in contractile reserve correlated with a decreased EF on follow-up and that it was a useful early marker for progressive deterioration of LV function.[19] Similarly, echocardiographic assessment of ventricular function during stress to identify contractile reserve may provide a more sensitive indicator of declining ability of the right ventricle to cope with volume overload. Brili et al.[20] assessed tissue Doppler indices of tricuspid annular motion and found that patients with TOF had lower resting values and smaller increase in response to dobutamine stress, indicating reduced contractile reserve. Measurement of TAPSE at rest and assessment of the change with stress provides a simple alternative measure that can easily be performed at routine clinical follow-up. However, the influence of exercise and pulmonary regurgitation on TAPSE in this population has not been well studied.

In this study, we observed that patients who had an abnormal RV long axis contractile reserve (42% of TOF patients), had higher RV volumes along with a higher TAPSE and tricuspid annular mean velocity at rest as compared to those TOF patients with preserved RV contractile reserve. Thus patients with larger RV volumes have relatively

TABLE 4 Comparison of characteristics of patients who have positive and negative right ventricular contactile reserve

	Positive contractile reserve (n = 8)	Negative contractile reserve (n = 15)	*P* value
Age	27 ± 4	31 ± 12	.67
RVEDV-Abs	198 ± 77	214 ± 60	.61
RVEDVi	112 ± 42	120 ± 32	.64
TAPSE at rest	1.48 ± 0.3	1.82 ± 0.4	.04
TCVAnnAcc at rest	3.95 ± 0.65	5.06 ± 1.15	.007
RVEF Abs	0.51 ± 0.08	0.57 ± 0.07	.11

Abbreviations: RVEDV-Abs, absolute right ventricular end-diastolic volume; RVEDVi, right ventricular end-diastolic volume indexed to body weight; TAPSE, tricuspid annular plane systolic excursion; TCVAnnAcc, tricuspid valve annular acceleration; RVEF Abs, absolute right ventricular ejection fraction.

"normalized" resting long axis function. During exercise these dilated RVs, however, decompensate under the influence of complex dynamic interactions between PR induced volume load, and failure of further RV contractile adjustment to the dynamic load. This is perhaps best rationalised by the Frank-Starling compensatory mechanism whereby an increase in preload triggers stroke volume augmentation. In other words the volume loaded ventricle has already undergone near maximal contractile adjustment, and exercise stress provokes and unmasks inability for further compensation. The ventricle copes well for a long time with PR but this mechanism ultimately fails, as suggested by the reduction in contractile reserve. It is important to note that despite the fact that patients with significant PR and RV dilation may have little reserve, their resting function may appear relatively normal or even as in some may appear increased. The apparent increased resting TAPSE in these patients, might reflect their RV functioning at the steepest region of the Frank-Startling curve even at rest due to the increased preload as reflected by increased RVEDVi. However, during exercise the RVs of these patients start the decline in the Frank-Startling curve as manifested by the negative RV contractile reserve.

4.2 | Limitations

The study is limited by the small sample size and the absence of 1:1 or greater control group. Although the transition from the treadmill to the echocardiography couch was immediate, the rate of heart rate degradation was variable among the subjects and difficult to control for. There was also variability among the fitness level of the controls. It is possible that the degree of RV dilation and pulmonary valve regurgitation might have worsened from the time of the cardiac MRI to the study, however, this is likely offset by the fact that all the patients had the study done within 12 months of the MRI.

5 | CONCLUSION

Resting RV long axis systolic function may be deceptively reassuring in patients with severe PR, and, therefore, in isolation provides only limited guidance in determining the spectrum of RV responses to volume load. Resting data should be complimented by dynamic exercise data in refining and identifying RVs that are compromised.

Contractile reserve is an attractive concept and provides an indicator of myocardial reserve. We recommend that patients undergoing evaluation for PVR should have volume, function and contractile reserve taken into account. Future studies should be designed to address the potential role of other hemodynamic and surgical factors that play a role in the dynamic responses of the RV to volume stress.

CONFLICT OF INTEREST

Authors claim no financial support and there are no conflict of interest.

AUTHOR CONTRIBUTIONS

Data collection: Kingsley, Shambrook, Veldtman
Data interpretation: Kingsley, Ahmad, Pappachan, Khambekar, Smith, Shambrook, Moore, Veldtman
Data approval: Kingsley, Ahmad, Pappachan, Smith, Baskar, Moore
Manuscript drafting: Ahmad, Baskar
Critical review: Pappachan, Khambekar, Smith, Shambrook, Baskar, Veldtman
Study design: Veldtman

ORCID

Shankar Baskar MD http://orcid.org/0000-0003-1022-6794

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

FIGURE S1

FIGURE S2 TAPSE

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