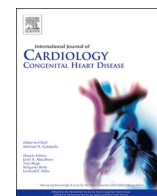




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Temporal change in cardiac function and clinical indices in adults with valvular pulmonic stenosis

Alexander C. Egbe^{*}, C. Charles Jain, Luke J. Burchill, Snigdha Karnakoti, Marwan H. Ahmed, Maan Jokhadar, Heidi M. Connolly

From the Department of Cardiovascular Medicine, Mayo Clinic Rochester, MN, 55905, USA

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ABSTRACT

Background: Patients with palliated pulmonary valve stenosis (PVS) have less cardiac remodeling and symptoms as compared to patients with repaired tetralogy of Fallot (TOF) presenting with similar severity of right ventricular outflow tract (RVOT) disease. What is not known is whether patients with PVS versus TOF presenting with similar severity of RVOT disease at baseline, would have similar (or different) pace of cardiac remodeling and disease progression over time. The study objective was to compare temporal changes in clinical and cardiac function indices between adults with palliated PVS and repaired TOF presenting with moderate/severe RVOT disease.

Methods: Cardiac function indices (based on strain imaging) and clinical indices (N-terminal pro-B-type natriuretic peptide [NT-proBNP], model for end-stage liver disease excluding international normalized ratio [MELD-XI], peak oxygen consumption [VO₂]), were assessed at baseline, 3 years, and 5 years. Temporal changes were calculated as relative changes from baseline (Δ). Cardiovascular adverse event was assessed as time-to-event outcome.

Results: Compared to TOF group (n = 173), the PVS group (n = 173) had less temporal change in right atrial reservoir strain ($-9 \pm 4\%$ versus $-21 \pm 6\%$, $p < 0.001$), RV free wall strain ($-8 \pm 4\%$ versus $-20 \pm 5\%$, $p < 0.001$), NT-proBNP ($8 \pm 5\%$ versus $17 \pm 6\%$, $p < 0.001$), MELD-XI ($6 \pm 4\%$ versus $19 \pm 4\%$, $p = 0.008$), and peak VO₂ ($-7 \pm 3\%$ versus $-12 \pm 7\%$, $p < 0.001$) at 5 years. The 5-year freedom from cardiovascular adverse event was higher in the PVS group (76% versus 54%, $p = 0.01$).

Conclusions: These data suggest that a less frequent clinical and imaging follow-up may be appropriate in patients with PVS (as compared to patients with TOF).

1. Introduction

Transcatheter and surgical pulmonary valve interventions are effective for the treatment of pulmonary valve stenosis (PVS) [1–4]. However, most patients develop either iatrogenic pulmonary regurgitation and/or recurrent right ventricular outflow tract (RVOT) stenosis leading to RV volume and/or pressure overload [1–4]. Chronic RV volume and/or pressure overload would, in turn, lead to RV remodeling, and cardiovascular symptoms [1–6]. This pathophysiologic cascade can be halted, and potentially reversed if the patients undergo pulmonary valve replacement (PVR) prior to the onset of irreversible RV dysfunction [7–9]. However, the long-term clinical benefits derived from PVR are limited by the risks associated with subsequent reinterventions because of the limited longevity of bioprosthetic valves [10–12]. Hence,

determining the optimal timing of PVR is important to avoid irreversible RV dysfunction and also minimize the risks associated with multiple RVOT reinterventions [10–12].

The decision to recommend PVR is based on a set of clinical and imaging criteria proposed in the guidelines for the management of adults with congenital heart disease [13–16]. However, most of the data supporting these recommendations were derived from studies conducted in patients with repaired tetralogy of Fallot (TOF). In the absence of robust longitudinal data from patients with PVS, these guideline recommendations (designed for patients with TOF) are often applied to patients with PVS [13–16].

Previous studies showed that patients with PVS had less RV dilation and systolic dysfunction, aerobic impairment, and cardiovascular symptoms as compared to patients with repaired TOF with similar severity of RVOT disease [2,4,7,16]. What is unknown is whether

^{*} Corresponding author. FACC Mayo Clinic and Foundation 200 First Street SW Rochester, MN 55905, USA.

E-mail address: egbe.alexander@mayo.edu (A.C. Egbe).

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Abbreviations

CMRI	Cardiac magnetic resonance imaging
IQR	Interquartile range
LA	Left atrium
LV	Left ventricle
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
MELD-XI	Model for end-stage liver disease excluding international normalized ratio
VO ₂	Oxygen consumption
PVS	Pulmonary valve stenosis
PVR	Pulmonary valve replacement
RVOT	Right ventricular outflow tract
TOF	Tetralogy of Fallot
RV-PA	Right ventricular to pulmonary artery
RVSP	Right ventricular systolic pressure

patients with PVS versus TOF presenting with similar severity of RVOT disease at baseline, would have similar (or different) pace of cardiac remodeling and disease progression over time. This is an important knowledge gap, as it will determine the frequency of clinical and imaging follow-up in patients with PVS, which would in turn, determine healthcare resource utilization. The purpose of this study was to compare the pace of cardiac remodeling and disease progression between adults with palliated PVS and those with repaired TOF presenting with similar severity of RVOT disease.

2. Methods

2.1. Study population

The Mayo Clinic Institutional Review Board approved this retrospective cohort study.

2.1.1. PVS group (case group)

We identified adults (age ≥ 18 years) with palliated PVS that received care at Mayo Clinic between January 1, 2003, and December 31, 2022. From this cohort, we selected consecutive patients with moderate/severe RVOT disease that had more than 2 years of clinical and imaging follow-up. Moderate/severe RVOT disease was defined as \geq moderate RVOT stenosis (Doppler derived maximum instantaneous gradient ≥ 36 mmHg) and/or \geq moderate pulmonary regurgitation.

Based on these criteria, the patients were divided into 3 RVOT disease group. (1) Isolated RVOT stenosis defined as RVOT Doppler derived maximum instantaneous gradient ≥ 36 mmHg with $<$ moderate pulmonary regurgitation. (2) Isolated pulmonary regurgitation defined as \geq moderate pulmonary regurgitation with RVOT Doppler derived maximum instantaneous gradient < 36 mmHg. (3) Mixed RVOT disease defined as RVOT Doppler derived maximum instantaneous gradient ≥ 36 mmHg with \geq moderate pulmonary regurgitation. The severity of pulmonary regurgitation was based on multiparametric qualitative Doppler assessment. Patients with prior palliative systemic-pulmonary shunt, and those without adequate echocardiographic images for offline strain analysis were excluded.

2.1.2. TOF group (control group)

We also identified a control group comprising of adults with repaired TOF presenting with moderate/severe RVOT disease. Similarly, we defined moderate/severe RVOT disease as \geq moderate RVOT stenosis (Doppler derived maximum instantaneous gradient ≥ 36 mmHg) and/or \geq moderate pulmonary regurgitation. The patients were also divided into 3 RVOT disease groups using the same criteria as the PVS group.

Patients with prior palliative systemic-pulmonary shunt, and those without adequate echocardiographic images for offline strain analysis were excluded.

We then performed 1:1 matching of patients with PVS to patients with TOF based on RVOT anatomy (native RVOT versus prosthetic pulmonary valve), and RVOT disease type (isolated RVOT stenosis versus isolated pulmonary regurgitation versus mixed RVOT disease).

2.2. Study objectives

(1) Compare temporal change in cardiac function indices between the PVS and TOF groups. (2) Compare temporal change in clinical indices (functional status, aerobic capacity, neurohormonal activation, and end-organ dysfunction) between the PVS and TOF groups. (3) Compare incidence of cardiovascular adverse events between the PVS and TOF groups.

2.3. Data collection

2.3.1. Cardiac function indices

A comprehensive assessment of cardiac structure and function was performed using 2-dimensional, Doppler and speckle tracking echocardiography according to contemporary guidelines [17–19]. The first echocardiogram performed within the study period showing moderate/severe RVOT disease was considered as the baseline echocardiogram. The baseline echocardiogram was reviewed to obtain the baseline cardiac function indices. Cardiac function indices at 3 years were determined based on the review of echocardiograms performed between 24 and 48 months from baseline encounter, while cardiac function indices at 5 years was determined based on a review of echocardiograms performed between 48 and 72 months.

Offline image analyses and measurements were performed, to determine the following cardiac function indices. (1) Right atrial (RA) function was assessed using RA reservoir strain. (2) Left atrial (LA) function was assessed using LA reservoir strain. (3) Right ventricular (RV) systolic function was assessed using RV free wall strain. (4) Left ventricular (LV) systolic function was assessed using LV global longitudinal strain. Temporal changes in cardiac function indices were calculated as relative changes from baseline values as follows: (indices from baseline echocardiogram minus indices from follow-up echocardiogram)/indices from baseline echocardiogram and expressed as %-change. Restrictive RV physiology was defined as pulmonary artery forward flow in atrial systole for > 3 cardiac cycles, and was assessed by pulsed wave Doppler of the pulmonary valve [20]. RV to pulmonary artery (RV-PA) coupling was assessed as the ratio of RV free wall strain/RV systolic pressure (RVSP) and tricuspid annular plane systolic excursion/RVSP ratio [21].

In addition to the above prespecified cardiac function indices, cardiac magnetic resonance imaging (CMRI) performed within 6 months from the baseline echocardiogram were reviewed and used to define the baseline characteristics.

2.3.2. Clinical indices

The clinic notes, cardiopulmonary exercise test, and laboratory tests were reviewed, and the data obtained within 6 months from the baseline and follow-up echocardiograms were used to define the clinical indices at the different time points. The following clinical indices were assessed. (1) Functional status was assessed using the New York Heart Association (NYHA) functional classification. (2) Aerobic capacity was assessed using predicted peak oxygen consumption (VO₂). (3) Neurohormonal activation was assessed using N-terminal pro-B-type natriuretic peptide (NT-proBNP). (4) End-organ function was assessed using the model for end-stage liver disease excluding international normalized ratio (MELD-XI). Similarly, temporal change in clinical indices was assessed as a relative change from baseline and calculated as: (indices from baseline assessment minus indices from follow-up assessment)/indices from

baseline assessment and expressed as %-change.

2.3.3. Cardiovascular adverse event

Cardiovascular adverse event was defined as a composite outcome of sustained atrial arrhythmias requiring medical intervention, heart failure hospitalization, or progressive functional impairment (progression in NYHA functional class). Cardiovascular adverse event was assessed time-to-event outcome, from baseline echocardiogram to the occurrence of cardiovascular adverse event or December 31, 2022. The patients without cardiovascular adverse events were censored at last clinical encounter, time of PVR or December 31, 2022.

2.4. Statistical analysis

Data were presented as mean \pm standard deviation, median (interquartile range [IQR]), and count (%). Between-group comparisons were performed using chi-square test, unpaired *t*-test, or Wilcoxon rank sum test, as appropriate. Pearson correlation was used to assess the correlations between continuous variables. Temporal change in cardiac function and clinical indices were assessed using paired *t*-test. RV and LV strain values were treated as absolute values in the assessment of temporal change in cardiac function indices. NYHA functional class was treated as continuous variable in the assessment of temporal change in clinical indices. The freedom from cardiovascular adverse event was assessed using the Kaplan Meier method and compared using log-rank test. All statistical analyses were performed with BlueSky Statistics software (version. 7.10; BlueSky Statistics LLC, Chicago, IL, USA), and JMP statistical software (version 17.1.0, JMP Statistical Discovery LLC, NC). *P* value < 0.05 was considered to be statistically significant for all analyses.

3. Results

3.1. Baseline clinical and cardiac function indices

They were 173 patients with PVS and 173 patients with TOF that met the study inclusion criteria. Both groups were adequately matched based on RVOT anatomy and RVOT disease type (Table 1). Compared to the TOF group, the patients in the PVS group were older at the time initial RVOT intervention (6.3 [IQR 1.2–17.9] versus 1.6 [IQR 0.9–3.1] years, *p* < 0.001), and at the beginning of the study period (35 [IQR 25–48] versus 28 [IQR 20–39] years, *p* < 0.001). The PVS group also had a lower prevalence of ventricular arrhythmia (1% versus 8 [5%], *p* = 0.03), higher aerobic capacity (predicted peak VO_2 73 \pm 22% versus 62 \pm 16%, *p* < 0.001), less neurohormonal activation (NT-proBNP 175 [IQR 85–337] versus 234 [IQR 107–561] pg/ml, *p* = 0.02), and less end-organ dysfunction (MLED-XI score 9.8 [IQR 9.4–10.6] versus 10.7 [IQR 9.8–11.4], *p* = 0.01) (Table 1).

Table 2 shows the baseline echocardiographic indices. Compared to the TOF group, the PVS group had better RA function (RA reservoir strain 36% [IQR 28–49] versus 25% [IQR 20–32], *p* < 0.001), RV systolic function (RV free wall strain $-25 \pm 4\%$ versus $-22 \pm 5\%$, *p* = 0.007), LA function (LA reservoir strain $38 \pm 9\%$ versus $31 \pm 10\%$, *p* = 0.008), and LV systolic function (LV global longitudinal strain $-23 \pm 5\%$ versus $-19 \pm 4\%$, *p* < 0.001). However, there was no significant between-group difference in RV-PA coupling between the PVS group versus the TOF group as measured by RV free wall strain/RVSP ratio (0.54 ± 0.93 versus 0.52 ± 1.06 %/mmHg, *p* = 0.1) or as measured by tricuspid annular plane systolic excursion/RVSP ratio (0.42 ± 0.39 versus 0.41 ± 0.32 mm/mmHg, *p* = 0.7) (Table 2). Similarly, there was no significant between-group difference in the prevalence of restrictive RV physiology (8% [*n* = 14] versus 9% [*n* = 16], *p* = 0.5).

CMRI data were available in 148 (86%) and 159 (92%) patients in the PVS and TOF groups, respectively. Compared to the TOF group, the PVS group had smaller RV end-diastolic volume index (126 ± 15 versus 139 ± 32 ml/m², *p* = 0.02), and RV end-systolic volume index (49 ± 14

Table 1
Comparison of baseline clinical indices.

	PVS (N = 173)	TOF (N = 173)	<i>p</i>
Demographic indices			
Age, years	35 (25–48)	28 (20–39)	<0.001
Male sex	81 (47%)	95 (53%)	0.2
Body mass index, kg/m ²	26 \pm 5	27 \pm 4	0.2
Body surface area, m ²	1.91 \pm 0.26	1.87 \pm 0.29	0.1
Initial RVOT intervention			
Age of initial RVOT intervention, years	6.3 (1.2–17.9)	1.6 (0.9–3.1)	<0.001
Type of initial RVOT intervention			<0.001
Balloon valvuloplasty	47 (27%)	0	
Transannular patch repair	29 (17%)	36 (21%)	
Non-transannular patch repair	97 (56%)	137 (79%)	
RVOT anatomy			
Pulmonary valve bioprosthesis	42 (24%)	42 (36%)	0.9
Native RVOT	131 (76%)	131 (76%)	
RVOT disease type			
Isolated RVOT stenosis	34 (20%)	34 (20%)	0.9
Isolated pulmonary regurgitation	97 (56%)	97 (56%)	
Mixed RVOT disease	42 (24%)	42 (24%)	
Comorbidities			
Atrial flutter/tachycardia	12 (7%)	21 (12%)	0.07
Atrial fibrillation	2 (1%)	3 (2%)	0.6
All atrial arrhythmias	12 (7%)	22 (13%)	0.05
Non-sustained ventricular tachycardia	2 (1%)	8 (5%)	0.03
Sustained ventricular tachycardia	0	0	–
Any ventricular arrhythmia	2 (1%)	8 (5%)	0.03
Hypertension	39 (23%)	32 (19%)	0.4
Coronary artery disease	6 (4%)	5 (3%)	0.6
NYHA functional class			
I	146 (84%)	138 (80%)	
II	27 (16%)	35 (20%)	
Aerobic capacity			
Peak VO_2 (ml/kg/min)	26 \pm 5	22 \pm 7	<0.001
Peak VO_2 (%-predicted)	73 \pm 22	62 \pm 16	<0.001
Medications			
Diuretics	29 (17%)	40 (23%)	0.03
Beta blockers	33 (19%)	42 (24%)	0.2
ACEI/ARB	36 (21%)	39 (23%)	0.6
Mineralocorticoid receptor antagonist	5 (3%)	8 (5%)	0.3
Laboratory data			
NT-proBNP, pg/ml	175 (85–337)	234 (107–561)	0.02
MELD-XI	9.8 (9.4–10.6)	10.7 (9.8–11.4)	0.01
Estimated GFR, ml/min/1.73 m ²	93 (79–109)	89 (76–102)	0.4

Abbreviations: ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin-II receptor blockers; GFR: glomerular filtration rate; MELD-XI: Model for end-stage liver disease excluding international normalized ratio; NYHA: New York Heart Association; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PVS: Pulmonary valve stenosis; RVOT: Right ventricular outflow tract; TOF: Tetralogy of Fallot; VO_2 : Oxygen consumption.

Footnote: *p* values were derived from pairwise comparisons using chi-squared test, unpaired *t*-test, and Wilcoxon rank sum test.

versus 63 ± 21 ml/m², *p* = 0.008), as well as a higher RV ejection fraction (54 ± 10 versus $47 \pm 13\%$, *p* = 0.01) (Table 2). There was a modest correlation between CMRI derived RV ejection fraction and echocardiography derived RV free wall strain in the PVS group (*r* = -0.56 , *p* = 0.004) and in the TOF group (*r* = -0.52 , *p* = 0.008). Similarly, there was a modest correlation between CMRI derived LV ejection fraction and echocardiography derived LV global longitudinal strain in the PVS group (*r* = -0.63 , *p* < 0.001) and in the TOF group (*r* = -0.61 , *p* < 0.001).

Table 2
Comparison of baseline cardiac indices.

Echocardiographic indices	VPS (N = 173)	TOF (N = 173)	p
RA indices			
RA volume index (ml/m ²)	35 (24–45)	37 (29–47)	0.2
RA reservoir strain (%)	36 (28–49)	25 (20–32)	<0.001
RA pressure (mmHg)	6 ± 3	8 ± 3	0.002
RV indices			
RV end-diastolic area index (cm ² /m ²)	15.7 ± 3.8	18.3 ± 4.2	0.008
RV end-systolic area index (cm ² /m ²)	9.8 ± 2.2	12.6 ± 3.1	0.01
RV fractional area change (%)	39 ± 8	36 ± 10	0.1
RVFWS (%)	−25 ± 4	−22 ± 5	0.007
TAPSE (mm)	19 ± 7	17 ± 6	0.1
≥Moderate tricuspid regurgitation	22 (13%)	28 (16%)	0.3
Pulmonary mean gradient (mmHg)	24 (13–41)	22 (9–38)	0.3
RVSP (mmHg)	46 (31–57)	41 (32–53)	0.6
Restrictive RV physiology	13 (8%)	16 (9%)	0.5
RVFWS/RVSP (%/mmHg)	0.54 ± 0.93	0.52 ± 1.06	0.1
TAPSE/RVSP (mm/mmHg)	0.42 ± 0.39	0.41 ± 0.32	0.7
LA indices			
LA volume index (ml/m ²)	25 ± 7	26 ± 8	0.7
LA reservoir strain (%)	38 ± 9	31 ± 10	0.008
Lateral E/e'	7.1 ± 2.8	8.4 ± 3.5	0.03
LV indices			
LV end-diastolic volume index (ml/m ²)	52 ± 15	55 ± 16	0.4
LV end-systolic volume index (ml/m ²)	21 ± 10	24 ± 11	0.1
LV ejection fraction (%)	61 ± 9	56 ± 8	0.06
LV global longitudinal strain (%)	−23 ± 5	−19 ± 4	<0.001
LV stroke volume index (ml/m ²)	43 ± 11	37 ± 8	0.03
Cardiac index (l/min/m ²)	2.98 ± 0.74	2.69 ± 0.71	0.01
CMRI indices (N = 148) (N = 159)			
RV end-diastolic volume (ml/m ²)	126 ± 15	139 ± 32	0.02
RV end-systolic volume (ml/m ²)	49 ± 14	63 ± 21	0.008
RV ejection fraction (%)	54 ± 10	47 ± 13	0.01
RV stroke volume index (ml/m ²)	78 ± 18	76 ± 21	0.8
Pulm regurgitant volume index (ml/m ²)	36 ± 12	38 ± 10	0.6
LV end-diastolic volume (ml/m ²)	79 ± 18	84 ± 26	0.1
LV end-systolic volume (ml/m ²)	38 ± 16	45 ± 14	0.06
LV ejection fraction (%)	62 ± 15	58 ± 16	0.3
LV stroke volume index (ml/m ²)	41 ± 12	39 ± 12	0.2

Abbreviations: CMRI: Cardiac magnetic resonance imaging; E/e': ratio of mitral inflow pulsed wave Doppler early velocity to tissue Doppler early velocity; LA: Left atrium; LV: Left ventricle; PVS: Pulmonary valve stenosis; RA: Right atrium; RV: Right ventricle; RVFWS: Right ventricular free wall strain; RVSP: Right ventricular systolic pressure; TOF: Tetralogy of Fallot; TAPSE: Tricuspid anular plane systolic excursion.

Footnote: p values were derived from pairwise comparisons using chi-squared test, unpaired t-test, and Wilcoxon rank sum test.

3.2. Temporal change in clinical and cardiac function indices

Compared to the TOF group, the PVS group had less temporal decline in RA function at 3 years (Δ RA reservoir strain $-6 \pm 3\%$ versus $-11 \pm 4\%$, $p = 0.007$) and 5 years (Δ RA reservoir strain $-9 \pm 4\%$ versus $-21 \pm 6\%$, $p < 0.001$). Similarly, the PVS group had less temporal decline in RV systolic function at 3 years (Δ RV free wall strain $-5 \pm 2\%$ versus $-9 \pm 4\%$, $p = 0.03$) and 5 years (Δ RV free wall strain $-8 \pm 4\%$ versus $-20 \pm 5\%$, $p < 0.001$) (Fig. 1). The temporal change in left-sided cardiac indices, compared to right-sided indices were less pronounced in both groups. There were no significant temporal changes in LA reservoir strain and LV global longitudinal strain in either group at 3 years. However, both groups showed statistically significant decline in LA reservoir strain and LV global longitudinal strain at 5 years, but the magnitude of change was similar in both groups (Fig. 1).

Fig. 2 shows temporal change in clinical indices. Compared to the TOF group, the PVS group had less temporal change in NT-proBNP ($8 \pm 5\%$ versus $17 \pm 6\%$, $p < 0.001$), MELD-XI ($6 \pm 4\%$ versus $19 \pm 4\%$, $p = 0.008$), and aerobic capacity (Δ predicted peak VO_2 $-7 \pm 3\%$ versus $-12 \pm 7\%$, $p < 0.001$) at 5 years follow-up (Fig. 2). However, there was no significant temporal change in NYHA functional class in either group

(Fig. 2).

The median follow-up was 6.9 (4.3–8.5) years and 5.8 (3.9–7.2) years in the PVS and TOF groups, respectively. During this period 31 (18%) patients experienced at least one cardiovascular adverse event, while 16 (9%) patients underwent PVR in the PVS. Similarly, 43 (25%) patients experienced at least one cardiovascular adverse event, while 29 (17%) patients underwent PVR in the TOF. The 5-year freedom from cardiovascular adverse event was higher in the PVS group as compared to the TOF group (76% versus 54%, $p = 0.01$), (Fig. 3).

4. Discussion

In this study, we compared temporal changes in cardiac function and clinical indices in patients with palliated PVS to patients with repaired TOF presenting with similar severity of RVOT disease. The main findings are follows: (1) The PVS group had better cardiac function and clinical indices at baseline compared to the TOF group. (2) The PVS group had less temporal decline in right-sided cardiac function indices (RA function and RV systolic function) as compared to the TOF group. (3) The patients with PVS had less temporal decline in clinical indices (neurohormonal activation, end-organ function, and aerobic capacity), and lower incidence of cardiovascular adverse events as compared to the patients with TOF.

About half of patients with palliated PVS would develop hemodynamically significant pulmonary regurgitation and/or recurrent RVOT stenosis on long-term follow-up [5,22]. While isolated recurrent RVOT stenosis typically responds to balloon pulmonary valvuloplasty, PVR is often required in patients with concomitant pulmonary regurgitation [4, 7,22]. The timing of PVR is dependent on the presence of clinical indices such as functional capacity (symptoms) and aerobic capacity, as well as cardiac function indices such as RV dilation and systolic dysfunction [13,14]. In the absence of well-defined criteria for PVR in patients with palliated PVS, the decision to proceed with PVR in this population is often based on extrapolation of data derived from studies conducted in patients with repaired TOF [13,14]. Similarly, the frequency of clinical and imaging surveillance for patients that currently do not meet criteria for PVR are also based on extrapolations from data derived from the TOF population [13,14]. The current study demonstrates a slower pace of disease progression in patients with PVS as compared to patients with TOF, as evidenced by a less temporal decline in clinical indices (aerobic capacity, neural hormonal activation, and hepatorenal function), and right-sided cardiac function indices (RA function and RV systolic function).

Previous studies have shown that patients with PVS had less symptoms and cardiac remodeling at baseline as compared to patients with TOF [4,22]. Joynt et al. compared CMRI data between 24 patients with PVS and 47 patients with TOF with similar severity of pulmonary regurgitation [23]. They observed that the PVS group had a higher RV ejection fraction and less late gadolinium enhancement as compared to the TOF group. Within the TOF group, RV systolic dysfunction and late gadolinium enhancement were more pronounced in the RVOT [23]. Similarly, Mercer-Rosa et al., observed a higher CMRI derived RV ejection fraction and aerobic capacity, as well as better functional capacity in patients with palliated PVS as compared to TOF [23]. While these previous studies demonstrated better baseline clinical status and cardiac function in patients with PVS (as compared to TOF), they do not provide data about the pace of disease progression during follow-up. The current study addressed this knowledge gap.

The observed differences in the pace of disease progression may be related to differences in disease pathophysiology and impact of initial palliative interventions [24]. Patients with TOF are exposed to cyanosis within the first year of life which may have long-term adverse effects on RV myocardial structure and function, leading to RV fibrosis and diastolic dysfunction [24]. This is consistent with the higher prevalence and severity of late gadolinium enhancement (marker of myocardial fibrosis) and diastolic dysfunction described in patients with TOF [22,24,25].

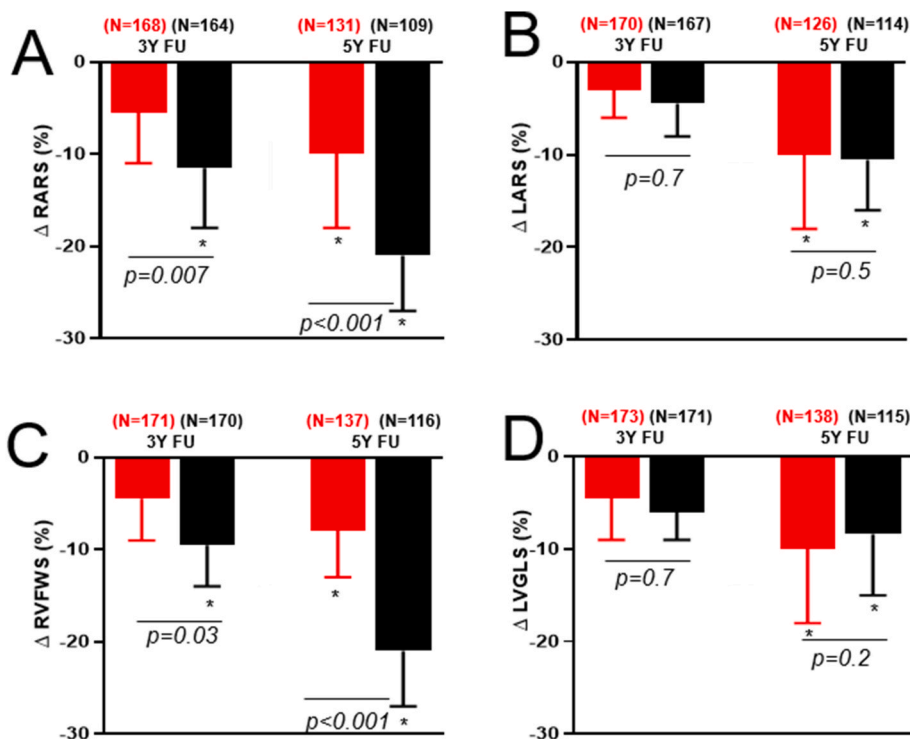


Fig. 1. Box and whisker plots comparing relative change in cardiac function indices between patients with pulmonary valve stenosis (PVS, red) versus tetralogy of Fallot (TOF, black). Data were presented as relative changes from baseline values. **Abbreviations:** FU: Follow-up; LARS: Left atrial reservoir strain; LVGLS: Left ventricular global longitudinal strain; RVFWS: Right ventricular free wall strain; RARS: Right atrial reservoir strain. **Footnote:** * statistically significant change from baseline value based on paired *t*-test. P values were derived from between-group comparisons using unpaired *t*-tests. N: Number of patients with available data at each time point.

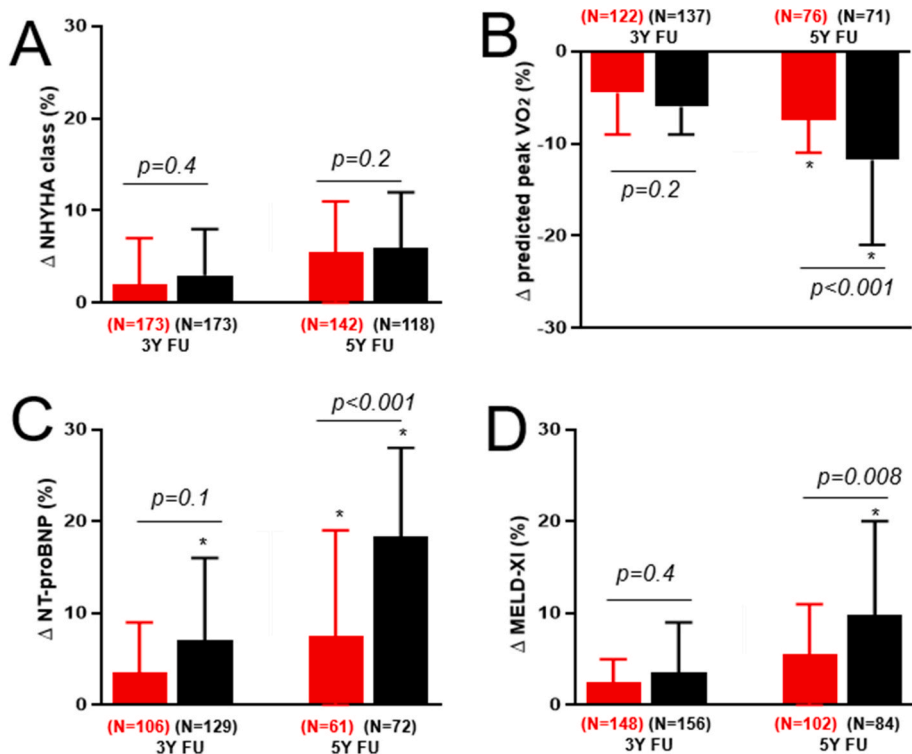


Fig. 2. Box and whisker plots comparing relative change in clinical indices between patients with PVS (red) versus TOF (black). Data were presented as relative changes from baseline values. **Abbreviations:** NYHA: New York Heart Association; MELD-XI: Model for end-stage liver disease excluding international normalized ratio; NT-proBNP: N-terminal pro-B-type natriuretic peptide; VO₂: Oxygen consumption. **Footnote:** * statistically significant change from baseline value based on paired *t*-test. P values were derived from between-group comparisons using unpaired *t*-tests. N: Number of patients with available data at each time point.

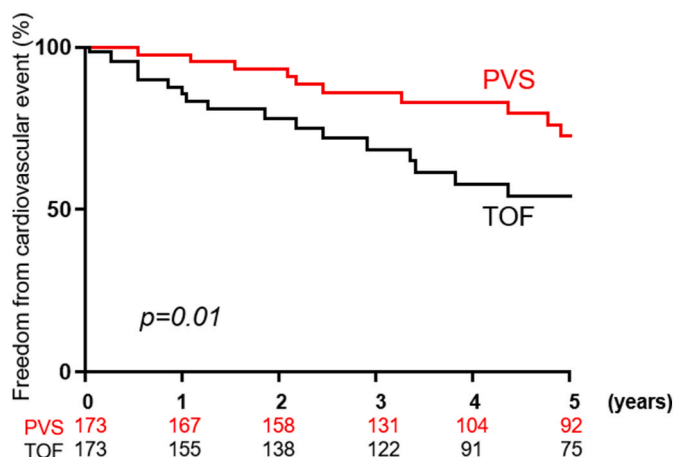


Fig. 3. Kaplan Meier curves comparing freedom from cardiovascular adverse events between patients with PVS (red) versus TOF (black). P value was derived from log-rank test.

This may explain the higher RA pressure observed in the TOF group in the current study. Since RA hypertension has been linked to right heart failure and hepatorenal dysfunction in adults with congenital heart disease, we postulate that RV fibrosis and diastolic dysfunction described in TOF patients in previous studies [26,27], may also explain the higher NT-proBNP and MELD-XI score observed in the TOF group in the current study. Other factors that may contribute to the rapid pace of disease progression in the TOF group include abnormal pulmonary artery compliance and worse RV to pulmonary arterial coupling that have been described in patients with TOF as compared to PVS [6,11,28].

Additionally, differences in the type of initial RVOT intervention may explain some of the observed differences in outcomes. About one-quarter of the patients in the PVS group underwent balloon pulmonary valvuloplasty, and hence were not exposed to the hypoxic-ischemic injury associated with cardiopulmonary bypass. Presumably, these patients started off with less RV myocardial injury as compared to those that underwent surgical repair.

An important negative finding from this study was the absence of temporal change in NYHA functional class in either group, even though both groups had decline in aerobic capacity and other clinical indices of disease severity. This is consistent with observation from previous studies showing a discordance between objectively measured aerobic capacity and subjective assessment of symptoms by the patient [29,30]. This highlights the limitations of relying solely on patient reported symptoms for clinical decision-making regarding timing of surgical or transcatheter interventions.

4.1. Clinical implications

Patients with PVS and residual RVOT disease not meeting the criteria for PVR require ongoing clinical and imaging surveillance [13,14]. The practice guidelines recommend transthoracic echocardiogram every 24 months in asymptomatic/mildly symptomatic (physiologic stage A/B) patients with palliated PVS, which is similar to the frequency of echocardiogram in TOF patients [13,14]. The slower pace of disease progression observed in the PVS group suggest that, perhaps, less frequent clinical and imaging follow-up may be appropriate in patients PVS. This will reduce healthcare resource utilization, and potentially increase economic productivity as it will reduce number of days spent off work because of medical evaluation.

Limitations: This is a retrospective single center study, and it is therefore prone to selection and ascertainment bias. The patient lost to follow and those that underwent PVR during follow-up were censored, further introducing a selection bias to the study. We did not have serial CMRI data to assess temporal change in cardiac remodeling over time.

However, by using strain imaging to assess cardiac function in all four chambers, we demonstrated that the hemodynamic effect of RVOT disease is not limited to the right heart, but also affects LA and LV function over time. Finally, we do not have invasive hemodynamic data, or data about ventricular dyssynchrony, and this limits our ability to make inferences about RV-PA coupling and ventricular interaction. Furthermore, there important molecular/genetic differences between PVS and TOF, that were not assessed in this study.

Conclusion: Patients with PVS had a slower pace of disease progression, as evidenced by less temporal decline in clinical indices and cardiac function indices, as well as lower cumulative incidence of cardiovascular adverse events as compared to patients with TOF. These data suggest that a less frequent clinical and imaging follow-up may be appropriate in patients with PVS (as compared to patients with TOF). This will likely reduce healthcare resource utilization and IMPROVE quality of life of the patients.

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Perspectives

Clinical competencies

Patients with PVS had a slower pace of disease progression, as evidenced by a less temporal decline in clinical and cardiac function indices, as well as lower cumulative incidence of cardiovascular adverse events as compared to patients with TOF.

Translational outlook

These data suggest that a less frequent clinical and imaging follow-up may be appropriate in patients with PVS (as compared to patients with TOF).

Clinical summary

Compared to the TOF group (n = 173), the PVS group (n = 173) had less temporal change in right atrial reservoir strain ($-9 \pm 4\%$ versus $-21 \pm 6\%$, $p < 0.001$), RV free wall strain ($-8 \pm 4\%$ versus $-20 \pm 5\%$, $p < 0.001$), NT-proBNP ($8 \pm 5\%$ versus $17 \pm 6\%$, $p < 0.001$), MELD-XI ($6 \pm 4\%$ versus $19 \pm 4\%$, $p = 0.008$), and peak VO_2 ($-7 \pm 3\%$ versus $-12 \pm 7\%$, $p < 0.001$) at 5 years. The 5-year freedom from cardiovascular adverse event was higher in the PVS group (76% versus 54%, $p = 0.01$). These data suggest that a less frequent clinical and imaging follow-up may be appropriate in patients with PVS (as compared to patients with TOF).

CRedit authorship contribution statement

Alexander C. Egbe: Writing – review & editing, Writing – original draft. **C. Charles Jain:** Writing – review & editing, Writing – original draft. **Luke J. Burchill:** Writing – review & editing, Writing – original draft. **Snigdha Karnakoti:** Writing – review & editing, Writing – original draft. **Marwan H. Ahmed:** Writing – review & editing, Writing – original draft. **Maan Jokhadar:** Writing – review & editing, Writing – original draft. **Heidi M. Connolly:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

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References

- [1] Cuypers JA, Witsenburg M, van der Linde D, Roos-Hesselink JW. Pulmonary stenosis: update on diagnosis and therapeutic options. *Heart* 2013;99:339–47.
- [2] Zdradzinski MJ, Qureshi AM, Stewart R, Petterson G, Krasuski RA. Comparison of long-term postoperative sequelae in patients with tetralogy of Fallot versus isolated pulmonic stenosis. *Am J Cardiol* 2014;114:300–4.
- [3] Skoglund K, Rosengren A, Lappas G, Fedchenko M, Mandalenakis Z. Long-term survival in patients with isolated pulmonary valve stenosis: a not so benign disease? *Open heart* 2021;8.
- [4] Mercier-Rosa L, Ingall E, Zhang X, McBride M, Kawut S, Fogel M, Paridon S, Goldmuntz E. The impact of pulmonary insufficiency on the right ventricle: a comparison of isolated valvar pulmonary stenosis and tetralogy of fallot. *Pediatr Cardiol* 2015;36:796–801.
- [5] Roos-Hesselink JW, Meijboom FJ, Spitaels SE, vanDomburg RT, vanRijen EH, Utens EM, Bogers AJ, Simoons ML. Long-term outcome after surgery for pulmonary stenosis (a longitudinal study of 22-33 years). *Eur Heart J* 2006;27:482–8.
- [6] Rommel JJ, Yadav PK, Stouffer GA. Causes and hemodynamic findings in chronic severe pulmonary regurgitation. *Cathet Cardiovasc Interv : off J Soc Card Angiography & Interv* 2018;92(3):197–203.
- [7] Lafamme E, Wald RM, Roche SL, Silversides CK, Thorne SA, Colman JM, Benson L, Osten M, Horlick E, Oechslin E, Alonso-Gonzalez R. Outcome and right ventricle remodelling after valve replacement for pulmonic stenosis. *Heart* 2022;108:1290–5.
- [8] Bokma JP, Winter MM, Oosterhof T, Vliegen HW, van Dijk AP, Pieper PG, Meijboom FJ, Groenink M, Mulder BJM, Bouma BJ. Pulmonary valve replacement after repair of pulmonary stenosis compared with tetralogy of fallot. *J Am Coll Cardiol* 2016;67:1123–4.
- [9] Bokma JP, Geva T, Sleeper LA, Lee JH, Lu M, Sompolinsky T, Babu-Narayan SV, Wald RM, Mulder BJM, Valente AM. Improved outcomes after pulmonary valve replacement in repaired tetralogy of fallot. *J Am Coll Cardiol* 2023;81:2075–85.
- [10] Egbe AC, Miranda WR, Said SM, Pislaru SV, Pellikka PA, Borlaug BA, Kothapalli S, Connolly HM. Risk stratification and clinical outcomes after surgical pulmonary valve replacement. *Am Heart J* 2018;206:105–12.
- [11] Egbe AC, Kothapalli S, Miranda WR, Pislaru S, Ammash NM, Borlaug BA, Pellikka PA, Najam M, Connolly HM. Assessment of right ventricular-pulmonary arterial coupling in chronic pulmonary regurgitation. *Can J Cardiol* 2019;35:914–22.
- [12] Egbe AC, Connolly HM, Miranda WR, Dearani JA, Schaff HV. Outcomes of bioprosthetic valves in the pulmonary position in adults with congenital heart disease. *Ann Thorac Surg* 2019;108:1410–5.
- [13] Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, Crumb SR, Dearani JA, Fuller S, Gurvitz M, Khairy P, Landzberg MJ, Saidi A, Valente AM, Van Hare GF. AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol* 2018;73:e81–192. 2019.
- [14] Baumgartner H, De Backer J. The ESC clinical practice guidelines for the management of adult congenital heart disease 2020. *Eur Heart J* 2020;41:4153–4.
- [15] Bokma JP, Winter MM, Oosterhof T, Vliegen HW, van Dijk AP, Hazekamp MG, Koolbergen DR, Groenink M, Mulder BJ, Bouma BJ. Preoperative thresholds for mid-to-late haemodynamic and clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. *Eur Heart J* 2016;37:829–35.
- [16] Bokma JP, Winter MM, Oosterhof T, Vliegen HW, van Dijk AP, Pieper PG, Meijboom FJ, Groenink M, Mulder BJ, Bouma BJ. Pulmonary valve replacement after repair of pulmonary stenosis compared with tetralogy of fallot. *J Am Coll Cardiol* 2016;67:1123–4.
- [17] Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. In: *Journal of the American society of echocardiography*, vol. 23. official publication of the American Society of Echocardiography; 2010. p. 685–713. quiz 786-8.
- [18] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. In: *Journal of the American society of echocardiography*, vol. 28. official publication of the American Society of Echocardiography; 2015. 1–39 e14.
- [19] Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, Horton K, Ogunyankin KO, Palma RA, Velazquez EJ. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American society of echocardiography. In: *Journal of the American society of echocardiography*, vol. 32. official publication of the American Society of Echocardiography; 2019. p. 1–64.
- [20] Egbe AC, Pellikka PA, Miranda WR, Bonnichsen C, Reddy YNV, Borlaug BA, Connolly HM. Echocardiographic predictors of severe right ventricular diastolic dysfunction in tetralogy of Fallot: relations to patient outcomes. *Int J Cardiol* 2020;306:49–55.
- [21] Ahmed M, Karnakoti S, Abozied O, Kandlakunta S, Younis A, Egbe AC. Prognostic role of tricuspid annular plane systolic excursion/right ventricular systolic pressure ratio in coarctation of aorta. *CJC Pediatr Congenit Heart Dis* 2023;2:167–73.
- [22] Joynt MR, Yu S, Dorfman AL, Ghadimi Mahani M, Agarwal PP, Lu JC. Differential impact of pulmonary regurgitation on patients with surgically repaired pulmonary stenosis versus tetralogy of fallot. *Am J Cardiol* 2016;117:289–94.
- [23] Lianza AC, Rodrigues ACT, Mercier-Rosa L, Vieira MLC, de Oliveira WAA, Afonso TR, Nomura CH, da Silva JP, da Silva LDF, Szarf G, Tavares GMP, Fischer CH, Morhy SS. Right ventricular systolic function after the cone procedure for ebstein's anomaly: comparison between echocardiography and cardiac magnetic resonance. *Pediatr Cardiol* 2020;41:985–95.
- [24] Geva T. Diffuse myocardial fibrosis in repaired tetralogy of fallot: linking pathophysiology and clinical outcomes. *Circulation Cardiovascular imaging* 2017;10.
- [25] Wald RM, Valente AM, Gauvreau K, Babu-Narayan SV, Assenza GE, Schreier J, Gatzoulis MA, Kilner PJ, Koyak Z, Mulder B, Powell AJ, Geva T. Cardiac magnetic resonance markers of progressive RV dilation and dysfunction after tetralogy of Fallot repair. *Heart* 2015;101:1724–30.
- [26] Egbe AC, Bonnichsen C, Reddy YNV, Anderson JH, Borlaug BA. Pathophysiologic and prognostic implications of right atrial hypertension in adults with tetralogy of fallot. *J Am Heart Assoc* 2019;8:e014148.
- [27] Egbe AC, Miranda WR, Anderson JH, Katta RR, Goda AY, Andi K, Kamath PS, Connolly HM. Determinants and prognostic implications of hepatorenal dysfunction in adults with congenital heart disease. *Can J Cardiol* 2022;38:1742–50.
- [28] Egbe AC, Miranda WR, Pellikka PA, Pislaru SV, Borlaug BA, Kothapalli S, Ananthaneni S, Sandhyavenu H, Najam M, Farouk Abdelsamid M, Connolly HM. Right ventricular and pulmonary vascular function indices for risk stratification of patients with pulmonary regurgitation. *Congenit Heart Dis* 2019;14:657–64.
- [29] Egbe A, Miranda W, Connolly H, Dearani J. Haemodynamic determinants of improved aerobic capacity after tricuspid valve surgery in Ebstein anomaly. *Heart* 2021;107:1138–44.
- [30] Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation* 2005;112:828–35.