Impact of Pulmonary Stenosis on Right Ventricular Global Longitudinal Strain in Repaired Tetralogy of Fallot Patients Post Transcatheter Pulmonary Valve Replacement

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October 3, 2023

Abstract

Background Mixed pulmonary disease with pulmonary regurgitation (PR) and stenosis (PS) in repaired tetralogy of Fallot (rTOF) can negatively impact ventricular health. Myocardial strain has been shown to be more sensitive at detecting occult ventricular dysfunction compared to right ventricular ejection fraction (RV EF). We hypothesize that rTOF patients with predominant PS will have lower RV global longitudinal strain (RVGLS) prior to and post-transcatheter pulmonary valve replacement (TPVR). Methods A retrospective cohort of rTOF patients who underwent cardiac magnetic resonance (CMR) and cardiac catheterization for right ventricular pressure (RVSP) measurement were analyzed at three time points: before valve implantation, at discharge and within 18 months post-TPVR. Patients were dichotomized into three groups based on RVSP: 0-49%, 50-74%, and >75%. RVGLS and left ventricular (LV) GLS by speckle tracking echocardiography (STE) were obtained from the apical 4-chamber using TomTec software (TOMTEC IS, Germany). Results Forty-eight patients were included. RV EF was not associated with a significant change in RV or LV GLS (p=0.7). RV GLS showed the greatest improvement immediately after valve implantation. Higher pre-implantation RVSP was found to correlate with worse strain (p=0.001). Overall, average RV strain magnitude was higher when pre-implantation RVSP was less than 50% and had greater improvement over the three time points. Higher post-implantation RVSP correlated with lower strain magnitude. Conclusion Patients with significant PS (>50%) may benefit from earlier PVR and not depend solely on RV size and EF. Myocardial strain may be a more sensitive marker of function; however, larger, prospective studies are needed.

Introduction

Following surgical augmentation of the right ventricular outflow tract (RVOT), patients with repaired TOF (rTOF) develop moderate to severe pulmonary regurgitation (PR), which causes ventricular dilation due to excess volume load [1]. Patients with rTOF may also have residual pulmonary stenosis (PS) or develop right ventricle-to-pulmonary artery (RVPA) conduit stenosis overtime, resulting in mixed pulmonary disease[2, 3]. The effects of excess volume loading and increased afterload result in abnormal ventricular remodeling and predispose patients to increased risk of ventricular dysfunction, arrhythmia, and death[4]. Mild PS in rTOF is thought to be cardioprotective against the need for pulmonary valve replacement (PVR); however, moderate to severe stenosis necessitates intervention[3]. Recent multicenter prospective data in patients with

rTOF demonstrated that right ventricular hypertrophy, right ventricular dysfunction, and older age at PVR is associated with death and sustained ventricular tachycardia (VT)[4]. Re-establishment of a competent pulmonary valve is essential to reverse abnormal ventricular remodeling and mitigate risks[5-8].

Due to increased risk of sudden cardiac death in patients with rTOF, function assessment is paramount for prognosis and risk stratification[9-11]. Myocardial strain imaging by speckle tracking echocardiography (STE) is a unique modality to assess ventricular function[12]. Strain imaging calculates the change in length between two specified areas of the myocardium or lengthening and shortening of the myocardium throughout the cardiac cycle[13, 14]. Studied extensively in heart failure, strain imaging has demonstrated ventricular dysfunction in the setting of preserved EF[15, 16]. In rTOF patients, function by ejection fraction (EF) and right ventricular global longitudinal strain (GLS) have been shown not to improve following reestablishment of a competent pulmonary valve [17, 18]. The goal of this paper was to evaluate the effect of significant pre-procedural afterload on RV and LV GLS by STE in rTOF patients with mixed pulmonary disease following TPVR. We hypothesize that mixed pulmonary disease with significant stenosis will have lower strain magnitude with minimal improvement in RV GLS overtime following TPVR.

Methods

Repaired TOF patients with native outflow tracts or RVPA conduits were referred for TPVR at a single institution between 2008-2019 were included in the retrospective analysis. All patients had at least moderate PR by CMR (pulmonary regurgitant fraction >20%). Pre-implantation CMR data was included for volumetric data analysis: EF, end-diastolic volume indexed (EDVI), end-systolic volume indexed (ESVI), and PR. RV mass/volume ratio was also calculated on pre-procedural CMR images available for review. CMR RV cine images were reanalyzed for RV mass/volume ratio using available software (MedisSuite MR, Medis Medical Imaging Systems BV, the Netherlands). Pre-implantation hemodynamic catheterization was included for analysis of degree of RVSP and pulmonic stenosis. RV end-diastolic pressure (RVEDP) was also included for analysis.

Myocardial Strain by Speckle Tracking Echocardiography

Serial echocardiography data was used for analysis: (a) prior to valve implantation, (b) at hospital discharge, and (c) within 18 months post valve implantation. An internal validation scale was used for assessing quality of GLS images: 0 = more than 2 segments not tracking; 1 = less than 1 segment not tracking; 2 = all segments tracking. Patients with poor quality imaging, assigned a 0, were excluded. GLS analysis using STE was obtained by tracing the RV and LV endocardium from the apical 4 chamber view using TomTec Imaging Systems (GmBH, Munich, Germany) (Figure 1). A less negative number is lower strain or abnormal strain magnitude, and a more negative number is higher strain magnitude or normal strain. A cut off of -17 is accepted as normal strain magnitude, previously validated in CMR controls with as the gold standard [12, 19-21].

Statistical Analysis

To account for the multiple strain measurements per patient, the univariable and multivariable associations with RV or LV GLS were modeled using linear mixed models with random intercepts for patients [22, 23]. The confidence intervals for these associations used profile likelihoods. Associations between other metrics, such as RV mass, RVSP pre-catheterization, were computed using linear models and confidence intervals were computed with the classical formula.

The associations between RV GLS and RVSP pre-implantation, LV GLS and RVSP pre- implantation, RV mass and RVSP pre- implantation, RV strain and RV end diastolic pressure (RVEDP), and RV GLS and RV mass, were adjusted for type of outflow. Adjusting for the type of outflow tract did not change the significance of any of the analyses. Other associations, including RV GLS with RVSP post- implantation, LV GLS with RVSP post- implantation, RV GLS with age, LV GLS with age, RV GLS with RV EF, LV GLS with RV EF, and LV GLS with LV end diastolic pressure (LVEDP), were unadjusted.

Additionally, GLS, grouped by right and left, over time were plotted using box plots. RV GLS, grouped by

RVSP pre-catheterization, was also plotted over time using boxplots. Similar plots were made for LV GLS grouped by RVSP pre-catheterization. All analysis was conducted in R version 4 [24]. Plots were created using ggplot2 [25].

Results

Forty-eight patients were included with pre-implantation and post-implantation catheterization data (Table 1). Of the 48 patients, 36 (77%) had CMR images available for analysis of RV mass (Table 2). Higher RV mass indexed to BSA was associated with higher RVSP, with a significantly higher average RV mass indexed seen with RVSP> 75% compared to 0%-49% (+31.9 g/m^2, CI 7.5-56.4, p=0.012). There was no association between RVEF and pre-implantation RVSP in this cohort (p=0.7).

Ventricular Longitudinal Strain versus Right Ventricular Systolic Pressure Relationship

Elevated RVSP was significantly associated with a decrease in RV GLS, with every 14.3% increase in RVSP above 28% associated with an absolute magnitude 1% lower RV GLS at preimplantation (p=0.001). When the average pre-implantation RV GLS in was split into 3 categories based preimplantation RVSP: 0-49%, 50-74%, and >75%, the RV GLS was an absolute magnitude of 3.4% lower in those with RVSP >75% compared to 0%-49% (p=0.014). There was no significant association between pre-implantation LV GLS and RVSP as a continuous variable (p=0.141) or by RVSP categories (> 75%, p=0.435). Similar to the effect of pre-implantation RVSP on strain, a 6.3% increase in RVSP above 28% post TPVR was associated with an absolute magnitude 1% lower RV longitudinal strain (p<0.001). Age was not associated with significant change in RV (p=0.354) or LV GLS magnitude (p=0.235).

Overall, the RV GLS magnitude increased after TPVR from pre-implantation over time, with the greatest improvement immediately after valve implantation; however, on follow-up imaging performed within 18 months, the RV GLS was closer to pre-implantation values. The same trend was visualized in LV GLS strain magnitude over time (Figure 1). When categorized into 3 groups by RVSPP (0%-49%, 50%-74%, > 75%), the average strain value showed greatest improvement immediately post TPVR at 0%-49% compared to > 75% (Figure 2).

Pre-implantation Filling Pressure Effect on Ventricular Longitudinal Strain

For every 1 mmHg higher pre-implantation RVEDP, RV GLS absolute magnitude decreased by 0.26% (p=0.04). The pre-implantation LVEDP was not significantly associated with worsened LV GLS magnitude (p=0.788).

Discussion

The goal of our study was to investigate the effects of increased afterload on ventricular function using STE analysis in rTOF patients requiring TPVR. We found that increasing RVSP, particularly RVSP> 75% systemic pressure, was associated with worse RV GLS despite no significant association with RVEF. Our data also suggests that higher RVSP, specifically > 75% systemic, prior to TPVR did not appear to show any improvement in the average RV GLS within 24 hours post or within 18 months post TPVR.

Increased ventricular afterload results in increased myocardial wall stress and decreased velocity of fiber shortening. Compensatory ventricular hypertrophy and increased wall thickness reduces myocardial wall stress and maintains cardiac output. Right ventricular hypertrophy also decreases the compliance of the RV and may mitigate the degree of pulmonary regurgitation, leading to the belief that leaving some degree of pulmonary stenosis may be beneficial in rTOF patients that typically suffer from “free” pulmonary insufficiency[3]. However, recent literature from large multicenter trials has shown that there may be pathological degrees of right ventricular hypertrophy, with increased RV mass/volume ratio a risk factor for major adverse cardiac events [4] . Our study shows that RV GLS is worse in patients with higher RVSP irrespective of age, which may be an early marker of myocardial dysfunction. This was also supported by the association between elevated RVEDP and worse RV GLS.

Though EF remains a well-established marker of ventricular function, we did not find a similar association with elevated RVSP. Our study suggests that strain is a more sensitive marker for ventricular dysfunction, which may show regional myocardial change before a global decline in EF, as seen in many other patient populations[15, 16, 26]. It also suggests that increased afterload can have a detrimental effect on RV function and may be a marker for adverse RV remodeling, which could be mitigated if patients undergo earlier TPVR at lower RVSP. As noted above, higher RV mass/volume ratio was seen in patients who had more stenosis on their pre-implantation catheterization, which is a marker of hypertrophy and has been shown to be an independent risk factor for ventricular tachycardia and death. Freedom from events in this population was less with concomitant risk factors, including ventricular dysfunction and older age[4]. With increasing afterload, hypertrophy worsens over time in rTOF patients and could place them at increased risk of poor clinical outcomes in mixed pulmonary valve disease with predominant afterload.

There are several limitations to this study. The retrospective cohort nature of our study has data limitations, including missing data. Though we present a sizeable number of patients with mixed pulmonary valve disease who underwent TPVR, some patients were excluded due to poor quality echocardiograms. Older patients often have poor acoustic windows, which make fully characterizing the RV endocardium challenging. For this reason, we also limited our strain analysis to just GLS; as opposed to circumferential or radial strain. Arrhythmia and bundle branch blocks, which are common in rTOF patients, can also create challenges when analyzing strain. The amount of pulmonary regurgitation varied in our population; however, we were not able to assess varying degrees of regurgitation and stenosis in distinct groups longitudinally. Also, due to the referral pattern of patients to our institution for TPVR, patients did not undergo a repeat CMR to evaluate the effect of valve implantation on volumetry and function within the follow-up evaluation period. Prospective multi-center studies with a long-term follow-up time are needed with myocardial strain by STE with validation by CMR strain prior to changing clinical practice. Finally, we have included many analyses presented at their nominal values and not adjusted for multiplicity. As such the results should be interpreted as exploratory.

Tables:

Table 1. Demographic Data

	Total Cohort (n=48)	**Native Outflow (n=21)**	**RV-to-PA Co**
Age (years)	17 (10, 54)	16 (10, 54)	18 (11, 40)
Sex (M/F)			
Male	26	12	14
Female	22	9	13
Height (cm)	163 (131, 185)	160 (138, 185)	164 (131, 183)
Weight (kg)	58.6 (30.8, 106.5)	60 (30.8, 104)	58.2 (32.8, 106.
BSA (cm/m2)	1.62 (1.09, 2.24)	1.62 (1.1, 2.13)	1.62 (1.09, 2.24
Implanted Transcatheter Valve-Type	Implanted Transcatheter Valve-Type		
Melody	36	13	23
Sapien	12	8	4

Data reported as median (minimum, maximum).

Table 2. Cardiac Magnetic Resonance and Catheterization Data

CMR Data (n=36)	
CMR RVEF (%)	45 (21, 70)
CMR RVEDVI (ml/m2)	134 (56, 218)
CMR RVESVI (ml/m2)	73 (22, 121)
CMR Pulmonary Regurgitant Fraction (%)	38 (8, 67%)

CMR Data (n=36)	
CMR LVEF (%)	57 (43, 78)
CMR LVEDVI (ml/m2)	74 (44, 109)
CMR LVESVI (ml/m2)	31 (12, 51)
CMR Raw Data (n=36)	
CMR RV M/V ratio	0.28 (0.09, 0.76)
Catheterization Data (n=48)	
RSVP pre (mmHg)	54, (28, 110)
RSVP post (mmHg)	36 (24, 90)
RSVP Pre (%)	57 (28, 131)
RSVP post (%)	35 (22, 84)
RVEDP (mmHg)	11 (5, 21)
LVEDP (mmHg)	10 (4, 26)

Data reported as median (minimum, maximum)

Figures:

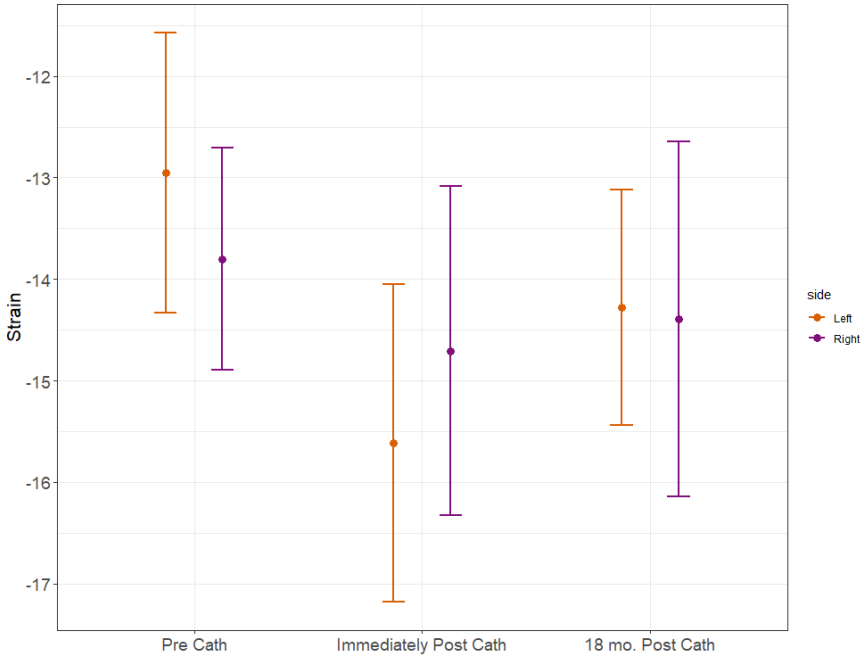

Figure 1. Average RV and LV GLS compared as a group at pre-implantation ("pre cath"), 24 hours post TPVR ("immediately post cath"), and within 18 months post TPVR ("18 mo. post cath").

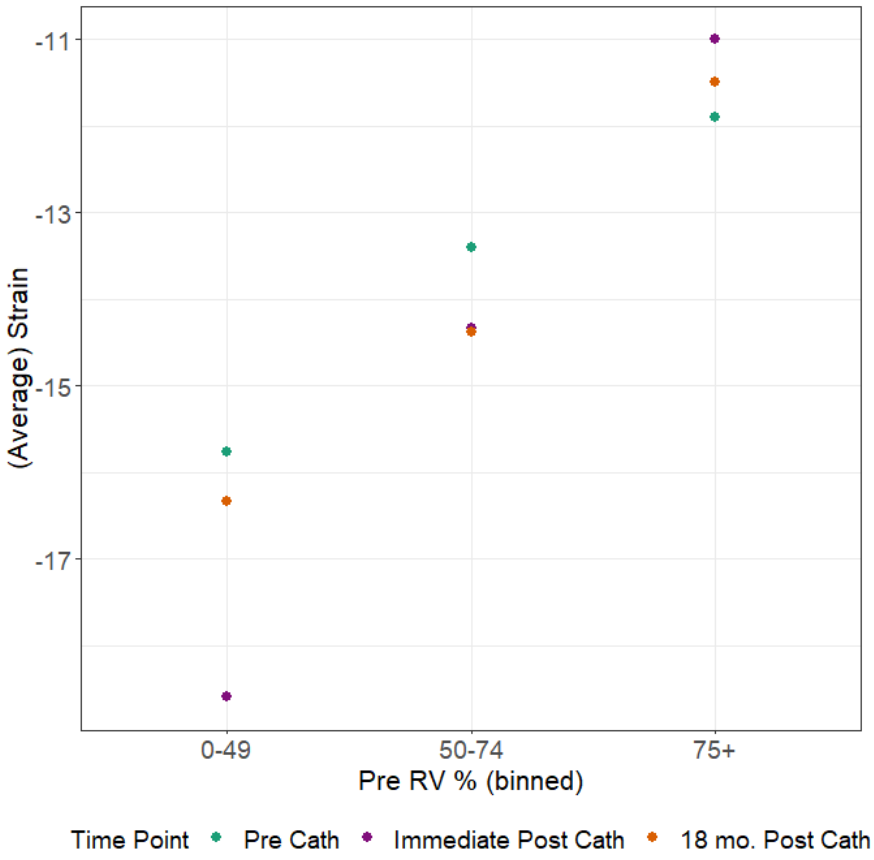

Figure 2. Average RV GLS separated by pre-implantation RVSP value. Green dots represent pre-implantation ("pre cath"), purple dots represent 24 hours post TPVR ("immediate post cath"), and orange dots represent within 18 months post TPVR ("18 mo. post cath"). This graph suggests that there is worse average RV longitudinal strain with *RVSP*> 75% systemic*at* pre-implantation without significant change within 24 hours post or within 18 months post TPVR.

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