Acute and Midterm Outcomes of Transcatheter Pulmonary Valve Replacement for Treatment of Dysfunctional Left Ventricular Outflow Tract Conduits in Patients With Aortopulmonary Transposition and a Systemic Right Ventricle

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Background—Transcatheter pulmonary valve replacement (TPVR) is an established therapy for dysfunctional right ventricular (RV) outflow tract conduits. TPVR in patients with congenitally corrected transposition of the great arteries, subpulmonary left ventricle, and left ventricular outflow tract (LVOT) conduit dysfunction has not been studied. Unique anatomic and physiological aspects of this population may contribute to distinct risks and outcomes.

Methods and Results—Across 10 US centers, 27 patients with a dysfunctional LVOT conduit were evaluated in the catheterization laboratory between December 2008 and August 2015 with the intent to perform TPVR. TPVR was successful in 23 patients (85%). Five serious adverse events occurred in 4 cases (15%), including pulmonary hemorrhage, hypotension requiring vasoactive support, conduit disruption requiring covered stent (n=2), and acute RV dysfunction with flash pulmonary edema. After TPVR, the LVOT peak systolic ejection gradient decreased from median of 35 to 17 mm Hg (P<0.001); pulmonary insufficiency was trivial/none in all but 1 patient, where it was mild. Worsening of systemic RV dysfunction or tricuspid regurgitation was seen in 12 patients (57%) and was associated with a significantly lower post-TPVR LVOT peak systolic ejection gradient (median 17 versus 21 mm Hg; P=0.02) and higher post-TPVR RV sphericity index (median 0.88 versus 0.52; P=0.004). Post-TPVR, there were 2 late deaths because of RV failure and 1 cardiac transplantation because of progressive RV dysfunction and tricuspid regurgitation.

Conclusions—TPVR in dysfunctional LVOT conduits is feasible but associated with an important rate of TPV nonimplantation and procedural serious adverse events. Worsening systemic RV function and tricuspid regurgitation may develop after LVOT TPVR. **(*Circ Cardiovasc Interv*. 2017;10:e004730. DOI: 10.1161/CIRCINTERVENTIONS.116.004730.)**

Key Words: catheterization ■ pulmonary valve ■ pulmonary valve insufficiency ■ transposition of great vessels

Transcatheter pulmonary valve replacement (TPVR) is an established therapy for rehabilitation of dysfunctional right ventricular (RV) outflow tract conduits.[1–3] After initial approval of the Melody TPV (Medtronic Inc, Minneapolis, MN) and recent approval of the Sapien XT (Edwards Lifesciences, Irvine, CA), clinical use has expanded beyond the dysfunctional RV outflow tract (RVOT) conduit to include TPVR within native and patch augmented RVOT and non-pulmonary positions.[4–6] Despite extensive characterization of TPVR in many populations,[7–9] TPVR for conduit dysfunction in patients with congenitally corrected transposition of the great arteries (CC-TGA) and related diagnoses after physiological repair with a left ventricular outflow tract (LVOT) conduit has not yet been systematically reported.

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WHAT IS KNOWN

- Transcatheter pulmonary valve replacement (TPVR) within the left ventricular outflow tract (LVOT) conduit, in the setting of aortopulmonary transposition and a systemic right ventricular (RV), poses unique physiological and anatomic challenges that may influence procedural success.
- Because of septal attachments of the tricuspid valve, alterations in the LV/RV pressure ratio with relief of LVOT obstruction after surgical LVOT conduit replacement have been associated with worsening of tricuspid regurgitation and systemic RV dysfunction in the setting of interventricular septal shift.

WHAT THE STUDY ADDS

- We have shown that LVOT TPVR does pose additional technical challenges compared with standard right ventricular outflow tract TPVR, with 85% procedural success and 15% incidence of procedural serious adverse events.
- Although TPVR is successful in improving LVOT conduit stenosis/insufficiency and New York Heart Association functional classification, 57% of patients developed worsening of tricuspid regurgitation and RV dysfunction in midterm follow-up, which was associated with lower residual LVOT peak gradient and greater interventricular septal shift.
- Relief of conduit obstruction during TPVR in the LVOT conduit should be approached with caution and with serial monitoring of tricuspid valve and RV function post-TPVR.

There are unique anatomic and physiological factors that may contribute to distinct procedural and patient outcomes after TPVR in the LVOT conduit. The nonorthotopic conduit position and frequent association of CC-TGA with dextrocardia may add to technical difficulties with the procedure, contributing to a lower rate of successful TPVR and increased risk of procedural serious adverse events (SAE). In addition, in the setting of a systemic RV and septal attachments of the tricuspid valve (TV), acute alterations to left ventricular (LV) pressure and LV/RV pressure ratio with relief of LVOT conduit obstruction may result in interventricular septal shift and increased severity of tricuspid regurgitation (TR) and RV dysfunction (RVD).[10–13] Thus, indications for, and the acute procedural goals of, TPVR in patients with a dysfunctional LVOT conduit may be different than those established for patients with RVOT conduit dysfunction.

The primary aim of this multicenter study, therefore, was to describe the feasibility and acute procedural outcomes after attempted TPVR for treatment of the dysfunctional LVOT conduit. We further sought to assess midterm outcomes after LVOT TPVR, with a focus on serial assessment of TR severity and RV systolic function (RVSF).

Methods

Patients and Study Protocol

This was a multicenter, retrospective cohort study involving 10 congenital cardiac centers within the United States. Institutional review board approval was obtained at each institution, with waiver of informed consent because of retrospective nature of the study design. Patients were eligible for inclusion if they had CC-TGA, or related anatomy, with a subpulmonary LV and had undergone physiological repair with placement of a surgical LVOT conduit or bioprosthetic valve. For the purposes of clarity in this population, LV refers to the morphological LV, the subpulmonary ventricle with its associated atrioventricular (mitral) valve, and RV refers to the morphological RV, the systemic ventricle with its associated atrioventricular (tricuspid) valve. Patients who underwent catheterization between December 2008 and August 2015 for intended TPVR within a LVOT conduit were included. Patients were identified using available center-specific TPVR databases.

Record abstraction, including echocardiography and catheterization reports, and angiography review were performed at the individual sites. Primary hemodynamic indications (stenosis, insufficiency, or mixed) and primary clinical indications (symptoms, prevention of symptoms, declining ventricular function, unknown, or other) were classified. New York Heart Association (NYHA) functional class was ascertained at baseline and most recent follow-up to assess clinical outcomes. Invasive hemodynamic variables, including LVOT peak systolic ejection gradient (PSEG) and LV/RV systolic pressure ratio, were obtained.

Longitudinal echocardiographic data were analyzed at the following time points: preprocedure, immediate postprocedure, midterm follow-up at 6±3 months postprocedure, and at most recent available clinical follow-up or last clinical follow-up before transplant/TPV explant/death. Baseline, immediate postprocedure, and most recent follow-up echocardiographic images were evaluated at a core laboratory and interpreted by a single blinded reviewer (J.T.T.) to assess RVSF, TR, and RV systolic sphericity index (SI) as a surrogate of interventricular septal shift.[12] RVSF was evaluated subjectively, and TR was assessed by measurement of the vena contracta of the regurgitant jet (mild<4 mm, moderate 4–6 mm, and severe>7 mm).[14,15] Inter-rater reliability of RVSF and TR grade was assessed using a 25% sample of studies reviewed by a second blinded reviewer.

Conduit location was classified as remote, partially apposed, or substantially apposed to the sternum according to the definition of conduit location described by McElhinney et al.[16] Serial imaging was assessed for interval worsening of TR/RVSF using 2 classification schemes: (1) any worsening was defined as an increase in TR by ≥1 grade or a decrease in RVSF by ≥1 grade while (2) new moderate or worse was defined by the presence of new moderate or worse TR and RVD. Assignment to the stable or worse TR/RVSF groups was made based on 6-month follow-up data to reduce the risk of introducing bias in the setting of discrepant follow-up durations.

Statistical Analysis

Data are presented as frequency with percentage for categorical variables and median with range (minimum–maximum) for continuous variables. An inter-rater reliability analysis using the κ statistic was performed to determine consistency among raters for grading TR and RVSF. Differences in hemodynamic variables before and after TPVR were assessed using Wilcoxon signed-rank test. Differences between cohorts with stable versus worse TR/RVSF were assessed using unpaired Student *t* test and Mann–Whitney test for normally and non-normally distributed variables, respectively. Statistical significance was set at 0.05. Freedom from development of new moderate or worse TR/RVD was calculated using Kaplan–Meier methods. The relationship between SI and both LVOT PSEG and LV/RV pressure ratio was assessed by linear regression, whereas differences between SI stratified by TR grade were assessed using Mann–Whitney test. Patients who had undergone TV replacement before TPVR were excluded from analysis of TR and RVSF end points.

Table 1. Baseline Clinical and Echocardiographic Characteristics (n=27)

Characteristic	n (%*), Median (Range)
Male	17 (63%)
Age, y	31 (11–56)
Weight, kg	74 (39–155)
Primary cardiac diagnosis	
Congenitally corrected TGA	22 (81%)
{S,L,L} Double outlet right ventricle	4 (15%)
D-TGA s/p atrial switch procedure	1 (4%)
Additional prior surgical procedures	
Pacemaker	4 (15%)
Tricuspid valve replacement	2 (7%)
Most recent LVOT conduit type	
Homograft conduit	11 (41%)
Bioprosthetic valve/valved conduit	10 (37%)
Synthetic conduit/tube	3 (11%)
Other	3 (11%)
Nominal conduit diameter at implant, mm	22 (18–24)
Procedure clinical indication	
Symptoms	19 (70%)
Declining subpulmonary ventricular function	5 (18%)
Prevention of symptoms in asymptomatic patient	1 (4%)
Other—conduit aneurysm	1 (4%)
Unknown	1 (4%)
Procedure hemodynamic indication	
Primary stenosis	8 (30%)
Primary insufficiency	6 (22%)
Mixed stenosis/insufficiency	13 (48%)
Echocardiography data	
Peak LVOT gradient, mm Hg	65 (33–84)
Mean LVOT gradient, mm Hg	32 (18–50)
Right ventricular systolic function	
Normal-mildly depressed	18 (67%)
≥Moderately depressed	9 (33%)
Left ventricular systolic function	
Normal-mildly depressed	19 (71%)
≥Moderately depressed	6 (22%)
Not available	2 (7%)
Tricuspid regurgitation	
None-mild	17 (63%)
Moderate-severe	8 (30%)
Not available	2 (7%)
Pulmonary insufficiency	
None-mild	5 (18%)
Moderate-severe	11 (41%)
Not available	11 (41%)

D-TGA indicates D-transpositon of the great arteries; LVOT, left ventricular outflow tract; and TGA, transposition of the great arteries.

*Percentages rounded to equal 100% within each category.

Results

Patients and Procedural Outcomes

Cardiac catheterization was performed in 27 patients during the study period, accounting for 3.5% of total TPVR cases performed across participating centers. TPVR was successful in 23 patients (85%), all of whom received a Melody TPV. Baseline clinical and echocardiographic characteristics are shown in Table 1. Primary cardiac diagnosis was CC-TGA ({S,L,L} or {I,D,D} segmental anatomy) in 22 patients (81%). Conduit stenosis (alone or mixed) was the primary hemodynamic indication for TPVR (78%). The most common clinical indication was the presence of symptoms felt to be related to conduit dysfunction.

Procedural characteristics are displayed in Table 2. A substantial proportion of all patients had a remote conduit location including in 3 of 4 patients in whom TPVR was not attempted. Notably, the catheter course in many patients was atypical with apical LV insertion of the conduit and long courses in the lateral chest (Figure 1). TPVR was successful in most cases

Table 2. Procedural Characteristics of Patients Who Received TPVR (n=23)

Characteristic	n (%)
Location of conduit relative to sternum	
Remote	8 (35%)
Partially apposed	10 (43%)
Substantially apposed	5 (22%)
Initial venous access site	
Femoral	16 (69%)
Internal jugular	2 (9%)
Both femoral and internal jugular accessed	5 (22%)
Access site for Melody TPV	
Femoral	19 (83%)
Internal jugular	4 (17%)
Coronary artery assessment performed	22 (96%)
Pre-stent used	18 (78%)
Melody TPV implant size, mm	
18	7 (30%)
20	9 (40%)
22	7 (30%)
TPV postdilation performed	4 (17%)

TPVR indicates transcatheter pulmonary valve replacement.

from a transfemoral approach (83%) although a change in primary access site was necessary in 3 cases (Figure 1). One patient underwent a staged approach to conduit rehabilitation and TPVR, secondary to extensive conduit calcification, ruptured angioplasty balloons, and lack of immediate availability of a covered stent during the first procedure.

TPV delivery was not attempted in 4 cases. In 2 cases, the operators detailed a difficult catheter course and heavily calcified conduit. Ultra high-pressure angioplasty balloons (Atlas, Bard Medical, Covington, GA) were either unable to be advanced across the calcified conduit or were ruptured with attempts at inflation. In both cases, advancement of the Melody TPV was not attempted because of insufficient conduit preparation. In the third case, TPVR was not attempted because conduit size was thought to be inadequate (initial conduit size of 16 mm, narrowed to 7 mm). In the fourth patient, the procedure was aborted because of concern for coronary compression by balloon testing before TPV pre-stenting. In no case was Melody TPV delivery attempted but not successful.

There were no procedural deaths. Five procedural SAE occurred in 4 of 27 cases (15%). First, conduit disruption developed in a stenotic 22-mm composite (Dacron/homograft) conduit during balloon angioplasty; covered Cheatham-Platinum stent (NuMED, Hopkinton, NY) placement successfully excluded the disruption before TPVR. Relief of severe LVOT conduit obstruction in this patient, however, led to acute RVD and TR resulting in flash pulmonary edema. In a second case with a 25-mm Hancock conduit, there was a contained conduit tear during conduit angioplasty. With covered stents unavailable, the procedure was electively aborted, and the patient returned to the catheterization laboratory 1 month later for successful covered stent and TPVR. The other 2 SAE were hemodynamic instability requiring vasoactive medications and pulmonary hemorrhage managed with protamine.

Acute Hemodynamic Results

After successful TPVR, LVOT PSEG decreased from a median of 35 (3–115) to 17 (1–48) mm Hg, $P<0.001$, and LV/RV pressure ratio decreased from median 0.69 (0.35–1.66) to 0.48 (0.36–0.85), $P=0.001$, Table 3. There was trivial or no pulmonary insufficiency in all but 1 patient in whom insufficiency was mild. There were no associations found between cardiac anatomy and successful TPVR or acute hemodynamic outcomes.

Midterm Follow-Up

During a median follow-up of 2.7 (0–6.9) years, 2 patients developed endocarditis at 0.6 and 2.7 years postprocedure for a rate of 2.9% per patient-year. Both received successful medical therapy without TPV reintervention. No Melody stent fractures were reported in follow-up. One patient had redilation of the Melody valve 8 months post-TPVR, during an unrelated diagnostic catheterization, in the setting of mild residual LVOT obstruction.

Excluding the 2 patients who had undergone TV replacement, any worsening of TR and RVSF occurred in 12 of 21 patients (57%) by midterm (6 month) follow-up: 4 patients had worsening RVSF only, 6 patients had worsening TR only, and 2 patients had worsening of both. The follow-up durations for patients with stable or worsening TR/RVSF were similar (median 2.9 years [interquartile range, 1.7–4.5] versus 3.2 years [interquartile range, 1.0–4.6]; $P=0.48$). One additional patient had late development of TR (at 4.9 years post-TPVR). The inter-rater reliability for echocardiographic assessment of TR ($\kappa=0.91$ [$P<0.001$]; 95% confidence interval, 0.73–1.09) and RVSF ($\kappa=0.86$ [$P<0.001$]; 95% confidence interval, 0.59–1.12) were both excellent. The distribution of grades of TR and RVD at baseline and follow-up is shown in Figure 2. There was a significantly lower LVOT PSEG post-TPVR in those patients who developed worsening TR/RVSF compared with those with stable TR/RVSF (Table 4). When comparing LVOT PSEG in all patients pre- and post-TPVR, the patients with the highest residual LVOT PSEG post-TPVR had stable TR/RVSF (Figure 3). All patients who developed worsening TR/RVSF had a residual LVOT PSEG <25 mm Hg. Both SI immediately post-TPVR and SI change from baseline were significantly higher in patients who developed worsening of TR/RVSF (Table 4). A higher SI was present in patients with moderate/severe TR compared with mild TR ($P=0.005$) and no TR ($P=0.01$; Figure 4). New≥moderate TR and RVD occurred in 9 patients (43%). Estimated freedom from the development of new≥moderate TR/RVD was 60% (95% confidence interval, 36%–77%) at 50 months and 45% (15%–71%) at 60 months (Figure 5).

There was an overall improvement in functional capacity of the cohort post-TPVR with an increase in patients in NYHA class I from 21% at baseline to 63% at latest follow-up (Figure 6). The improvement in NYHA class appeared more robust in patients who had stable TR/RVSF. No patients with stable TR/RVSF were NYHA III or IV post-TPVR, whereas 4 patients were classified NYHA III or IV in the worse TR/RVSF cohort. Of these 4 patients, 1 underwent cardiac transplant, 1 is listed for transplant, and 2 have died.

Three adverse clinical outcomes occurred during follow-up, including 2 deaths and 1 cardiac transplantation. One mortality occurred 187 days post-TPVR, secondary to RV failure requiring ventricular assist device and extracorporeal membrane oxygenation support, in a 29-year-old patient with pre-existing severe RVD and moderate TR. The second mortality occurred 6.9 years post-TPVR in a 46-year-old patient with baseline moderate RVD and TR. Symptoms, biventricular systolic function, and TR worsened over years, necessitating conduit and TV replacement. Surgery was complicated by abdominal compartment syndrome, extracorporeal membrane oxygenation, multiorgan system failure, and death 10 days postoperatively. Finally, a third patient underwent cardiac transplantation 289 days post-TPVR. This asymptomatic 11-year-old patient had normal RV and LV function, moderate TR, and moderate bioprosthetic pulmonary valve stenosis and insufficiency at baseline. She underwent TPVR with decrease in LVOT PSEG from 31 to 16 mm Hg and final LV/RV ratio of 0.38. She had new mild RVD immediately post-TPVR. At 6-month follow-up, RVD and TR had worsened to moderate and severe, respectively. Cardiac transplantation was pursued in the setting of symptomatic cardiac dysfunction.

At latest follow-up, valve function was well maintained in 21 of the 23 patients, with LVOT mean gradient≤35 mm Hg in all patients and trivial or no pulmonary insufficiency in all but 2 patients (who had mild and moderate pulmonary insufficiency).

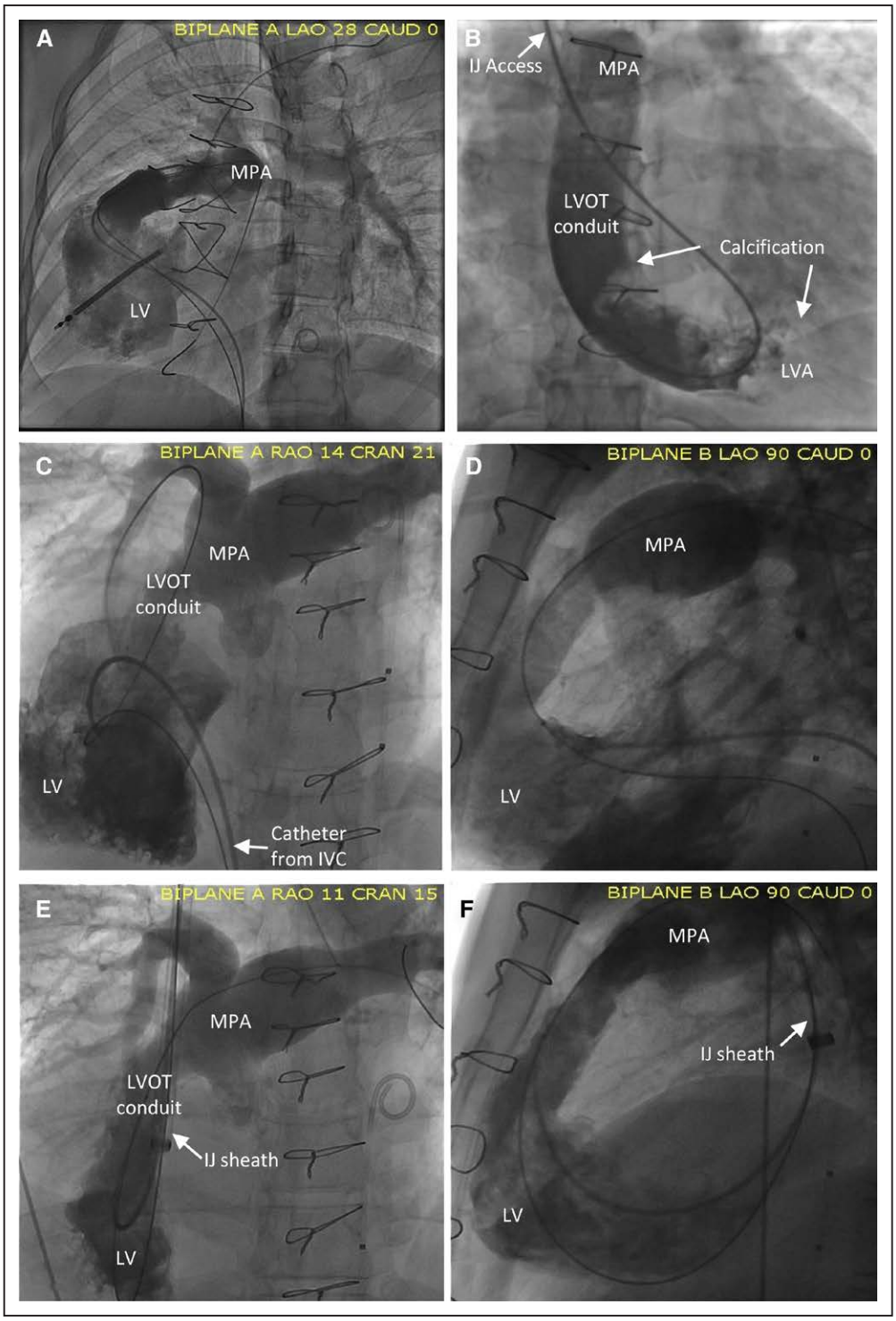

Figure 1. Angiographic examples of left ventricular outflow tract (LVOT) conduit positions and catheter/wire courses. **A**, Anterior-posterior projection of a patient with a rightward conduit orientation, dextrocardia, and stenotic bioprosthetic valve in the LVOT position. **B**, Homograft conduit sewn to a Gortex tube and inferior ventriculotomy at the apex of the left ventricle (LV) with heavy calcification. Transcatheter pulmonary valve replacement (TPVR) was unsuccessful in this patient because of the inability to advance angioplasty balloons across the area of proximal conduit calcification. **C**–**F**, Dextrocardia, {S,L,L} double outlet right ventricle with remote conduit position. Access via the femoral approach, with distal wire position in the right pulmonary artery (shown in anterior-posterior [**C**] and lateral [**D**] projections) did not allow for advancement of angioplasty balloons and required conversion to a transjugular approach with distal left pulmonary artery wire position (shown in anterior-posterior [**E**] and lateral [**F**] projections). IJ indicates internal jugular vein; IVC, inferior vena cava; LVA, LV apex; LVOT, LV outflow tract; and MPA, main pulmonary artery.

Follow-Up of Patients Who Did Not Undergo TPVR

Four patients did not undergo TPVR. Of this group, 1 died 1 year after catheterization of unrelated infection while 3 underwent surgical PVR at 1 day, 5 months, and 6 months after catheterization. Initial indication for attempted TPVR in all patients was primary stenosis or mixed stenosis/insufficiency,

Table 3. Hemodynamic Data in All Patients Pre- and Immediately Post-TPVR (n=23)

	Pre-TPVR	Post-TPVR	*P* Value
Left ventricular systolic pressure, mm Hg	69 (35–126)	50 (32–75)	<0.001
Mean pulmonary artery pressure, mm Hg	17 (9–33)	22 (11–44)	0.002
Peak LVOT gradient, mm Hg	35 (3–115)	17 (1–48)	<0.001
LV/RV pressure ratio	0.69 (0.35–1.66)	0.48 (0.36–0.85)	0.001

Data are presented as median (range). LV/RV indicates left ventricle to right ventricle; LVOT, left ventricular outflow tract; and TPVR, transcatheter pulmonary valve replacement.

and ultimate indication for PVR in these patients was worsening symptoms and conduit stenosis. All have had symptomatic improvement since PVR while 1 patient has evidence of new moderate TR and RVD.

Discussion

Acute Procedural Success and Safety

In this retrospective multicenter study, we offer the first report focused on TPVR in patients with subpulmonary LVOT conduit dysfunction. Procedural success for the LVOT cohort (85%) was lower compared with TPVR in dysfunctional RVOT conduits described in the Melody United States Investigational Device Exemption (US IDE) trial (89%–91%)[2,3] and post-approval study (98%).[17] Although a lower rate of procedural success might be anticipated in clinical practice compared with a prospective clinical trial cohort, we do think that the rate of procedural success presented herein represents a true difference between the RVOT and LVOT populations. Furthermore, the rate of SAE is apparently higher in the LVOT conduit cohort, likely indicative of the complex anatomy and physiology present in these patients. Notably, there was not an obviously increased incidence of catastrophic conduit injury in the LVOT population despite conduits typically positioned in a peripheral and less protected location in the chest. Thus, although transcatheter treatment of the dysfunctional LVOT conduit may pose distinct challenges with conduit preparation and TPV implantation, our findings suggest that TPVR for LVOT conduit dysfunction is technically feasible and results in acute relief of conduit stenosis and restoration of pulmonary valve competency.

Unique characteristics of the LVOT population can make TPVR more challenging. Apical and nonorthotopic conduit anastomosis to the LV, remote conduit course within the thorax, and atypical cardiac orientation (dextrocardia is common) all serve to make catheter manipulation and delivery of large interventional equipment difficult. Despite these potential challenges, most patients still had successful delivery of the valve via the femoral approach. Anticipating a difficult catheter course, 20% of patients in this study had access obtained in both the femoral and internal jugular veins, yet in all but 1 case, operators were able to proceed with transfemoral TPVR. There were 2 patients in the present study who did not undergo TPVR because of the inability to advance angioplasty balloons into the conduit for pre-TPVR conduit rehabilitation. The operators in these cases felt that this limitation was secondary to extensive conduit calcification and complex catheter course. This rate of failure (7%) was not encountered in the Melody US IDE trial and is likely a direct reflection of this unique anatomy.

Outcomes Related to TR and RVSF

Given that RVOT conduit dysfunction can lead to RV dilation and dysfunction, exercise intolerance, increased arrhythmia burden, and increased mortality risk, including sudden death,[18–20] relief of RVOT obstruction and restoration of pulmonary valve competency are standard-of-care goals with RVOT conduit rehabilitation and TPVR. In contrast, there is a growing body of echocardiographic and surgical data to suggest that the same approach may not be desired in the setting

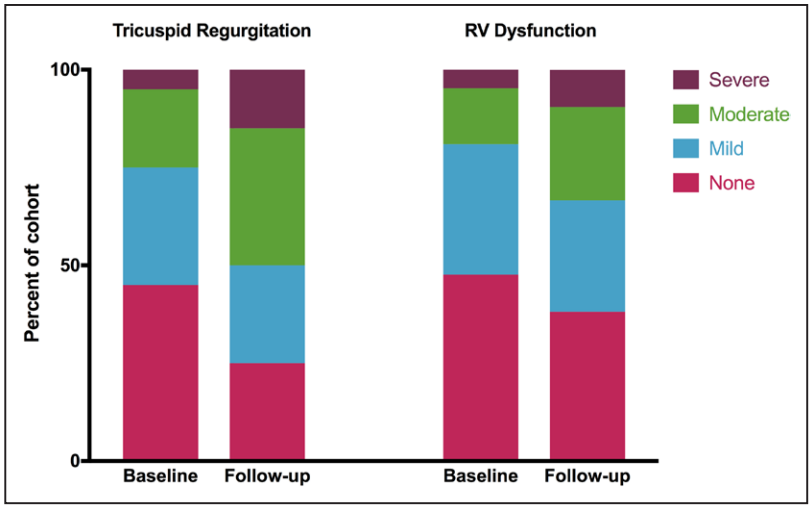

Figure 2. Distribution of grades of tricuspid regurgitation (TR) and right ventricular (RV) dysfunction by echocardiography. The left 2 columns show the distribution of TR grades at baseline and highest grade in follow-up post–transcatheter pulmonary valve replacement. In the right 2 columns, the distribution of RV dysfunction at baseline and highest grade in follow-up post-TPVR.

Table 4. Selected Invasive and Noninvasive Measures at Baseline and Post-TPVR Stratified by TR and RVSF

	Stable TR/RVSF (n=9)	Worse TR/RVSF (n=12)	*P* Value
LVOT PSEG, mm Hg			
Baseline	50 (20 to 115)	31 (3 to 80)	0.08
Post-TPVR	21 (11 to 48)	17 (4 to 25)	0.02
Change in PSEG, mm Hg	24 (–5 to 67)	15 (–5 to 74)	0.29
LV/RV systolic ratio			
Baseline	0.78 (0.6 to 1.66)	0.67 (0.35 to 1.6)	0.21
Post-TPVR	0.57 (0.36 to 0.85)	0.47 (0.38 to 0.66)	0.06
Change in LV/RV systolic ratio	0.21 (–0.05 to 0.86)	0.16 (–0.08 to 1.12)	0.38
Sphericity index			
Baseline	0.61 (0.40 to 1.04)	0.53 (0.44 to 0.98)	0.49
Immediate post-TPVR	0.52 (0.38 to 0.88)	0.88 (0.62 to 1.09)	0.004
Change from baseline	–0.04 (–0.19 to 0.08)	0.17 (–0.01 to 0.34)	0.02

LV/RV indicates left ventricle to right ventricle; LVOT, left ventricular outflow tract; PSEG, peak systolic ejection gradient; RVSF, RV systolic function; TPVR, transcatheter pulmonary valve replacement; and TR, tricuspid regurgitation.

of CC-TGA and a dysfunctional LVOT conduit. Although we have demonstrated that TPVR in the LVOT conduit may be technically feasible and acutely successful in relieving anatomic stenosis/insufficiency, complete relief of LVOT conduit obstruction may have deleterious effects on systemic atrioventricular valve regurgitation and ventricular function.

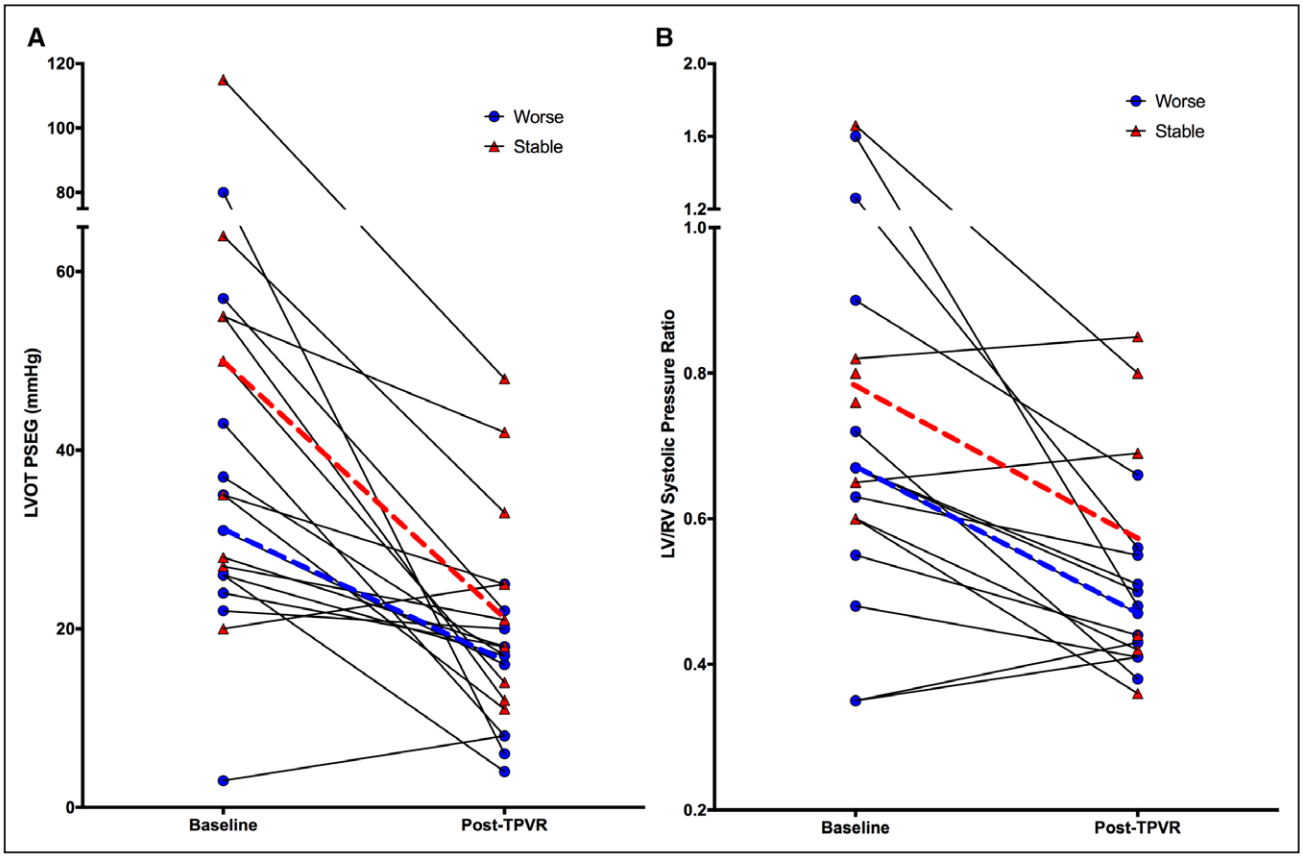

Figure 3. Change in left ventricular outflow tract (LVOT) peak systolic ejection gradient and left ventricular (LV)/right ventricular (RV) pressure ratio post–transcatheter pulmonary valve replacement (TPVR). Change in LVOT peak systolic ejection gradient (PSEG; **A**) and LV/RV systolic pressure ratio (**B**) from baseline to post-TPVR. Patients who had stable tricuspid regurgitation (TR) and/or RV systolic function (RVSF) are shown with red triangles with lines connecting their baseline and post-TPVR values. Those patients who had worsening of TR/RVSF are shown with blue circles. Medians of the stable and worse groups are displayed with dashed red and blue lines, respectively.

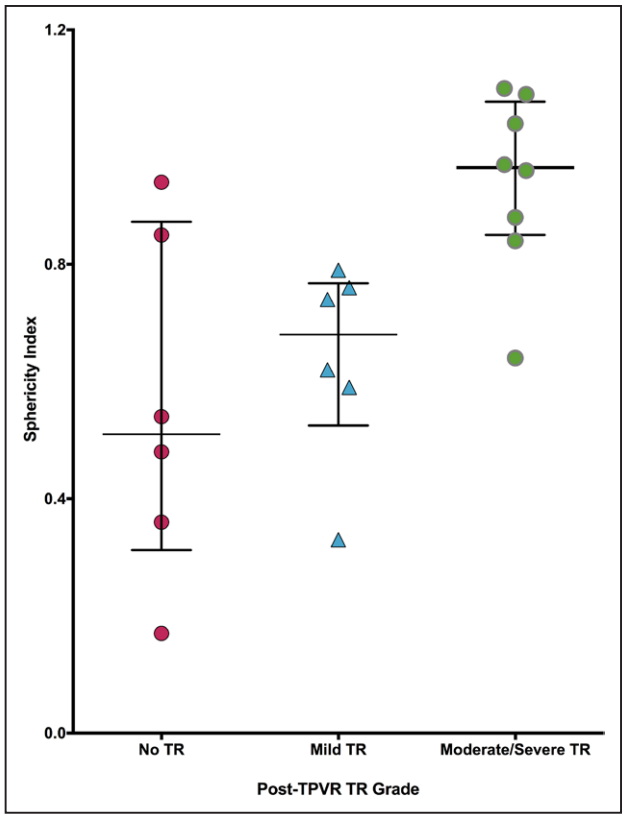

Figure 4. Sphericity index and tricuspid regurgitation (TR) grade post–transcatheter pulmonary valve replacement (TPVR). Relationship between right ventricular sphericity index and TR grade post-TPVR, shown with median and 95% confidence intervals.

Using the RV and TV in the systemic circulation creates a unique anatomic circumstance whereby the TV, because of septal attachments, is affected by relative interventricular septal position and the LV/RV systolic pressure ratio.[11,12] Multiple studies have shown that interventions to increase subpulmonary LV pressure (eg, pulmonary artery band) result in decreased TR and, in contrast, interventions that decrease LV pressure (eg, surgical replacement of obstructed LVOT conduit) may result in an increase in TR.[10–13,21] Recently, Buber et al[11] described RV geometry and TV function after surgical conduit intervention in 38 patients with LVOT conduits. They found worse TR in 65% of patients after conduit intervention compared with only 15% in a control cohort. A larger decrease in LV/RV pressure ratio and conduit gradient after surgical intervention correlated with worse TR at follow-up. Importantly, in 39% of the patients who developed increased TR, there was also progressive RVD.[11] In patients with systemic RV, the degrees of TR and RVD are closely related to clinical outcomes, including morbidity and mortality,[22–25] but there is a yet undefined risk of adverse clinical outcomes because of sequelae of untreated LVOT conduit dysfunction. The LV that classically faces systemic pressure and vascular resistance may be better able to tolerate long-term pressure overload than the RV. Given these physiological considerations and the existing outcome data after surgical LVOT conduit intervention, indications for transcatheter intervention on the dysfunctional LVOT conduit ought to be distinct from those surrounding RVOT conduit dysfunction. Specifically, allowing for higher subpulmonic LV pressure may retain a more favorable systemic RV geometry by limiting systolic septal shift toward the LV.

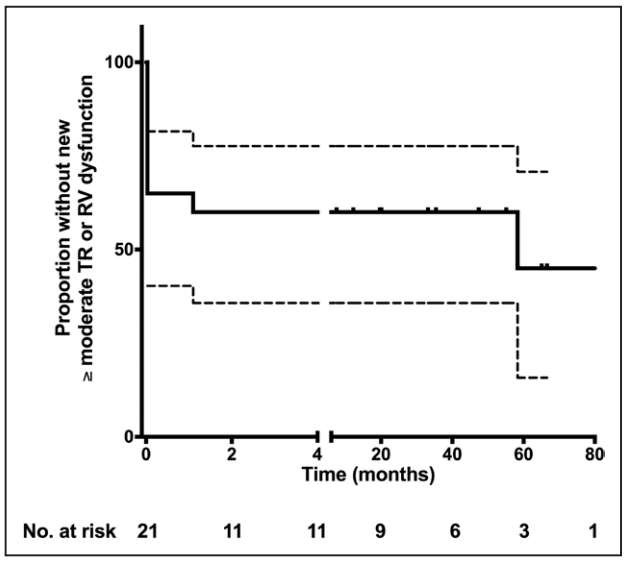

Figure 5. Freedom from development of new moderate or worse tricuspid regurgitation (TR) or right ventricular dysfunction (RVD). Kaplan–Meier curve of freedom from development of moderate or worse TR/RVD. Freedom from development of new moderate or worse TR/RVD was 60% (95% confidence interval, 36%–77%) at 50 months and 45% (15%–71%) at 60 months.

In the present study, we demonstrated progression to worse TR/RVSF post-TPVR in the majority of patients, similar to findings reported in surgical series. Among patients with worsened TR/RVSF were 3 major adverse outcomes in follow-up, including 2 deaths and 1 heart transplant. In fact, the patient who underwent heart transplant had normal baseline RV function with the onset of RVD immediately after TPVR. These outcomes should create pause for the interventionalist approaching a patient with subpulmonary LVOT conduit dysfunction. Although progressive TR and RVD are a component of the natural history of physiologically repaired CC-TGA,[22–24] transcatheter intervention to relieve LVOT conduit obstruction may initiate or accelerate this progression. We demonstrated an association between lower post-TPVR LVOT PSEG and the development of worsening TR/RVSF. Although there is not an established residual LVOT gradient to target, in our series, no patient developed worse TR/RVD when left with a post-TPVR LVOT PSEG of ≥25 mm Hg. Importantly, we also investigated the physiological relationship between LVOT conduit obstruction and interventricular septal position, demonstrating that SI increased significantly after TPVR in patients who went on to develop worsened TR/RVSF. This is consistent with a more rounded systemic RV in the face of a lower pressure subpulmonary LV. Overall, SI was progressively higher by TR grade, consistent with a mechanistic link between septal shift and TR severity.

TPVR in the LVOT conduit does improve functional capacity in most patients. However, consistent with the known clinical course of worsening TR/RVD in the CC-TGA population, this subgroup of patients manifested worse NYHA classification. Importantly, despite the potential for relief of LVOT conduit obstruction to precipitate symptomatology,

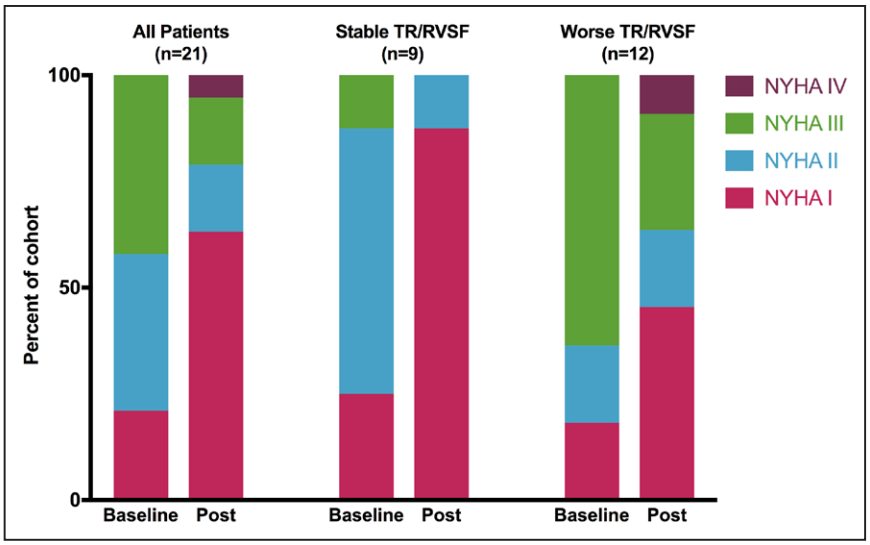

Figure 6. New York Heart Association (NYHA) functional class. Bar graph showing the distribution of NYHA functional class at baseline and post–transcatheter pulmonary valve replacement in all patients (**left**), in patients with stable tricuspid regurgitation (TR)/right ventricular systolic function (RVSF; **center**), and in patients with worse TR/RVSF (**right**).

among patients in whom TPVR was unsuccessful, all developed progressive clinical symptoms and underwent surgical conduit replacement in follow-up. Given this potential narrow therapeutic window, whereby unintervened conduit dysfunction leads to progressive symptoms but therapeutic intervention may hasten cardiac dysfunction, we suggest a cautious approach toward pre- and intraprocedural decision making. Vigilant post-TPVR follow-up of TR and RVSF is necessary. Finally, if intervention is deemed warranted, it stands to reason that targeting incomplete gradient relief while relieving severe obstruction and regurgitation may be a reasonable course of action.

Limitations

Although this study is unique in describing this subpopulation of patients with LVOT conduit dysfunction undergoing attempted TPVR, there are important limitations. First, this is a retrospective study assessing nonstandardized care delivered across multiple centers. Quantitative MRI data were not available for most patients and, therefore, it was necessary to rely on echocardiography to assess changes in RVSF and TR. Although inclusion of an echocardiographic core laboratory with interrater reliability assessment is a strength, the subjective nature of RVSF assessment and inherent differences in image quality and completeness across studies remain problematic. In addition, objective measures of exercise tolerance and symptoms pre- or post-TPVR were unavailable in most patients. Therefore, clinical follow-up was assessed by NYHA functional classification alone. Despite the large multicenter collaboration, this study details a small cohort of patients. The resultant sample size limitations may have impacted our ability to detect clinically meaningful associations, such as the relationship between post-TPVR hemodynamics and severity of TR/RVD, and limits the detection of rare adverse events. Moreover, sample size limitations drove the use of a combined TR/RVD end point, which, compared with the analysis of these end points independently, might generate different findings. Finally, follow-up duration of this cohort was limited at present, and ongoing follow-up will be necessary to fully understand the long-term durability of TPVR and risk of progressive TR/RVD.

Conclusions

TPVR in the dysfunctional LVOT conduit poses unique technical challenges secondary to complex anatomic relationships present in this cohort, which result in modest rates of both procedural failure and SAE. However, successful TPVR was accomplished in most cases. New and worsening TR/RVD may develop after TPVR and could be sequelae of greater relief of LVOT conduit obstruction with resultant interventricular septal shift. Longer term follow-up data from a larger cohort are necessary to further evaluate this potentially important interaction. In the meantime, caution is recommended when approaching relief of conduit stenosis and TPVR in patients with LVOT conduit dysfunction.

Disclosures

Drs Armstrong, Gillespie, and Jones have research grants through Medtronic. Drs Gillespie and Jones also serve as consultants for Medtronic. The other authors report no conflicts.

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Acute and Midterm Outcomes of Transcatheter Pulmonary Valve Replacement for Treatment of Dysfunctional Left Ventricular Outflow Tract Conduits in Patients With Aortopulmonary Transposition and a Systemic Right Ventricle

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