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Transcatheter Pulmonary Valve Replacement Reduces Tricuspid Regurgitation in Patients With Right Ventricular Volume/Pressure Overload

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ABSTRACT

BACKGROUND Tricuspid regurgitation (TR) is a common and important comorbidity in patients with postoperative right ventricular outflow tract (RVOT) obstruction or pulmonary regurgitation (PR). Transcatheter pulmonary valve replacement (TPVR) has become a useful tool in the management of postoperative RVOT obstruction and PR, but it is unknown whether relief of the right ventricular volume and/or pressure overload by TPVR will have a beneficial effect on TR, as is often seen with surgical pulmonary valve replacement.

OBJECTIVES This study sought to assess the prevalence of and factors associated with significant TR in patients undergoing TPVR for RVOT obstruction or PR.

METHODS Data were combined from 3 prospective multicenter trials of patients referred for TPVR. Follow-up data through 5 years post-implantation were analyzed.

RESULTS Of 300 patients studied, 77 (25.6%) had moderate or severe TR at baseline. After TPVR, TR severity was improved in 65% of those patients, and more than one-half had mild TR or less TR at discharge. Of 13 patients with severe TR pre-implantation, only 1 had severe TR at 1-year follow-up and beyond. Moderate or severe baseline TR was associated with shorter freedom from RVOT reintervention after TPVR.

CONCLUSIONS In this prospective multicenter study of post-operative patients with RVOT obstruction and/or PR, TR was common. In patients with significant baseline TR, TPVR resulted in clinically relevant acute reductions in TR that persisted over at least 5 years of follow-up. These observations support the application of TPVR therapy in patients with RVOT obstruction or PR who are anatomically suitable, even in the setting of significant concomitant TR.
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Tricuspid regurgitation (TR) is one of the most frequent and important comorbidities that can develop in patients with repaired tetralogy of Fallot (TOF) and other lesions involving the right side of the heart (1). Studies have documented moderate or severe TR in anywhere from 12% to 44% of patients with repaired TOF (2–5), as well as in similar percentages of patients with valvular pulmonary

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

PAIVS = pulmonary atresia with intact ventricular septum

PR = pulmonary regurgitation

PS = pulmonary stenosis

PVR = pulmonary valve replacement

RV = right ventricular

RVOT = right ventricular outflow tract

TOF = tetralogy of Fallot

TPV = transcatheter pulmonary valve

TPVR = transcatheter pulmonary valve replacement

TR = tricuspid regurgitation

TV = tricuspid valve

stenosis (PS) or pulmonary atresia with intact ventricular septum (PAIVS), both before and after intervention, particularly when there is significant pulmonary regurgitation (PR) (6–9). The natural history of TR after repair of TOF and related anomalies has not been defined, and the frequency of significant TR likely depends on many factors (1). TR is thought to develop in these patients partially as a result of right ventricular (RV) enlargement and/or hypertension, with consequent annular dilation and inadequate tricuspid valve (TV) coaptation (1,10,11). In some congenital anomalies of the RV outflow tract (RVOT), such as PAIVS, RV volume and/or pressure overload can be compounded by intrinsic anatomic abnormalities of the TV that also contribute to TR (12). In most published guidelines, severe TR is specified as an adjunctive indication for pulmonary valve replacement (PVR) in patients with TOF who have important PR (13).

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Transcatheter PVR (TPVR) has become a useful tool in the management of postoperative RVOT obstruction and PR in patients with TOF, other conotruncal anomalies, or an RVOT conduit as part of a Ross procedure (14,15). However, it is unknown whether relief of the RV volume and/or pressure overload by TPVR will have a salutary effect on TV function in patients with important TR. Surgical PVR provides an opportunity to repair the TV that TPVR does not, although the long-term benefit of surgical tricuspid valvuloplasty in these populations of patients is uncertain (1). As TPVR therapy becomes more deeply integrated into the management of patients with RVOT dysfunction, it will be important to determine whether and to what extent TPVR leads to improvement in TV function, a variable that will help inform decisions regarding referral for transcatheter management or surgical PVR with TV repair. There is limited published information on which to base such discussions (16). The purpose of this study was to characterize the burden to TR in a large cohort of patients treated with TPVR, as well as to assess factors associated with the severity of and post-TPVR changes in TR.

METHODS

STUDY SUBJECTS AND PROTOCOLS. The inception cohort for this study included all patients who underwent catheterization with the intention to implant a Melody valve (Medtronic, Inc., Minneapolis, Minnesota) for RVOT conduit dysfunction under the auspices of 3 ongoing prospective multicenter studies sponsored by Medtronic: 1) the Post-Approval Study of the original U.S. Investigational Device Exemption (IDE) cohort (NCT00740870); 2) the U.S. Post-Approval Study (PAS) (NCT01186692); and 3) the Melody TPV Post-Market Surveillance Study (PMSS) in Europe and Canada (NCT00688571). Details of these trials and various results have been described in previous reports (15,17–21). Of particular relevance for this study, TR severity was not considered as an inclusion or exclusion criterion for any of the trials. Data were obtained from the prospective, de-identified databases maintained by Medtronic, which were locked for the current study between July and October 2015. Only patients who underwent successful TPVR and left the hospital with the valve intact were analyzed for this study. Data from the pre-intervention evaluation (baseline), pre-discharge, and annual follow-up echocardiograms were analyzed out to 5 years when available. All patients provided written informed consent for participation in the trials. Investigative sites for the 3 studies are listed in the Online Appendix.

Data on the number of previous open heart operations and RVOT conduits were recorded in the trial databases, but information about previous TV interventions was not collected. Moreover, the presence of a pacemaker with a lead across the TV before TPVR was not routinely captured in the trial databases, and no information was available about pacing- or lead-related TR (22). Implantations of

Melody IDE trial; and served as a proctor and consultant for Medtronic. Dr. Cabalka served as an investigator in the Medtronic-sponsored PAS. Dr. Benson served as an investigator in the Medtronic-sponsored PMSS; and served as a proctor and consultant for Medtronic. Dr. Balzer served as an investigator in the Medtronic-sponsored PAS; and served as a proctor for Medtronic and St. Jude Medical; and served as a consultant for Medtronic. Dr. Cheatham served as an investigator in the Medtronic-sponsored Melody IDE trial; served as a proctor for Medtronic; and served as a consultant for Medtronic, NuMED, and Beijing Med-Zenith Medical Scientific. Dr. Eicken served as an investigator in the Medtronic-sponsored PMSS; and served as a proctor and consultant for Medtronic. Dr. McElhinney served as an investigator in the Medtronic-sponsored Melody IDE trial; and served as a proctor and consultant for Medtronic.

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TABLE 1 Criteria for Echocardiographic Grading of TR Used in the Trial Protocols

TR Grade	Description
None	No systolic color flow visualized on the atrial side of the leaflets
Mild	Regurgitant jet is narrow at its origin
Moderate	Regurgitant jet is wide at its origin, but systolic flow reversal is not seen in the hepatic veins
Severe	Regurgitant jet is wide at its origin, and systolic flow reversal is seen in the hepatic veins

TR = tricuspid regurgitation.

transvenous rhythm devices with RV leads crossing the TV during follow-up were recorded.

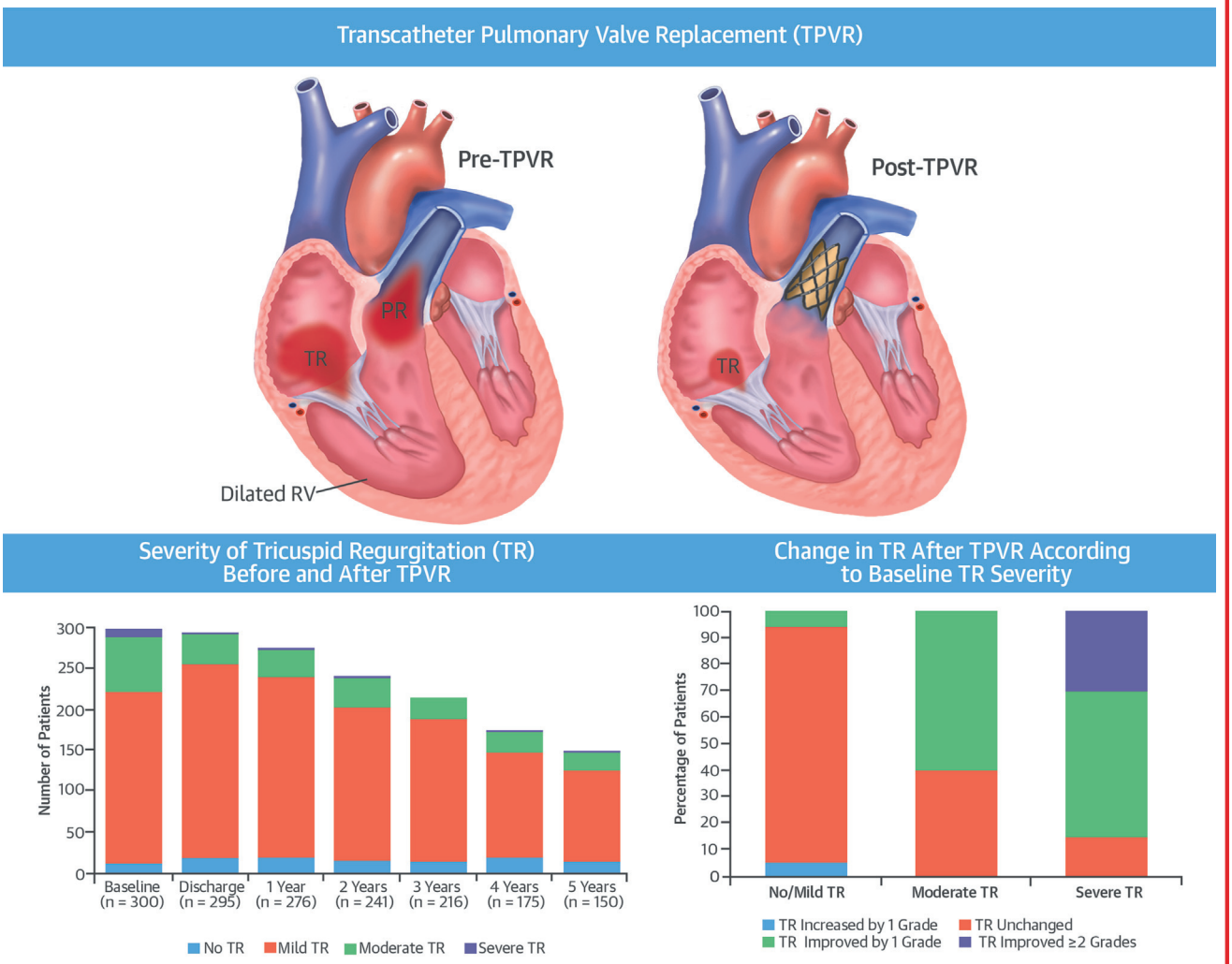
ASSESSMENT OF TR AND RV HEMODYNAMICS. TR (all 3 trials) and TV annulus dimensions (IDE and PMSS trials only) were evaluated by echocardiography and reported in a standardized fashion, as summarized later and in Table 1. For many analyses, moderate TR and severe TR were considered together, and they are referred to here as significant TR. The lateral TV annulus diameter was measured at end-diastole in the apical 4-chamber view as the distance between the inner edges of the attachments of the leaflets at each side of the annulus. The *z*-scores were calculated for the TV annulus diameter on the basis of body surface area. The presence of TR was interrogated with continuous wave and color Doppler imaging from multiple views. TR severity was graded by visual assessment of the width of the regurgitant jet at its origin and by assessment of systolic flow reversal in the hepatic veins. If TR was detected, a continuous wave Doppler recording of the maximal regurgitant velocity from each transducer position was obtained. If significant TR was observed, a pulsed wave Doppler recording was obtained from the hepatic veins to allow assessment of systolic flow reversal. All reported pressures in this study were estimated by Doppler echocardiography: RVOT obstruction was assessed and reported as the mean gradient, and RV systolic pressure was estimated on the basis of the TR jet velocity, assuming a right atrial pressure of 10 mm Hg. PR severity was graded echocardiographically from none to severe, according to previously reported methodology (21). Echocardiograms were read by a designated investigator at each study center. Cardiac magnetic resonance (CMR) imaging was performed as a protocol study only for the IDE trial (i.e., not for the PAS or PMSS trials), and only at baseline and at 6 months, so CMR data were not analyzed for this study.

STATISTICAL ANALYSIS. Data are presented as mean ± SD, median (minimum-maximum), or frequency (%). Between-group differences in categorical predictor variables were assessed using the Fisher exact test and reported with odds ratios and 95% confidence intervals (CIs). Differences in continuous variables were assessed with the Student *t* test or Wilcoxon rank sum test. Comparison of paired data was performed with the paired Student *t* test, Wilcoxon signed rank test, or the McNemar test. Multivariable logistic regression was performed with baseline moderate or severe TR as the dependent variable and forward stepwise selection of independent variables, which were considered for inclusion in the model if they were significant at $p \leq 0.10$ on univariable testing. Associations between baseline TR and time-related outcomes, including freedom from reintervention and TPV explantation, were analyzed using Kaplan-Meier and Cox regression analyses. Freedom from event analysis for this study was focused on the relationship between TR and outcomes, although adjustments for other important baseline variables were also performed if indicated. In analyses of freedom from time-dependent outcomes, TR severity was analyzed both as a pre-implantation measure and as a time-varying variable after TPVR. The counting process method was used to handle the time-dependent variable in PROC PHREG of SAS software (SAS Institute, Cary, North Carolina). With this method, there are multiple records for every patient, with each record corresponding to a time interval during which all covariates are assumed to be constant. If the interval did not end in an event, it was coded as censored. The last-observation-carried-forward imputation method was used when a variable was unable to be assessed at a visit. Hazard ratios were presented with 95% CIs.

RESULTS

TR BEFORE TPVR. A total of 313 patients underwent catheterization and TPVR as part of the IDE, PAS, and PMSS trials. Of these patients, 309 left the hospital with the TPV intact and were included in this study. Of the 309 patients in the study cohort, the TR grade was reported before intervention in 300 patients. At baseline, only 10 patients (3.3%) had no TR, whereas 213 (71.0%) had mild TR, 64 (21.3%) had moderate TR, and 13 (4.3%) had severe TR (Central Illustration). The percentage of patients with significant TR did not differ among trials (20% to 31%; $p = 0.26$). Moderate or severe PR, which was present in 75.3% of the cohort, was more common in patients with significant TR than in those with less TR, although the difference

CENTRAL ILLUSTRATION **Impact of Transcatheter Pulmonary Valve Replacement in Tricuspid Regurgitation**



Jones, T.K. et al. J Am Coll Cardiol. 2016;68(14):1525–35.

(Upper Panel) Significant tricuspid regurgitation (TR) in association with severe pulmonary regurgitation (PR) and dilation of the right ventricle (RV) before transcatheter pulmonary valve replacement (TPVR) **(left)** and reduction of pulmonary regurgitation after placement of a transcatheter pulmonary valve and elimination of the PR **(right)**. **(Lower Panel)** The bar graphs on the **lower left** depict the distribution of TR grades at baseline, discharge, and annual evaluations; and those on the **lower right** depict changes in TR severity from baseline to discharge, according to the TR grade pre-TPVR. They demonstrate a substantial reduction in the severity of TR after TPVR, most notable in patients with pre-implantation severe TR, and persistence of this improvement over time, through 5 years post-implantation.

was not statistically significant (82.7% vs. 72.9%; $p = 0.09$) (Figure 1A). Although there was no difference in the RVOT gradient between patients with significant TR and those with less TR, the pre-implantation RV systolic pressure was higher in patients with moderate or severe TR than in those with no or mild TR (Table 2). The TV annulus z-score was higher in patients with moderate or severe TR than in those with less TR ($p < 0.001$). The severity of TR varied across diagnostic groups (Figure 1B), and it was moderate or severe in anywhere from 14.6% of patients with truncus arteriosus to 61.5% of patients with valvular PS or PAIVS combined. Patients with PS or PAIVS were more likely to have pre-implantation moderate or severe TR than were patients with other diagnoses (odds ratio: 5.1; 95% CI: 1.6 to 16.0; $p = 0.006$). There were no other significant demographic or diagnostic associations with baseline TR severity (Table 2).

ACUTE CHANGES IN TR AFTER TPVR. Among the 76 patients with significant TR before intervention and a discharge echocardiogram, 49 (64.5%) experienced an acute improvement of 1 or more grades (**Central Illustration**), and 42 of these patients (55.3%) had mild or less TR at discharge ($p < 0.001$) (**Table 3**). Of 13 patients with severe pre-implantation TR, all but 2 improved acutely after TPVR (**Central Illustration**). TR improved consistently across all diagnostic categories, except for the cohort of patients with underlying PAIVS or PS (**Table 3**).

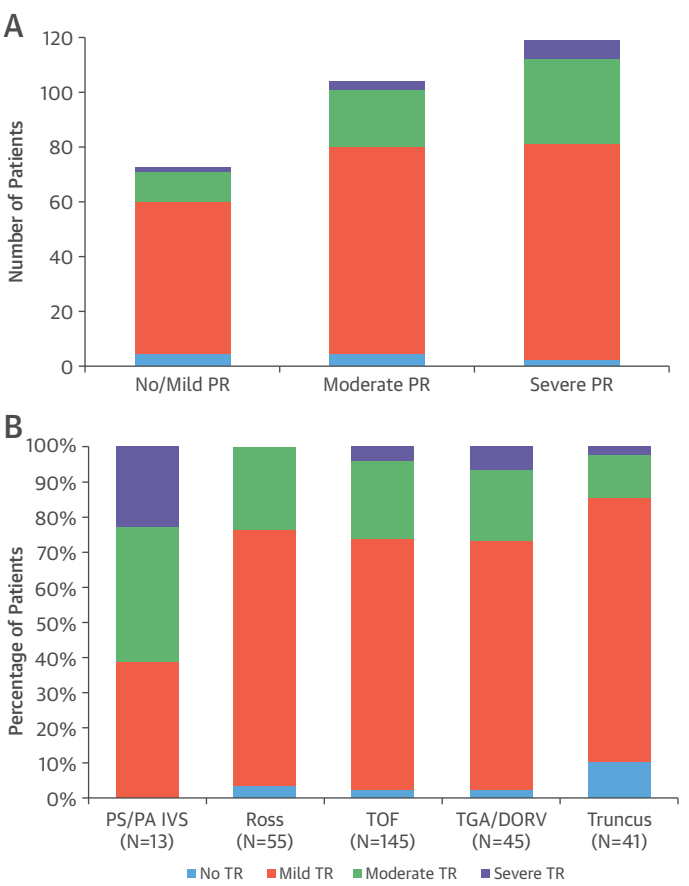
Overall, 21.0% of patients experienced a reduction in TR from pre-implantation to discharge, whereas 3.7% ($n = 11$) of patients had an increase from no or trivial TR to mild TR ($n = 5$) or from mild TR to moderate TR ($n = 6$). Patients with moderate or severe TR pre-intervention were more likely to improve than those without ($p < 0.001$), and patients who improved had a higher pre-implantation RV systolic pressure and a greater reduction in RV pressure than did patients who did not improve (**Table 4**). Improvement in TR did not correspond to the RVOT gradient before or after TPVR or to the magnitude of gradient reduction. Baseline PR was not significantly associated with TR reduction after TPVR. PR was trivial or absent in 95% of patients after TPVR, thus precluding meaningful analysis of the relationship between post-implantation PR and TR.

There was a significant reduction in TV annulus *z*-score from pre-TPVR to discharge, as well as in the percentage of patients with a dilated TV annulus (**Table 4**). Patients who had a reduction in TR severity had larger TV annulus *z*-scores pre-implantation, but there was no difference after TPVR (**Table 4**). Patients with persistent annular dilation at discharge had higher post-implantation RV pressure at 1 year (61.2 ± 16.7 mm Hg vs. 52.5 ± 15.4 mm Hg; $p = 0.003$), but there was no association with the severity of pre-implantation PR. There was a modest decrease in TV annulus *z*-score from pre-TPVR to post-TPVR in patients with moderate or severe TR pre-implantation, from a median of 2.3 (−1.3 to 7.3) to 1.8 (−2.2 to 6.2), but this was not significant ($p = 0.17$). Discharge TV *z*-score remained higher in patients with pre-implantation moderate or severe TR than in those with less TR ($p < 0.001$).

FOLLOW-UP EVALUATION OF TR. At 1 year, 24.2% of patients had a lower grade of TR than pre-TPVR, and significant TR was less common than pre-intervention (13.8% vs. 25.7%; $p < 0.001$) (**Central Illustration**). Among the 69 patients with moderate or severe TR pre-implantation and a 1-year echocardiogram, 41 (59.4%) had less than moderate TR, and 73.9% had improved by 1 or 2 grades from pre-implantation. Of the 13 patients with severe TR before TPVR, 10 had moderate TR and 1 had severe TR at 1 year. Pre-implantation RV systolic pressure was higher in patients whose 1-year TR grade was improved from baseline (78.6 ± 20.6 mm Hg vs. 71.9 ± 17.2 mm Hg; $p = 0.03$), but no other factors were associated with the status of improvement. Among patients with mild or less TR pre-implantation, 10 had moderate TR at 1 year (4.8%), and in 1 patient TR had progressed from moderate pre-implantation to severe at 1 year.

Patients with moderate or severe TR 1 year after device implantation had significantly higher TV

FIGURE 1 Relationships Between Baseline TR and Underlying Diagnosis and Right-Sided Heart Physiology



These bar graphs depict the relationship of baseline tricuspid regurgitation (TR) with **(A)** the severity of pre-implantation pulmonary regurgitation (PR) and **(B)** the underlying cardiac diagnosis. Important TR was present across all grades of PR, but it was more common in patients with severe PR. Similarly, clinically relevant TR was found across all diagnostic subgroups, but it was more pronounced in patients with pulmonary atresia with intact ventricular septum (PAIVS) or congenital pulmonary valve stenosis (PS), followed by patients with tetralogy of Fallot (TOF) or transposition of the great arteries (TGA). DORV = double-outlet right ventricle; truncus = truncus arteriosus.

TABLE 2 Demographic, Historical, and Diagnostic Data in Patients According to the Severity of Baseline TR

	No/Mild TR (N = 223)	Moderate/Severe TR (N = 77)	p Value
Age, yrs	19 (7 to 53)	18 (10 to 59)	0.9
Adult, ≥18 yrs	122 (54.7)	40 (51.9)	0.68
Primary indication for TPVR			0.30
RVOT obstruction	64 (28.7)	16 (20.8)	
Pulmonary regurgitation	105 (47.1)	37 (48.1)	
Mixed obstruction and regurgitation	54 (24.2)	24 (31.2)	
Primary diagnosis	n = 222		0.03
Valvular pulmonary stenosis or PAIVS	5 (2.3)	8 (10.4)	
Ross	42 (18.9)	13 (16.9)	
Tetralogy of Fallot	107 (48.2)	38 (49.4)	
TGA/DORV	33 (14.9)	12 (15.6)	
Truncus	35 (15.8)	6 (7.8)	
Number of previous open heart operations	2 (1 to 6)	2 (1 to 8)	0.05
Total number of surgical RVOT conduits	1 (0 to 5)	2 (1 to 4)	0.03
Age at first surgical conduit, yrs	4 (0 to 45)	3 (0 to 45)	0.80
Implanted duration of current conduit, yrs	9.8 (0.1 to 37.7)	9.5 (0.2 to 24.8)	0.46
Conduit diameter at surgical implantation, mm	21 (11 to 31)	21 (16 to 30)	0.83
Angiographic conduit diameter pre-TPVR, mm	13.1 (4.5 to 23.1)	13.0 (5.0 to 21.8)	0.88
Angiographic: implanted conduit diameter ratio	0.63 (0.2 to 1.0)	0.63 (0.3 to 1.1)	0.84
Baseline mean RVOT gradient, mm Hg*	34.0 ± 13.5	33.2 ± 14.3	0.68
Baseline RV systolic pressure, mm Hg*	70.8 ± 17.8	79.8 ± 19.3	<0.001
Baseline TV annulus *z*-score†	1.30 (−2.5 to 7.8)	2.30 (−1.3 to 7.3)	<0.001

Values are median (minimum to maximum), frequency (% of total), mean ± SD. *Doppler echocardiographic estimates. †Data collected only for the IDE and PMSS study cohorts.

DORV = double-outlet right ventricle; IDE = Investigational Device Exemption; PAIVS = pulmonary atresia with intact ventricular septum; PMSS = Post-Market Surveillance Study; RV = right ventricular; RVOT = right ventricular outflow tract; TGA = transposition of the great arteries; TPVR = transcatheter pulmonary valve replacement; TR = tricuspid regurgitation; truncus = truncus arteriosus; TV = tricuspid valve.

annulus *z*-scores before implantation, at discharge, and at 1 year than did patients with less TR (all $p < 0.01$). Similarly, TV *z*-scores at 1 year were higher in patients with significant pre-implantation TR than in patients with less TR ($p = 0.001$). There was further reduction in the TV annulus *z*-score from discharge to 1 year, to a median of 0.75 (−3.2 to 8.0; $p < 0.001$), as well as a decrease in the percentage of patients with annular dilation (from 26.7% to 18.1%; $p = 0.001$). The RV pressure was higher at 1 year in patients with persistent moderate or severe TR (63.4 ± 25.1 mm Hg vs. 50.5 ± 15.2 mm Hg; $p = 0.001$) and in patients with continued TV annular dilation (61.2 ± 16.7 mm Hg vs. 52.5 ± 15.4 mm Hg; $p = 0.003$) than in patients with less severe TR or a smaller TV annulus *z*-score.

Two- and 3-year annual follow-up echocardiograms were available in 241 and 216 patients, respectively. At both points, the frequency of moderate or severe TR was similar to earlier follow-up intervals (14.9% and 12.5%, respectively) (**Central Illustration**). At 2 and 3 years, almost two-thirds (61.7% and 65.3%, respectively) of patients with significant pre-implantation TR who underwent follow-up echocardiograms had mild or less TR, including 10 of the 13 patients with severe TR at baseline, and 75% and 81.6% of patients had improved by at least 1 grade. Regardless of the severity of TR after TPVR, patients with moderate or severe pre-implantation TR continued to have higher Doppler-estimated RV systolic pressure at all annual follow-up visits than did patients with mild or less TR (difference in median pressure ranged from 7.2 to 11.3 mm Hg; all $p < 0.05$), despite similar RVOT gradients. Among 175 patients with 4-year follow up, 15% had moderate (n = 26) or severe (n = 1) TR, 7 of whom had progressed from less than moderate at 3 years. Similarly, at 5 years, among 150 patients whose TR data were available, 16% had moderate TR (n = 21) or severe (n = 3) TR, and in 8 of these patients TR had progressed from less than moderate at 4 years. TR over time for the 188 patients who had echocardiographic data at every time point is depicted in Online Figure 1.

TPV FUNCTION. There were no significant changes in TPV function from early post-TPVR throughout follow-up. Specifically, no more than 1% to 2% of patients had significant PR at any post-implantation evaluation point, and median RVOT gradient (mean Doppler) ranged from 15 to 17 mm Hg from discharge through 3 years, compared with 35.2 mm Hg before TPVR.

REINTERVENTIONS AND OTHER EVENTS RELATED TO TR. There were no reported injuries to the TV during the TPVR catheterization procedure. During follow-up, there was 1 adverse event related to TR. A patient with a Ross procedure and moderate TR before TPVR developed recurrent RVOT obstruction that was treated with a second TPV 6 months after the initial implantation. The TR had progressed to severe in conjunction with the recurrent obstruction, and the patient underwent TPV explantation and TV repair 4.4 years after the initial implantation as a result of severe TR and symptoms of right-sided heart failure. A patient with severe recurrent RVOT obstruction and acute RV dysfunction in the setting of endocarditis underwent TPV explantation and concomitant TV annuloplasty for moderate TR. Four patients had a new dual-chamber transvenous pacemaker/defibrillator implanted 0.8 to 3.4 years after TPVR; these patients all had mild TR that did change in severity after device implantation.

Moderate or severe TR before TPVR was associated with shorter freedom from RVOT reintervention after implantation and from TPV explantation on Cox regression analysis, even when adjusted for discharge

RVOT gradient (Figures 2A and 2B). There was no association between significant TR at discharge and reintervention. However, when post-implantation TR grade was analyzed as a time-varying covariate, there was a significantly higher risk of explantation among patients with significant TR (hazard ratio: 4.5; 95% CI: 2.3 to 8.8; $p < 0.001$), although there was no difference in freedom from any RVOT reintervention (catheter or surgical). On multivariable analysis of freedom from explantation that included both pre-implantation TR severity and time-varying post-implantation TR grade, only the latter was significant (hazard ratio: 3.9; 95% CI: 1.8 to 8.7; $p < 0.001$). Among the 33 patients who underwent TPV explantation 0.4 to 7.3 years after TPVR, pre-implantation TR was severe in 3 and moderate in 11, but, at discharge, TR was moderate in 8 and less in the remainder. Other than the cases mentioned earlier, there were no apparent differences in the indications for reintervention in patients with and without significant TR.

TABLE 3 Pre-Implant Data in Patients With Significant Baseline TR According to Whether the TR Remained Significant or Improved to Mild or Less After TPVR

	TR Improved to Mild or Less After TPVR (N = 42)	TR Remained Significant After TPVR (N = 34)	p Value
Age, yrs	18 (10 to 59)	19 (11 to 43)	>0.99
Adult, age ≥18 yrs	21 (50.0)	18 (52.9)	0.82
Primary indication			0.91
RVOT obstruction	8 (19)	8 (23.5)	
Pulmonary regurgitation	20 (47.6)	16 (47.1)	
Mixed obstruction and regurgitation	14 (33.3)	10 (29.4)	
Primary diagnosis			0.02
Valvular pulmonary stenosis or PAIVS	1 (2.4)	7 (20.6)	
Ross	11 (26.2)	2 (5.9)	
Tetralogy of Fallot	19 (45.2)	18 (52.9)	
TGA/DORV	7 (16.7)	5 (14.7)	
Truncus	4 (9.5)	2 (5.9)	
Number of previous open heart operations	2 (1 to 8)	3 (1 to 5)	0.07
Total number of surgical RVOT conduits	2 (1 to 3)	1.5 (1 to 4)	0.48
Age at first surgical conduit, yrs	3 (0 to 45)	4 (0 to 40)	0.65
Implanted duration of current conduit, yrs	9.1 (1.4 to 24.8)	11.9 (0.2 to 20.3)	0.34
Conduit diameter at surgical implantation, mm	21 (16 to 30)	20 (17 to 30)	0.98
Angiographic conduit diameter pre-TPVR, mm	12.9 (5 to 21.8)	13.1 (8 to 18.9)	0.63
Angiographic: implanted conduit diameter ratio	0.6 (0.3 to 1.1)	0.6 (0.3 to 1.0)	0.71
Baseline mean RVOT gradient, mm Hg*	33.7 ± 15.8	33.0 ± 12.4	0.83
Baseline RV systolic pressure, mm Hg*	80.0 ± 19.4	79.6 ± 19.5	0.88
Baseline TV annulus *z*-score†	2.5 (−1.3 to 7.3)	2.3 (0.2 to 5.9)	0.60
Moderate or severe PR‡	34 (82.9)	27 (81.8)	>0.99

Values are median (minimum to maximum), frequency (% of total), or mean ± SD. *Doppler echocardiographic estimates. †Data collected only for the IDE and PMSS study cohorts. ‡Data available for 41 patients whose TR improved and 33 in whom TR remained significant.

Abbreviations as in Table 2.

DISCUSSION

PREVALENCE AND OUTCOMES OF TR IN PATIENTS UNDERGOING TPVR. In this cohort of postoperative patients with RVOT obstruction and/or PR, TR was common across all diagnostic subgroups, including TOF, other conotruncal anomalies, valvular PS, PAIVS, and left-sided heart disease after a Ross procedure. Significant TR was present in one-fourth of patients, and it was more common in patients with an underlying diagnosis of PS or PAIVS, although few patients had these anomalies. TPVR was associated with a decrease in the severity of TR overall, particularly in patients with moderate or severe TR at baseline; TR in 55% of these patients improved to mild or less and remained at a lower grade throughout follow-up. For the most part, the reduction in TR after TPVR was modest, by 1 or 2 grades, and TR was rarely eliminated altogether. Progression of TR during post-TPVR follow-up was uncommon. Complementing these observations, a small, short-term study of patients with PR who underwent TPVR with the SAPIEN valve (Edwards Lifesciences, Irvine, California) reported a reduction in the TR jet area after valve implantation (16). Taken together, these findings suggest that TPVR may lead to acute and lasting improvement in patients with significant baseline TR, but further evaluation will be necessary to determine factors associated with improvement in TR and persistence of this benefit.

We did not assess the mechanisms of TR in this study, so it was not possible to determine why TR improved or to identify morphological factors associated with the likelihood of improvement. Given the heterogeneity of the study cohort, there were likely multiple underlying factors contributing to TR, including TV structural abnormalities, chronic RV volume overload, chronic RV hypertension, and possibly others. Studies have shown that TPVR reduces RV volume and pressure, although the ejection fraction is often unchanged (14,15). In this series, significant TR was more common in patients with severe PR and was associated with larger TV annulus diameter *z*-scores. These findings support the hypothesis that TR was related, in part, to RV and TV annulus dilation resulting from PR, a mechanism that has been substantiated in patients with TOF and severe PR (1). Although TR severity and TV annulus size were both reduced after TPVR, there was no relationship between baseline PR severity and improvement in these parameters. Therefore, we cannot conclude that improvement in TR was related solely to reduction of RV volume. The correlation between RV pressure and baseline TR grade in this series is consistent with findings in patients with pulmonary

TABLE 4 Changes in TV and Right-Sided Heart Measures After TPVR in the Study Cohort (N = 300)

	Pre-TPVR	Early Post-TPVR	p Value
Moderate or severe TR (n = 295)	76 (25.8)	40 (13.6)	<0.001
RVOT gradient, mm Hg	33.7 ± 13.6	17.7 ± 7.6	<0.001
RV systolic pressure, mm Hg	74.1 ± 18.7	55.9 ± 16.4	<0.001
Baseline TV annulus *z*-score*	1.5 (−2.5 to 7.8)	1.3 (−2.6 to 6.2)	0.003
Baseline TV annulus dilated (*z*-score >2)*	63 (37.1)	46 (27.1)	<0.001
	TR Improved After TPVR (N = 62)	**TR Did Not Improve After TPVR (N = 233)**	**p Value**
Age, yrs	21.7 ± 10.4	20.8 ± 9.4	0.71
Baseline moderate or severe TR	49 (79.0)	27 (11.6)	<0.001
Baseline RVOT gradient, mm Hg	33.5 ± 14.0	33.8 ± 13.8	0.88
Baseline RV systolic pressure, mm Hg	79.7 ± 19.7	71.6 ± 18.2	0.008
Baseline TV annulus *z*-score*	2.2 ± 1.9	1.4 ± 1.6	0.02
Baseline TV annulus dilated (*z*-score >2)*	21 (60.0)	49 (30.4)	0.002
Post-TPVR moderate or severe TR	7 (11.3)	33 (14.2)	0.68
Post-TPVR RVOT gradient, mm Hg	16.7 ± 7.8	17.9 ± 7.6	0.23
Post-TVPR RV systolic pressure, mm Hg	56.9 ± 18.2	54.9 ± 16.5	0.50
RV pressure reduction from pre- to post-TPVR, mm Hg	−23.4 ± 23.1	−16.6 ± 16.5	0.046
Post-TPVR TV annulus *z*-score*	1.5 (-2.2 to 6.2)	1.1 (-2.8 to 5.8)	0.12
Post-TPVR TV annulus dilated (*z*-score >2)*	12 (34.3%)	35 (25.0%)	0.29

Values are n (%), mean ± SD, or median (minimum to maximum). *TV annulus *z*-score was collected only for the IDE and PMSS study cohorts, and it was available pre-implantation in 196 patients and post-implantation in 170. Comparison of pre- and post-TPVR included only patients with both measurements.

Abbreviations as in Table 2.

hypertension or valvular PS, and it suggests a causal relationship between RV hypertension and TR (7,10,23). There was also an association between improvement in TR after TPVR and post-implantation RV pressure reduction that reinforces observations in patients treated for valvular PS or chronic thromboembolic pulmonary hypertension who often had improvement in TR after relief of RV hypertension (7,23). Little is known about the frequency or mechanism of TR in patients with anomalies represented in this cohort, such as transposition of the great arteries, truncus arteriosus, and left-sided heart disease treated with a Ross procedure, although a study reported that 10% of reoperations after a Ross procedure during childhood included a component of TV repair (24). This finding suggests that the 24% prevalence of significant TR in patients who underwent Ross procedures in this series was not exceptional.

Patients with moderate or severe baseline TR in the current study had shorter freedom from RVOT reintervention and TPV explantation than did patients with mild or less TR, and post-TPVR TR grade treated as a time-varying covariate was associated with a higher risk of explantation, but not reintervention overall. The reasons for and the significance of these associations were not clear. Along with the observation that RV pressure remained higher in patients with significant TR after valve implantation, despite no difference in RVOT gradient, these findings suggest complex pathophysiology that was not elucidated in this study. Alternatively, the shorter freedom from reintervention and explantation may be a function of selection or treatment bias because the existence of important TR is an additional factor that may influence subsequent treatment decisions, independent of RVOT hemodynamics.

CONSIDERATION OF TRANSCATHETER AND SURGICAL PVR IN PATIENTS WITH TR. Although surgical PVR provides an opportunity to repair the TV that TPVR does not, it is unclear whether tricuspid valvuloplasty in such circumstances is necessary or particularly beneficial. Kogon et al. (25) evaluated changes in TR after PVR operations with or without concomitant TV repair and found that the severity of TR was reduced to a similar degree in both cohorts, a finding that suggests both that RV volume reduction by PVR has a beneficial effect on TR and that TV repair is not effective at improving TV function beyond what is achieved with RV volume reduction alone. In a follow-up study, the same group observed not only that acute reduction in TR was similar in patients who did and did not undergo annuloplasty at the time of PVR, but also that TV function was actually worse in the annuloplasty cohort over longer-term follow-up (26). Other studies reported a reduction in TR among patients who underwent PVR and a slight increase in TR over time in those who did not, thereby suggesting that PVR can have a beneficial effect on TR in some patients (27,28). However, those reports did not specify whether TV repair was performed concomitantly with PVR, and it is therefore unclear whether the improvements in TR were related to reverse RV remodeling or to surgical modifications of the TV proper. On the basis of this limited information, it seems that surgical PVR, with or without TV repair, can yield improvement in some patients with significant TR. The durability of such improvements, however, has not been well established (1,29).

In another series of patients with TOF and other anomalies, TV repair was acutely successful in reducing TR, but there were some recurrences in limited follow-up (30). Thus, even though significant TR is recommended as an adjunct indication for PVR in patients with repaired TOF and PR, it is unclear how much benefit patients derive specifically from surgical treatment with regard to the TR. Similarly, there are limited data on valve- or surgery-related adverse events in patients undergoing TV repair at

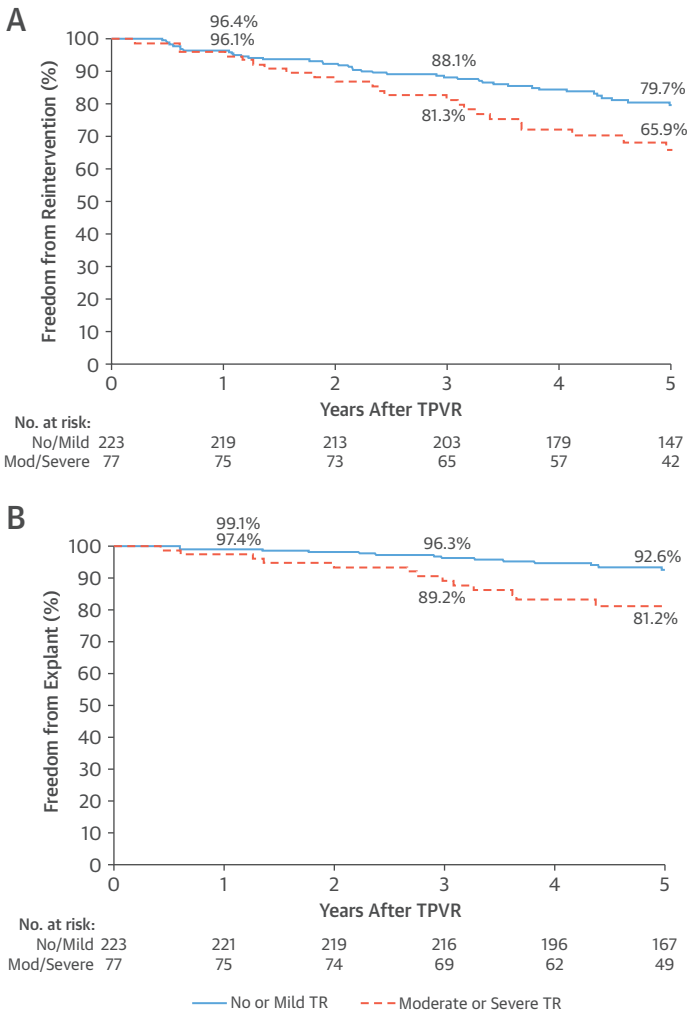
the time of PVR, and these events may be important considerations. For instance, in a large study, TV repair in patients with congenital diseases other than Ebstein anomaly was associated with a 2.5% operative mortality rate (9). This is an even greater consideration in patients whose alternative may be TV replacement, which has a higher surgical mortality rate than repair (1,31).

Although this study does not provide a conclusive answer to the question whether patients with RVOT conduit dysfunction and significant TR should undergo TPVR or surgical PVR, it does show that more than 60% of patients with moderate or severe TR at baseline had mild or less TR at discharge and up to 3 years post-TPVR. Assessment of the relative benefits of TPVR and surgical PVR in patients with significant TR is limited by the paucity of information about the efficacy or durability of TR improvement with surgical treatment. Also, the patients in the current cohort differ from the published surgical populations, which consist primarily of patients with TOF and a transannular patch. Regardless of limitations in the data, this decision must be individualized on the basis of a combination of factors, and, ultimately, the best long-term option is uncertain. If a patient has clear symptoms and sequelae of TR, such as atrial arrhythmias, then surgical intervention may be indicated because it is currently the only method of repairing the TV. However, even in such circumstances, if a patient is sufficiently ill that the operative risk is high or TV replacement would be required, TPVR may be a good temporizing option. Namely, decreasing the RV volume and/or pressure load may yield sufficient improvement in TR that no further intervention is necessary, or, even if it does not preclude surgical treatment altogether, that the patient's operative risk is reduced.

As increasing numbers of patients with repaired TOF and related conditions reach older adulthood, the prevalence and importance of TR will likely rise. Functional TR has also been reported as an emerging issue in other forms of adult congenital heart disease (32). Percutaneous methods to treat TR are in development and will conceivably allow combined TPVR and transcatheter TV repair or replacement in some circumstances (33–35), although at present the only clinically accepted approach for TV repair in this population remains surgical.

STUDY LIMITATIONS. In this study, which analyzed combined data from 3 prospective trials with nearly identical study protocols, TR was graded echocardiographically using qualitative parameters. Although not ideal, qualitative assessment is the norm for studies of

FIGURE 2 Kaplan-Meier Curves Depicting Freedom From Reintervention on the TPV



These Kaplan-Meier curves depict freedom from **(A)** any right ventricular outflow tract (RVOT) reintervention (n = 69; explantations and transcatheter reinterventions including angioplasty or repeat transcatheter pulmonary valve replacement [TPVR]) and **(B)** transcatheter pulmonary valve (TPV) explantation (n = 33) after TPVR, according to the severity of baseline tricuspid regurgitation (TR). Patients with moderate or severe (Mod/Severe) tricuspid regurgitation are represented by the **dashed lines,** and those with none or mild are represented by the **solid lines**. Most reinterventions were for recurrent RVOT obstruction, commonly associated with valve stent fracture or, less often, endocarditis. For freedom from RVOT reintervention, the unadjusted hazard ratio for moderate or severe TR was 1.7 (95% confidence interval [CI]: 1.0 to 2.7; p = 0.04); the adjusted hazard ratio, including mean RVOT gradient on the discharge echocardiogram and angiographic RVOT dimension, was 1.7 (95% CI: 1.0 to 2.9; p = 0.04). For freedom from transcatheter pulmonary valve explantation, the unadjusted hazard ratio for pre-implantation moderate or severe TR was 2.3 (95% CI: 1.1 to 4.5; p = 0.02); the adjusted hazard ratio, including mean RVOT gradient on the discharge echocardiogram and angiographic RVOT dimension, was 2.1 (95% CI: 1.0 to 4.4; p = 0.05).

patients with congenital heart disease, and TR in these trials was assessed systematically according to a predefined grading scale by designated echocardiographers at each study site. The performance of echocardiographic measurements by each site, rather than a core laboratory, may also have introduced bias, although comparison of site and core data from the IDE trial found high concordance (21). There was potential for regression to the mean in the comparison of pre-TPVR versus post-TPVR TR severity, although we do not believe that this possibility had an impact on the interpretation or clinical relevance of the reported findings. CMR-derived quantitative data on TR fraction, RV volumes, and RV function were not available for this study, and this is important in light of the purported relationship between TR and RV dilation. The TV annulus *z*-score was used as an indicator of annular dilation and as a surrogate for RV volume, although the relationship between TV annulus *z*-score and CMR-derived RV volume is suboptimal (21). In addition, although TR was not an inclusion or exclusion criterion for the trials, it may have been considered in investigators' and referring cardiologists' assessments of patients' suitability for TPVR.

Echocardiograms were not required beyond 1 year in the PAS trial, and although clinically obtained data were submitted for many patients, later echocardiographic data were missing for others. Moreover, this cohort and the findings of this study may not be directly comparable to the population of patients with TOF who have significant PR and TR after transannular patch repair. However, because there is little information on the frequency of TR and its response to surgical PVR in patients with RVOT conduits, an apt comparison cohort is not available.

CONCLUSIONS

In patients with RVOT conduit dysfunction and significant TR, TPVR frequently results in improved TV function. Although the mechanisms of this finding cannot be determined from this study, and not all patients improved, these observations support the use of TPV therapy in patients with significant TR. If severe TR is thought to be the primary clinical problem in a patient with significant conduit dysfunction, TPVR may yield some improvement, but there is no evidence to support the relative value of TPVR in this unusual circumstance. To determine which patients with important TR will be better served by surgical or transcatheter treatment, more rigorous quantitative data on TR and additional information about TV functional changes after both surgical PVR and TPVR will be essential.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with repaired congenital heart disease and an RVOT conduit, normalization of RV loading after TPVR can reduce the severity of TR.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Substantial TR is not a contraindication to TPVR and is likely to improve after the procedure.

TRANSLATIONAL OUTLOOK: Further studies are needed to elucidate the mechanisms by which TPVR reduces the severity of TR and to define long-term outcomes of TPVR in this patient population.

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KEY WORDS catheterization, cohort studies, congenital, heart defects, percutaneous valve, prospective studies, tetralogy of Fallot

APPENDIX For the investigative sites of the 3 studies and a supplemental figure, please see the online version of this article.