Background—The advent of the Melody Transcatheter Pulmonary Valve (TPV) has had an indelible impact on the field of congenital cardiovascular interventions. However, the magnitude of this impact has been tempered by limitations inherent to this new technology, including delivery system and valve size, the durability of the stent supporting the valve, and the suitability of current TPVs to complex ventricular outflow tracts.¹ In addition, the Melody TPV is approved exclusively for use in dysfunctional, circumferential, surgically placed right ventricle-to-pulmonary artery conduits that were equal to or greater than 16 mm when originally implanted, an indication present in only a small proportion of the patients who would clinically benefit from restoration of RVOT function. However, knowledge on the performance of the Melody TPV in this setting is limited.

Methods and Results—The US FDA permits the off-label use of approved medical devices according to physician’s best knowledge and judgment, provided they are well informed about the product, base its use on firm scientific rationale and on sound medical evidence, and maintain records of the product’s use and effects. Under this rubric, Melody TPVs have been placed in a number of off-label clinical situations and anatomic locations.²–⁶ Among these, placement in nonconduit RVOTs likely presents the greatest opportunity to extend this therapy to the largest population and has the potential to significantly modify our approach to postsurgical RVOT dysfunction. Although several investigators have described innovative and potentially useful methods of implanting the Melody valve in unconventional ways in patients with large native RVOTs, these are unlikely to be broadly applicable.²,⁷ Otherwise, there are several small

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WHAT IS KNOWN

- Transcatheter pulmonary valve implantation is a safe and effective alternative to surgical pulmonary valve replacement in select populations.
- The Melody Transcatheter Pulmonary Valve is approved exclusively for use in dysfunctional, circumferential, surgically placed right ventricle-to-pulmonary artery conduits.
- The off-label extension of the Melody Transcatheter Pulmonary Valve to patients with nonconduit outflow tracts has the potential to vastly expand the population of patients eligible to benefit from nonsurgical restoration of right ventricular outflow tract function.

WHAT THE STUDY ADDS

- Melody Transcatheter Pulmonary Valve implantation is feasible in selected patients with outflow tracts comprised solely or predominantly native tissue.
- In early follow-up, valve competency seems preserved, and similar to experience in circumferential outflow tract conduits, the dominant mechanism of valve dysfunction seems to be stent fracture with recurrent obstruction.
- Given the differences in the anatomy and dynamic nature of the RVOT in this patient population, more data will be necessary to understand how best to safely expand Transcatheter Pulmonary Valve therapy to this population.

series of Melody valve implantations into the native RVOT,7–9 and cases have been included in other large series,10 but there is limited information on outcomes in this population.

Methods

This is a retrospective review of the multicenter experience of use and performance of the Melody TPV when placed in native or post-surgical, nonconduit RVOTs. Five centers contributed data. Inclusion criterion was Melody TPV implantation in an operated or unoperated RVOT in which at least a portion of the circumference was composed of native in situ tissue (eg, after transannular patch repair of TOF, balloon valvuloplasty of valvar pulmonary stenosis, etc.). Piventricular or other hybrid approaches and implantations outside of the RVOT were not included. In addition, patients brought to the cardiac catheterization laboratory with the intention of placing a valve in this situation, but in whom no valve was placed were not included. The study was approved by each institution’s Committee on Human Research.

All cardiac catheterizations and interventions were performed as a part of routine clinical care, and no aspect of the implantation procedure was specified by this study. As a result, the implant technique and protocol may have varied from institution to institution. Similarly, type and frequency of follow-up data acquisition were at the discretion of the implanting institution. All study data were collected at the performing institution, anonymized, and transferred for central compilation and analysis.

Analysis of fluoroscopic imaging was performed by the implanting institution and included position and movement of the RVOT in relation to the sternum and measurement of initial and postimplant minimal RVOT diameter. In addition, given that RVOT anatomy can vary substantially in this population and may be highly dynamic, we hypothesized that RVOT geometry might be associated with the risk of stent fracture. In an attempt to explore this possibility, we measured RVOT angulation. RVOT angulation was measured on lateral projection as the degree of RVOT deviation from a straight line in the area of Melody implantation (Figure 1) and did not include consideration of right or leftward angulation. Analysis of stent fracture or embolization was obtained from chest films and fluoroscopy, both being recorded as present or absent, with a subsequent description of degree of stent fracture (eg, single or multiple fractures) and affect Melody valve appearance (eg, compression, etc.). Analysis of echocardiographic imaging was performed by the implanting institution and included RVOT mean and maximum instantaneous gradients (MIG), degree of tricuspid regurgitation (none, mild, moderate, or severe), and degree of Melody valve regurgitation (none, mild, moderate, or severe).

Figure 1. Method of calculation of right ventricular outflow tract (RVOT) angulation. The angle of the RVOT was calculated prior to (A) and after (B) Melody valve implantation. Although a greater degree of angulation may have existed between the RVOT and main pulmonary artery (a, inset), only the RVOT in the area of intervention was considered in the calculation.
Statistical Analysis
Descriptive statistics are presented as means±SD or median (range) as appropriate to their characteristics and distributions. Comparison of means and proportions between populations was performed by unpaired t test or Wilcoxon signed-rank test based on distribution and by Fisher exact tests, respectively. Because complete longitudinal follow-up imaging was not available for appropriate time-dependent analysis of factors related to stent fracture, simple logistic regression was used with the addition of follow-up time to the model. Analysis of All predictor (change in minimal RVOT diameter, change in RVOT angulation, substernal location, and prestenting) and outcome (stent fracture, Doppler-derived estimated RVOT gradient at last echocardiogram) variables were prespecified. Echocardiogram-derived RVOT gradients were classified as mild (MIG<35 mm Hg or mean<20 mm Hg), moderate (MIG, 35–50 mm Hg or mean, 20–35 mm Hg), or severe (MIG>50 mm Hg or mean>35 mm Hg). Because higher and particularly early postimplant catheterization and Doppler RVOT gradients are predictive of subsequent Melody valve fracture and dysfunction,11 we chose a relatively low threshold for Melody valve dysfunction as greater than mild obstruction (MIG<35 mm Hg or mean<20 mm Hg) or insufficiency, which differs from the initial investigational device exemption studies.11–13 This threshold was chosen as a point of concern and was not chosen to reflect a threshold for reintervention. More granular data on degree of RVOT obstruction and reintervention are reported separately.

Results
Baseline and Procedural Characteristics
Melody TPVs were placed in native or postsurgical, nonconduit RVOTs in 31 patients. The median age at implantation was 24 years (range, 7–66), and the median weight was 62 kg (range, 23–157). Approximately half of the patients were male. Indications for RVOT intervention included primarily valvular insufficiency in 14 (45%), obstruction in 3 (10%), and mixed obstruction and insufficiency in 14 (45%). The underlying diagnosis was some form of pulmonary stenosis with ventricular septal defect (eg, tetralogy of Fallot, double-outlet right ventricle) in 24 patients (77%), with 3 patients having a history of isolated pulmonary valve stenosis, 2 with carcinoid-related pulmonary valve dysfunction, and one each having transposition with pulmonary stenosis and pulmonary atresia with intact ventricular septum (Figure 2).

Procedural and valve implantation characteristics are presented in Table 1. Twenty-nine of 31 procedures were performed under general anesthesia. Ectal fixation of the RVOT was noted in 2 patients. Preimplantation balloon sizing was performed in the majority of patients. Prestenting, or placement of a bare metal stent in the area of subsequent Melody valve implantation, was performed in 22 of 31 (71%) cases, with a single stent in 21 patients and 2 stents in one. All patients had prestenting and Melody implantation within the RVOT, without unconventional measures to ensure RVOT stent stability (eg, deliberate branch pulmonary artery jailing with extension into the RVOT, implantation of Melody valves into the branch pulmonary arteries, etc.).2,7 The majority of valves were deployed on a 22-mm delivery system. Postdilation of the implanted Melody valve was performed in 5 (16%) patients with balloons ranging from 22 to 24 mm. Additional interventions were performed in 10 (32%) patients.

Immediate Outcomes
Melody valve implantation was successful in all patients with no procedural mortality. After intervention, the median minimal luminal RVOT diameter was increased from 14 to 20 mm, and in those with obstruction there was a significant reduction in right ventricular hypertension, with no patient having greater than a 20 mm Hg peak systolic pressure drop across the area of intervention (Table 2).

Figure 2. Anteroposterior (A, C) and lateral (B, D) angiograms in the right ventricle prior to (A, B) and in the main pulmonary artery after implantation (C, D) of a Melody Transcatheter Pulmonary Valve (TPV) in a nonconduit right ventricular outflow tract (RVOT) of a patient after tetralogy of Fallot repair. After TPV implantation, the RVOT stenosis at the level of the valve has been relieved, and the Melody valve is competent. A single bare metal stent was implanted in the RVOT prior to Melody valve placement.
Table 1. Procedural Characteristics

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Baseline</th>
<th>Post-Melody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balloon sizing prior to TPV implant</td>
<td>30/31</td>
<td>97%</td>
</tr>
<tr>
<td>RVOT presten placed prior to TPV implant</td>
<td>22/31</td>
<td>71%</td>
</tr>
<tr>
<td>Presten type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmaz</td>
<td>19/22</td>
<td>86.5%</td>
</tr>
<tr>
<td>Genesis XD</td>
<td>1/22</td>
<td>4.5%</td>
</tr>
<tr>
<td>EV3</td>
<td>1/22</td>
<td>4.5%</td>
</tr>
<tr>
<td>CCPS+Palmaz</td>
<td>1/22</td>
<td>4.5%</td>
</tr>
<tr>
<td>TPV deployment balloon delivery size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 mm</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>20 mm</td>
<td>5</td>
<td>16%</td>
</tr>
<tr>
<td>22 mm</td>
<td>24</td>
<td>77%</td>
</tr>
<tr>
<td>24 mm*</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Postdilation performed</td>
<td>5/31</td>
<td>16%</td>
</tr>
<tr>
<td>Postdilation balloon size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVOT</td>
<td>22–24 mm</td>
<td></td>
</tr>
<tr>
<td>Additional interventions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery intervention</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Atrial septal defect closure</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Coarctation stent placement</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
| CCPS, Covered Cheatham platinum stent; RVOT, right ventricular outflow tract; and TPV, Transcatheter Pulmonary Valve. *Cheatham et al.14

Serious complications were reported in 2 (6%) patients. One patient developed a contained RVOT tear during balloon dilation, without hemotherax or hemopericardium, that was treated with covered stent placement prior to Melody valve implantation. One patient developed an iatrogenic aortopulmonary connection during RVOT/pulmonary artery intervention that was closed during the same catheterization with a septal occlusion device.

Follow-Up

The median duration of follow-up was 15 months (range, 1 month–3.8 years). At last clinical evaluation, all patients were alive. The most recent echocardiogram was performed at a median of 12 months from Melody implant (range, 1–36 months). Excluding patients with explanted valves, no patient had greater than mild TPV insufficiency, and the median MIG across the RVOT was 23 mm Hg (range, 0–70 mm Hg).

Table 3. Eight patients developed moderate or greater TPV obstruction, defined as a Doppler-derived MIG of 35 mm Hg or mean gradient of 20 mm Hg or higher, and all 8 patients with MIGs greater than 40 mm Hg were associated with an identified stent fracture.

Adequate imaging of stent integrity was obtained in only 19 (61%) patients. Follow-up stent fluoroscopy was more common in those with higher Doppler-derived estimates of RVOT obstruction. Patients who underwent fluoroscopic imaging had median MIGs of 30 mm Hg (range, 0–70), whereas those without adequate imaging had median MIGs of 17.5 (range, 9–34). Among the 19 patients with adequate imaging, 6 (32%) had evidence of stent fracture. Stent fracture was observed in 3/6 (50%) of patients who did not have presenting of their RVOT prior to Melody implantation, whereas it was observed in 3/13 (23%) of patients who underwent presenting (OR, 0.34; 95% CI 0.04–2.97; P=0.34). Similarly, the change in RVOT angulation was 9.7° in those with documented stent fracture versus 0° in those without (OR, 1.1; 95% CI 0.95–1.13; P=0.19), whereas in those without adequate imaging of stent integrity it was 1°. There were no documented stent or stent fragment embolizations. Because documentation of stent integrity was incomplete for the cohort, we were unable to more rigorously assess predictors of stent fracture.

During the follow-up period, there were 5 reinterventions in 3 patients. Three patients underwent repeat Melody valve placement because of stent fracture and recurrent obstruction at 5, 14, and 32 months after initial implant. There were 2 Melody valve explantations, both of whom had undergone a second Melody valve implantation. The first patient developed multiple stent fractures and underwent repeat Melody valve implantation =14 months after initial TPV. Although the second valve demonstrated minimal obstruction and no insufficiency, both valves were explanted during a subsequent surgical repair of a complex coarctation of the aorta. One additional patient developed stent fracture and reobstruction 5 months after initial TPV implantation. She was brought back to the cardiac catheterization laboratory where additional bare metal stents were placed, followed by an additional Melody valve. However, she subsequently developed ventricular tachycardia and had all stents explanted several days later. The ventricular tachycardia was thought possibly related to the position of the additional bare metal stents.

Three patients were treated for either endocarditis or blood stream infection, 2 of whom had vegetations identified on the Melody valve. Two of these patients were previously reported.15 All were treated with antibiotics and none required Melody explantation.

Discussion

Potential Utility of TPV Replacement for Native RVOT Dysfunction

The advent of the Melody TPV replacement therapy represents an important advance in congenital cardiovascular interventions. However, there remain substantial limitations to this novel technology. The off-label extension of the Melody TPV

Table 2. Acute Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Post-Melody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal luminal diameter, mm</td>
<td>14.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Peak-to-peak right ventricular outflow tract gradient, mm Hg</td>
<td>22</td>
<td>8.0</td>
</tr>
<tr>
<td>Right ventricular outflow tract angle, degrees</td>
<td>156.5</td>
<td>165</td>
</tr>
</tbody>
</table>
to patients with outflow tracts comprised solely or predominantly native tissue and has the potential to vastly expand the population of patients eligible to benefit from nonsurgical restoration of RVOT function. However, the existing knowledge on the use and performance of the Melody TPV in this setting is limited to short-term observations of technical success. Momenah et al. reported technically successful results of Melody TPV implantation in 4 patients who had undergone RVOT transannular patch surgery, stressing the importance of adequate RVOT assessment and preparation prior to Melody valve implantation. In contrast, Boudjemline et al. reported the technical outcomes of using either sequential RVOT stents to narrow large RVOTs or intentional pulmonary artery jailing as mechanisms of RVOT preparation. Finally, Bosshoff et al. reported technical results of TPV implantation in 10 patients, in whom the majority underwent a separate antecedent procedure for bare metal stent placement prior to TPV implantation. This study presents a more extended evaluation of Melody TPV implantation and follow-up in this setting.

The population presented is characteristic of the broader range of underlying diagnoses that stand to benefit from extended TPV technology. The vast majority were subjects with anatomic variation of pulmonary stenosis with ventricular septal defect, including tetralogy of Fallot and double-outlet right ventricle. The inclusion of 3 patients with isolated pulmonary valve stenosis, at least 2 of whom underwent initial nonsurgical balloon pulmonary valvuloplasty early in life, reminds us that pulmonary regurgitation can be an important adverse consequence of balloon pulmonary valvuloplasty.16

All procedures were technically successful, with stable valve position and no early residual RVOT obstruction. At follow-up, 74% of patients in this cohort had RVOT MIGs of <35 mm Hg and no important pulmonary insufficiency.

### Adverse Events

Serious complications were encountered in 2 patients. The first occurred in a young patient with a relatively small native RVOT in whom a contained tear occurred during initial balloon angioplasty. The successful use of a covered stent to repair the tear highlights the potential utility of large-diameter covered stents in managing RVOT complications associated with TPV implant procedures. The second serious complication was the result of intervention unrelated to Melody TPV implantation. The development of ventricular tachycardia in 1 patient with RVOT stents is of unclear significance. Although the presence of myocardial cells in the area of intervention capable of an arrhythmogenic focus makes a causal relationship plausible, the existing literature on RVOT stent placement is not supportive.17-19 Nevertheless, it seems reasonable that, whenever possible, RVOT stents should be positioned with as little protrusion into areas of contracting muscle as possible, a practice that may also reduce the risk of stent fracture, and vigilance for arrhythmia must be maintained.

Three patients were treated for blood stream infections or presumed endocarditis. There have been several recent reports looking at endocarditis after Melody valve implantation.15,20 Although this series is too small to add substantially to that discussion, and some of the patients who developed endocarditis in this cohort were included in a prior report, it is important to recognize that endocarditis can and does occur after Melody valve placement in patients with a native postoperative RVOT as well as those with homograft or bioprosthetic conduits.

Similar to Melody TPV performance under traditional indications, valve competency in this cohort seems to be relatively well preserved, at least within the time frame encompassed by this study. Consistent with historical observations,11,12 the dominant mechanism of Melody TPV dysfunction seems to be stent fracture and reobstruction. Unfortunately, because the series was relative small and documentation of stent integrity was incomplete, we were unable to assess predictors of Melody valve stent fracture after implant into a native RVOT. However, there was a suggestion of prophylaxis through RVOT preparation with bare metal stent placement prior to Melody TPV implantation, a technique with clear benefit in more traditional Melody implantations.11,21 Nevertheless, in the current population, stent fracture occurred in 3 patients despite prestenting. In 2 of these, there was a residual waist in the Melody stent after implant. Without knowing what proportion of patients without stent fracture had residual waists, the significance of this must remain uncertain. However, given prior evidence suggesting that multiple pre-Melody stent implantations may be more beneficial than a single prestent in preventing important Melody stent fracture,11 native outflow tract preparation with multiple bare metal stents may therefore be appropriate in some patients. Keeping this in mind, appropriate caution should be taken not to overextend the findings of Melody performance from conduits to native outflow tracts. Many of the more important risk factors for stent fracture in conduit patients (eg, substernal location, dynamic compression, etc.) are rarely found in this population, and so the risk factors for stent fracture in this situation are likely different. The native postoperative RVOT in this population can be highly variable anatomically and is frequently subject to significant dynamic variability throughout the cardiac cycle.22 This dynamic background may be one of the important factors contributing to fatigue and fracture of the Melody valve frame. If Melody valve implantation in the native or augmented postoperative RVOT is going to continue, and it likely is, it will be worthwhile trying to understand risk factors for stent fracture and protecting against fracture with prestenting.
Future Directions

TPV therapy has become an important tool in the management of patients with postoperative RVOT dysfunction, but its reach remains relatively limited. The successful extension of TPV therapy has the potential not only to expand the existing candidate population, but also to change fundamentally the management of postsurgical RVOT dysfunction. The deleterious effects of postoperative pulmonary insufficiency on right ventricular mechanics are immediate, and the chronic effects are progressive and at some point, presumably, irreversible. Prior to the availability of TPV technology, decisions about the timing of RVOT reintervention necessarily weighed the benefits of RVOT restoration against the risks and morbidity of surgical pulmonary valve replacement. As a result, in patients not amenable to TPV implantation, current practice might be characterized as favoring pulmonary valve replacement when it is not too late rather than when it is best for the right ventricle. However, as the risks and morbidity of RVOT intervention decrease, as with TPV therapy, the balance of the equation should change. Based on the evolving understanding of RVOT dysfunction and its implications, along with the shifting balance of risk/morbidity and benefit, it may be reasonably argued that earlier intervention on dysfunctional RVOTs is warranted in some if not all patients. One strategy for extending the reach of currently available TPV technology might be to implant bare metal stents in selected patients with a native postoperative RVOT at a relatively young age, before the degree of RVOT enlargement precludes Melody valve placement. This approach could turn a traditional drawback of stent placement in younger children—that the stents do not grow while children do—into a desirable feature, effectively creating an RVOT dilation limiter that could serve at a landing zone for placement of additional stents and a TPV in the future.

Limitations

There are limitations to the results obtained from this observational cohort. Valve performance is not ideally measured in months, but in years, and limited patient numbers and follow-up constrain extended inference from this study. Also, because we did not have complete longitudinal data on all patients, our ability to fully analyze predictors of important time-dependent outcomes such as stent failure was limited. For example, although we measured RVOT angle, we did not assess the dynamic nature of the RVOT, which may be an important factor in the cause of stent fracture. Similarly, the degree of stent recoil was not routinely captured and may provide additional insight. Finally, because patients who were considered for TPV implant but were found not to be anatomically suitable were not ascertained for this study, we do not have sufficient information to draw clear conclusions about which patients are good candidates for extended use of TPVs. Given that native RVOTs tend to remain highly distensible, it seems likely that RVOTs with diameters >22 mm by preprocedural imaging are unlikely to be good candidates although this has not been studied systematically. Although the ability to deliver TPVs on 24-mm balloons with apparent reasonable function in the short term may expand the candidate population further, further characterization is clearly desirable.

Conclusions

Melody TPV implantation is feasible in selected patients with outflow tracts comprised solely or predominantly native tissue and has the potential to expand the population of patients eligible to benefit from nonsurgical restoration of RVOT function. In early follow-up, valve competency seems preserved, and similar to experience in circumferential outflow tract conduits, the dominant mechanism of valve dysfunction seems to be stent fracture with recurrent obstruction. Given the differences in the anatomy and dynamic nature of the RVOT in this patient population, more data will be necessary to understand how best to safely expand TPV therapy to this population.

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We deeply appreciate the work of Joanne Chisolm in data collection.

Disclosures

J.P.C. is a consultant, proctor, and primary investigator for Medtronic. M.J.G. is a consultant for and research support from Medtronic. E.M.Z. and D.B.M. are consultants and proctors for Medtronic. The other authors report no conflicts.

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Use and Performance of the Melody Transcatheter Pulmonary Valve in Native and Postsurgical, Nonconduit Right Ventricular Outflow Tracts

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