

INTERVENTIONAL CARDIOLOGY

Implantation of the Melody Transcatheter Pulmonary Valve in Patients With a Dysfunctional Right Ventricular Outflow Tract Conduit

Early Results From the U.S. Clinical Trial

Evan M. Zahn, MD,* William E. Hellenbrand, MD,† James E. Lock, MD,‡
Doff B. McElhinney, MD‡

Miami, Florida; New York, New York; and Boston, Massachusetts

- Objectives** This study was designed to evaluate the safety, procedural success, and short-term effectiveness of the Melody transcatheter pulmonary valve (Medtronic, Inc., Minneapolis, Minnesota) in patients with dysfunctional right ventricular outflow tract conduits.
- Background** Conduit dysfunction has recently been treated with transcatheter pulmonary valve placement. There have been no prospective, multicenter trials evaluating this technology.
- Methods** Standardized entry criteria, implantation, and follow-up protocols were used. Nonimplanting core laboratories were used to evaluate results.
- Results** Between January 2007 and September 2007, 34 patients underwent catheterization for intended Melody valve implantation at 3 centers. Mean age was 19.4 ± 7.7 years. Initial conduit Doppler mean gradient was 28.8 ± 10.1 mm Hg, and 94% of patients had moderate or severe pulmonary regurgitation (PR). Implantation was successful in 29 of 30 attempts and not attempted in 4 patients. Procedural complications included conduit rupture requiring urgent surgery and device removal ($n = 1$), wide-complex tachycardia ($n = 1$), and distal pulmonary artery guidewire perforation ($n = 1$). Peak systolic conduit gradient fell acutely from 37.2 ± 16.3 mm Hg to 17.3 ± 7.3 mm Hg, and no patient had more than mild PR. There were no deaths or further device explants. At 6-month follow-up, conduit Doppler mean gradient was 22.4 ± 8.1 mm Hg, and PR fraction by magnetic resonance imaging was significantly improved ($3.3 \pm 3.6\%$ vs. $27.6 \pm 13.3\%$, $p < 0.0001$). Stent fracture occurred in 8 of 29 implants; 3 of these were treated with a second Melody valve for recurrent stenosis later in follow-up.
- Conclusions** Implantation of the Melody valve for right ventricular outflow tract conduit dysfunction can be performed by experienced operators at multiple centers, appears safe, and has encouraging acute and short-term outcomes. (J Am Coll Cardiol 2009;54:1722-9) © 2009 by the American College of Cardiology Foundation

Since being described more than 40 years ago, the use of right ventricle (RV)-to-pulmonary artery (PA) conduits has facilitated repair of numerous congenital heart defects. The life span of right ventricular outflow tract (RVOT) conduits is limited, however, and patients may undergo multiple re-interventions over the course of a lifetime to treat conduit dysfunction (1-3). Modes of conduit dysfunction include stenosis and regurgitation, often in combina-

tion. Although surgical conduit replacement can be performed with low mortality, these operations may be associated with significant morbidity and are often palliative, with newly placed conduit valves often displaying evidence of dysfunction within a year (4). Placement of bare-metal stents has been shown to postpone surgery, but is only useful to treat conduit stenosis and frequently worsens pulmonary regurgitation (PR), as the most common area of stenosis typically involves the conduit valve leaflets (5,6). Mounting evidence suggests that PR can have deleterious effects, including progressive RV dilation and dysfunction, diminished exercise tolerance, and an increased risk of arrhythmias and sudden death (7,8). Timely restoration of pulmonary valve function may benefit patients with PR (9,10). In 2000, Bonhoeffer et al. (11) reported the first successful transcatheter pulmo-

From the *Division of Cardiology, Miami Children's Hospital, Miami, Florida; †Division of Cardiology, Morgan Stanley Children's Hospital, New York, New York; and the ‡Department of Cardiology, Children's Hospital Boston, Boston, Massachusetts. Drs. Zahn, Hellenbrand, and McElhinney all act in consultant and/or investigator roles for Medtronic, Inc., the manufacturer of the Melody valve. Dr. Lock receives royalties on products sold by Cook and NMT, unrelated to this article.

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nary valve implantation, and the successor to that valve, the Melody transcatheter pulmonary valve (Medtronic, Inc., Minneapolis, Minnesota), has been available in Europe and Canada for several years. This study describes short-term results of the U.S. Melody feasibility study, the first prospective multicenter trial of this valve with standardized entry criteria, implantation protocol, and follow-up evaluation.

Methods

Study design. This was a prospective, nonrandomized study designed to assess the safety, procedural success, and short-term effectiveness of the Melody valve in patients with dysfunctional RVOT conduits. Patient selection was based on specific inclusion and exclusion criteria (Table 1). Patients were categorized as having a primary implant indication of stenosis, PR, or mixed stenosis and PR. Pre-implantation and follow-up studies were performed at pre-determined intervals (Table 2), and results of cardiac magnetic resonance imaging (cMRI), echocardiography, cardiopulmonary exercise testing (CPET), and computed tomography (CT) pulmonary angiography were interpreted by independent core laboratories. Each case was reviewed and approved by an independent pediatric cardiologist and cardiac surgeon before enrollment.

Outcome measures. Primary outcome measures were defined for safety, procedural success, and short-term effectiveness (Table 3).

Echocardiography. Conduit mean gradients were determined by tracing the border of continuous-wave spectral Doppler recordings and integrating the area under the curve. PR was assessed using color and pulse wave Doppler interrogation in the RVOT proximal to the conduit, main PA, and proximal branch PAs and was categorized as none, trace, mild, moderate, or severe, based on regurgitant jet

width relative to conduit width and the extent of PA diastolic flow reversal (Table 1).

cMRI. Short-axis cine images were obtained using a steady-state free precession technique, covering both ventricles from the apex to the base. Flow measurements were obtained by selecting a plane through the main PA and performing a breath-through, velocity-encoded, phase-contrast acquisition. Ventricular mass and volumes were calculated by manually tracing the epicardial and endocardial contours, without separate exclusion of trabeculae not continuous with the mural surface on each slice.

CPET. CPET was performed using bicycle ergometry with a ramp protocol. Peak oxygen consumption (VO_2) at anaerobic threshold was measured by the V-slope method and cross-checked with the ventilatory equivalent method.

CT pulmonary angiography. CT pulmonary angiography was performed using 16, 32, or 64 detector-row scanners and thin-section images obtained using an intravenous bolus of contrast, with image acquisition timed from opacification of the main PA. Distal PA vasculature was examined for findings of acute or chronic thromboembolism.

Cardiac catheterization protocol. Patients who met entry criteria underwent cardiac catheterization using general endotracheal anesthesia. The peak-to-peak RV-PA gradient was calculated as the difference in systolic pressure between RV body and main PA distal to the conduit. If stenosis was the primary indication and the RV/aorta systolic pressure ratio was ≤ 0.66 , the patient was excluded and implantation not attempted. Angiography was performed in the RV, conduit, and aortic root. If there was suspicion that a coronary artery was at risk for compression from valve implantation, coronary angiography was performed with an angioplasty balloon simultaneously inflated in the conduit. Patients with coronary compression were excluded from implantation. Conduit pre-dilation was performed in all patients using a balloon ≥ 2 mm larger than the narrowest diameter of the conduit and $< 110\%$ the original conduit diameter. If the balloon waist measured between 14 and 20 mm on subsequent low-pressure (≤ 8 atm) balloon sizing, Melody valve implantation was attempted; otherwise, the conduit was considered anatomically unsuitable, and no implantation was attempted. After Melody valve implantation, hemodynamics and PA angiography were repeated. Post-dilation of the valve was permitted at the discretion of the operator. Additional interventional procedures during the same catheterization procedure, including stenting of the conduit with a bare-metal stent, were not permitted. All patients received

Abbreviations and Acronyms

- cMRI** = cardiac magnetic resonance imaging
- CPET** = cardiopulmonary exercise test/testing
- CT** = computed tomography
- NYHA** = New York Heart Association
- PA** = pulmonary artery
- PR** = pulmonary regurgitation
- RV** = right ventricle
- RVOT** = right ventricular outflow tract
- VO_2** = oxygen consumption

Table 1 Inclusion/Exclusion Criteria for Study Entry

Inclusion Criteria	Exclusion Criteria
Age ≥ 5 yrs	Active endocarditis
Weight ≥ 30 kg	Major progressive noncardiac disease
Original conduit diameter ≥ 16 mm	Central vein occlusion or significant obstruction
Echocardiographic RVOT conduit dysfunction	Pregnancy
Patients classified as NYHA functional class II, III, IV: Doppler mean gradient ≥ 35 mm Hg or \geq moderate PR*	Intravenous drug abuse
Patients classified as NYHA I: Doppler mean gradient ≥ 40 mm Hg or severe PR† associated with TV annulus z-score ≥ 2 or RVFS $< 40\%$	Contraindication to MRI
	Unable/unwilling to sign informed consent or comply with follow-up

*Moderate PR = regurgitant color Doppler jet width 20% to 40% of the valve annulus or diastolic flow reversal extending into the distal main pulmonary artery. †Severe PR = regurgitant color Doppler jet width $> 40\%$ of the valve annulus or diastolic flow reversal extending into proximal branch pulmonary arteries.

NYHA = New York Heart Association; MRI = magnetic resonance imaging; PR = pulmonary regurgitation; RVFS = right ventricle fractional shortening; RVOT = right ventricular outflow tract; TV = tricuspid valve.

Evaluation/Visit	Pre-Implantation	Discharge	1 Month	3 Months	6 Months	Annual
Clinical assessment	X	X	X	X	X	X
Echocardiogram	X	X	X	X	X	X
Chest X-ray		X	X	X		X
Fluoroscopy					X	
Urinalysis		X			X	X
ECG	X				X	
cMRI	X				X	
CPET	X				X	X
CTA	X				X	

cMRI = cardiac magnetic resonance imaging; CPET = cardiopulmonary exercise testing; CTA = computed tomography pulmonary angiography; ECG = electrocardiogram.

heparin to maintain an activated clotting time >250 s and antibiotic prophylaxis during and after the procedure.

Chest radiography. Standard posteroanterior and lateral chest radiography was performed before discharge and at all follow-up visits except 6 months. At the 6-month visit, cinefluoroscopy was performed to enhance the ascertainment of stent fracture, using multiple projections to optimize visualization and dynamic imaging to evaluate the possibility of variable strut separation across the cardiac cycle with minor fractures.

Melody valve and Ensemble (Medtronic, Inc.) delivery system. The device and delivery system and their use have been described previously (11,12).

Data Safety Monitoring Board. A Data Safety Monitoring Board consisting of a biostatistician, a cardiothoracic surgeon, and an interventional cardiologist assessed interim safety.

Statistical analysis. The subset evaluated for safety included all patients who underwent catheterization. The subset evaluated for procedural success included only patients in whom implantation was attempted. The subset evaluated for short-term effectiveness included patients in whom a Melody valve was implanted and was not explanted

during the first 24 h. Statistical analyses were performed using SAS (SAS Institute Inc., Cary, North Carolina) version 9.1 software. The Wilcoxon signed-rank test was used to evaluate the change in continuous paired data (before implantation to 6 months). The Hochberg procedure was implemented to account for multiplicity (13,14). Adjusted p values are presented in the text and tables. An adjusted p value <0.05 was considered statistically significant. The study was approved by the Institutional Review Board at each institution, and written informed consent was obtained from each patient or his/her parents before the baseline echocardiogram.

Results

Patients. The study population consisted of 34 patients who underwent catheterization after meeting inclusion criteria. On the basis of echocardiographic entry criteria, the primary indication for study entry was PR in 23 patients, conduit stenosis in 6 patients, and mixed PR and conduit stenosis in 5 patients, although most patients with a primary indication of stenosis had some degree of PR, and patients with a primary indication of PR had some stenosis. Baseline characteristics are provided in Table 4. The majority of patients were symptomatic (82% with New York Heart Association [NYHA] functional class II or III). Nearly all (94%) had had moderate or severe PR, and 35% had moderate or severe tricuspid regurgitation.

Procedural success. Melody valve implantation was attempted in 30 of 34 patients who underwent catheterization. Implantation was not attempted in 4 patients due to risk of coronary compression (n = 2), need for concomitant pulmonary artery stenting (disallowed by protocol) (n = 1), and an RV/aorta pressure ratio <0.66 in a patient with stenosis as the primary indication (n = 1). Average procedure time was 182.0 ± 84.4 min, and average hospitalization was 1.3 ± 1.2 days. Three patients experienced procedural adverse events: conduit rupture treated with emergent surgery (n = 1), wide-complex tachycardia treated with cardioversion (n = 1), and a distal pulmonary artery branch perforation secondary to a guidewire treated with transcatheter vascular occlusion (n = 1). All 3 patients were

Safety
Percentage of patients with procedure- or device-related mortality during 6 months of follow-up
Percentage of patients with procedure- or device-related AEs during 6 months of follow-up
Procedural success
Percentage of patients with successful valve implantation, defined as:
• Valve fixed within desired location
• RV-PA peak gradient measured by catheter <35 mm Hg
• Trivial or less pulmonary regurgitation*
• Freedom from valve explant 24 h after implantation
Short-term effectiveness
Percentage of patients with acceptable valve function at 6 months, defined as:
• Pulmonary regurgitant fraction <20%†
• RVOT Doppler mean gradient ≤30 mm Hg

*Measured by angiography, †Measured by cardiac magnetic resonance imaging.
AE = adverse event; PA = pulmonary artery; RV = right ventricle; RVOT = right ventricular outflow tract.

Table 4 Clinical Characteristics of Study Patients (n = 34)

Variable/Category	
Weight, kg	61.1 ± 15.3
Sex	
Male	26 (77)
Female	8 (23)
Age, yrs	19.4 ± 7.7
Original diagnosis	
Tetralogy of Fallot	18 (52)
Truncus arteriosus	4 (12)
Aortic valve disease (Ross procedure)	4 (12)
Transposition of the great arteries	3 (9)
Other	5 (15)
NYHA functional classification	
I	6 (18)
II	23 (67)
III	5 (15)
IV	0 (0)
RVOT conduit type	
Homograft	27 (79)
Biologic valved conduit	3 (9)
Other*	4 (12)
RVOT conduit size	20.0 ± 2.1
Primary indication for implantation	
Stenosis	6 (18)
Regurgitation	23 (67)
Mixed stenosis and regurgitation	5 (15)
Pre-existing stents in RVOT conduit	
No pre-existing stents in RVOT conduit	19 (56)
Single stent in RVOT conduit	12 (35)
Multiple stents in RVOT conduit	3 (9)
Number of previous open surgeries	2.2 ± 1.0
PR by echocardiography	
None	0 (0)
Trace	0 (0)
Mild	1 (3)
Moderate	12 (35)
Severe	20 (59)
Unable to assess	1 (3)
Average conduit Doppler mean gradient (mm Hg)	28.4 ± 11.4

Data are presented as mean ± SD for continuous data or n (%) of subjects for categorical data.
 *Other conduit types were nonvalved "tube grafts," nonvalved homograft, and bioprosthesis.
 Abbreviations as in Table 1.

discharged within 7 days. Criteria for procedural success were met in 93% (28 of 30) of attempted implantations. In addition to the patient with conduit rupture, the other patient categorized as a procedural failure had a post-implantation RV-PA peak gradient of 37 mm Hg. The

gradient across the Melody valve was only 5 mm Hg, but there was subvalvar muscular obstruction, which resulted in the elevated RV-PA gradient. In subsequent follow-up, this patient's conduit Doppler mean gradient was consistently <25 mm Hg, and no further intervention was performed.

Short-term effectiveness. In terms of the short-term effectiveness criteria defined in Table 3, 29 patients retained the Melody valve at 24 h, and 24 (83%) had acceptable hemodynamics at the 6-month time point. Follow-up data are presented for the 29 patients who retained a Melody valve at 24 h.

ACUTE HEMODYNAMIC RESULTS. After valve implantation, RV systolic pressure, RV-PA gradient, and the RV/aortic pressure ratio were significantly lower, and the PA diastolic pressure was significantly higher than before implantation (Table 5). Pre-discharge echocardiography demonstrated no PR or trivial PR in 86% of patients and mild PR in 14%.

CLINICAL ASSESSMENT. NYHA functional class improved after Melody valve implantation (Fig. 1). Of 24 patients who were NYHA functional class II or III before implantation, 19 (79%) had an improvement of at least 1 class; no patient experienced a decline in NYHA functional class.

ECHOCARDIOGRAPHY. Valve competence was maintained during follow-up, with 93% of patients having no/trivial PR and no patient having more than mild PR 6 months after implantation. Improvement of conduit obstruction was maintained for the group as a whole, with average Doppler mean gradient improving from 28.8 ± 10 mm Hg before implantation to 22.4 ± 8.1 mm Hg at 6 months (p < 0.001). Five patients had Doppler mean gradients >30 mm Hg at 6-month follow-up. One of these patients had a major stent fracture and underwent a successful second Melody valve implantation, 1 had asymmetric expansion of the Melody valve and was treated successfully using high-pressure balloon angioplasty, 1 was discovered at subsequent catheterization to have obstruction below the conduit, 1 had stent fracture but had not undergone repeat catheterization, and in 1 patient there was no obvious explanation. All 5 were in NYHA functional class I at most recent follow-up.

cMRI. Twenty-five patients (83%) had paired cMRI data before and 6 months after implantation (Table 6). Significant reductions in PR fraction and RV end-diastolic volume were seen. The median PR fraction was 3.1% at 6 months

Table 5 Acute Hemodynamic Catheterization Data (n = 29)

Variable	Pre-Implantation	Post-Implantation	p Value
RV systolic pressure, mm Hg	67.7 ± 16.1 (68; 32-108)	48.9 ± 13.7 (46; 26-82)	<0.001
RV/aortic systolic pressure ratio	0.7 ± 0.2 (0.7; 0.3-1.0)	0.4 ± 0.1 (0.4; 0.3-0.75)	<0.001
RV-PA gradient, mm Hg	37.2 ± 16.3 (39; 9-69)	17.3 ± 7.3 (18; 5-37)	<0.001
PA diastolic pressure, mm Hg	11.0 ± 5.2 (10; 1-28)	14.7 ± 5.1 (15; 4-28)	<0.001

Data are presented as mean ± SD (median; minimum-maximum).
 Abbreviations as in Table 3.

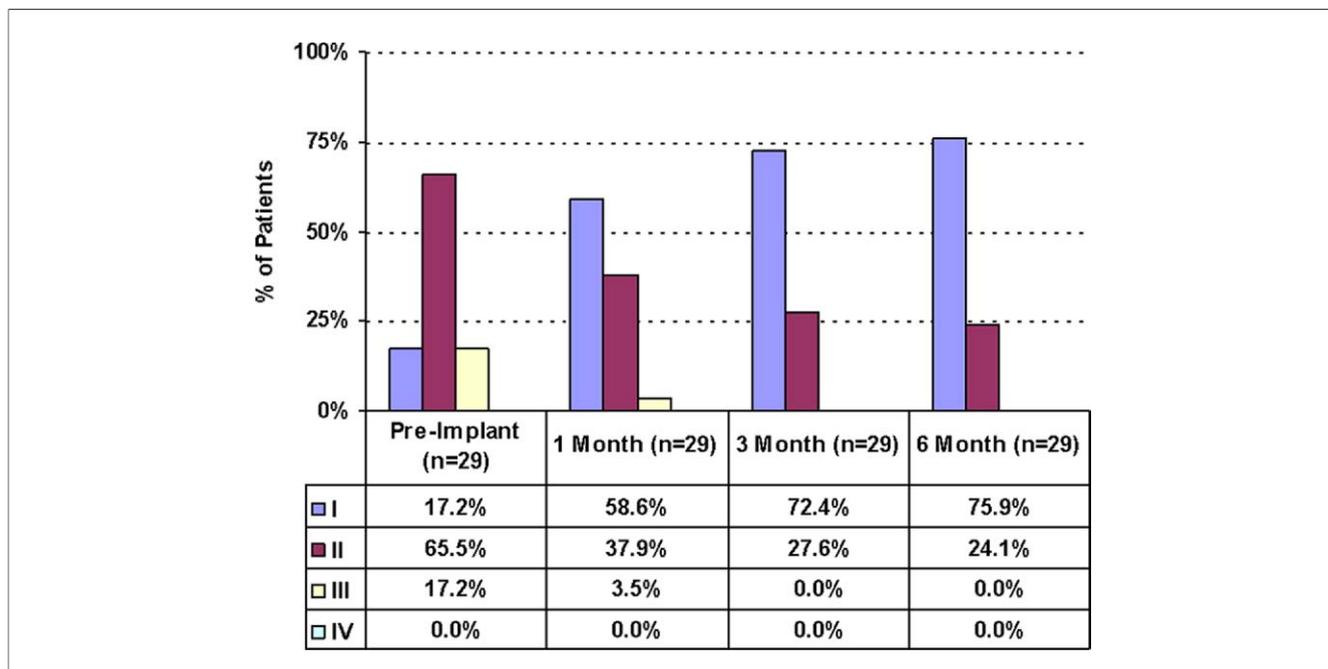


Figure 1 New York Heart Association Functional Classification as a Function of Time for Patients Receiving a Melody Valve (Medtronic, Inc.) (n = 29)

and was no higher than 11.6% in any patient. No significant changes were noted in RV or left ventricular ejection fraction or left ventricular end-diastolic volume.

CPET. Twenty-nine patients had paired CPET data from before and 6 months after implantation. There were no differences between pre-implantation and 6-month follow-up peak VO₂ (21.6 ± 6.8 ml/kg/min vs. 22.7 ± 7.1 ml/kg/min, p = 1.0) or anaerobic threshold (15.0 ± 4.7 ml/kg/min vs. 15.5 ± 5.6 ml/kg/min, p = 1.0).

CT PULMONARY ANGIOGRAPHY. Twenty-nine patients had paired CT pulmonary angiography before and 6 months after implantation, and no new findings of pulmonary emboli were discovered. One patient had findings of chronic pulmonary emboli in the right upper lobe noted on the pre-implantation CT, which remained unchanged at 6-month follow-up.

RADIOGRAPHY/CINEFLUOROSCOPY. Stent fractures were observed in 8 of 29 patients (28%) during follow-up, 1 at 3 months and the others at 6 months. When diagnosed, all 8

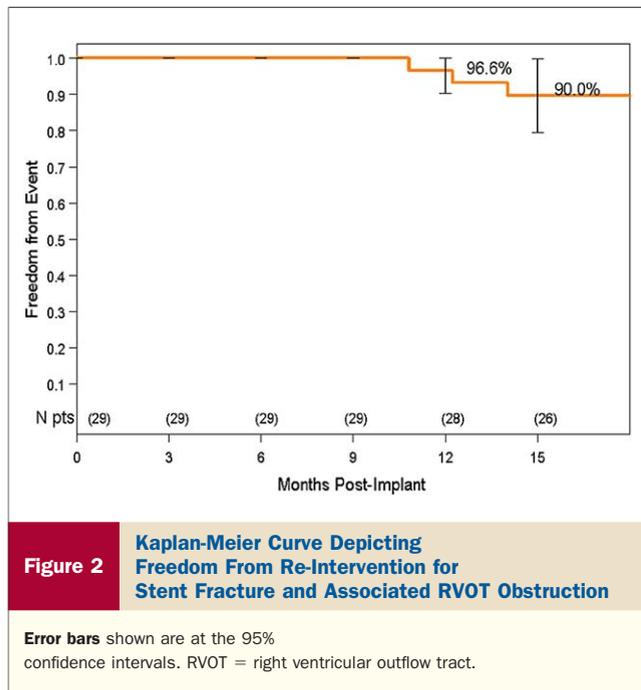
patients were NYHA functional class I, and all but 1 had less than trace PR and a conduit Doppler mean gradient <30 mm Hg. Although most of these fractures were minor (i.e., a single wire break with no loss of stent integrity), 3 patients had a second Melody valve implanted 11, 12, and 14 months after the initial implantation to treat progressive conduit obstruction associated with multiple fracture points, loss of stent integrity, and progression to NYHA functional class II. Implantation of a second Melody valve was uncomplicated and preceded by placement of bare-metal stainless steel stents in all 3 cases. Hemodynamic results after repeat Melody valve implantation were similar to initial implantation. The other 5 patients with minor stent fractures remained stable in NYHA functional class I without evidence of a loss of stent integrity or progressive RVOT obstruction. Freedom from re-intervention for stent fracture associated with recurrent RVOT obstruction was 96.6% at 1 year (Fig. 2).

Safety. Aside from the procedural adverse events, stent fractures, and re-interventions summarized above, no other

Table 6 Cardiac Magnetic Resonance Imaging Results Before and 6 Months After Melody Valve (Medtronic, Inc.) Implantation (n = 25)

Variable	Pre-Implantation	Post-Implantation	p Value
PR fraction, %	27.6 ± 13.3 (29.8; 4.3-61.0)	3.3 ± 3.6 (3.1; 0.0 - 11.6)	<0.001
RV EDV index, ml/m ²	144.7 ± 54.8 (133.5; 72.5-290.8)	117.3 ± 48.3 (109.5; 54.3-256.1)	<0.001
RV ejection fraction, %	40.8 ± 14.6 (39.8; 10.5-72.7)	42.0 ± 12.1 (39.8; 23.8-63.8)	0.86
LV EDV index, ml/m ²	84.5 ± 18.9 (85.7; 43.9-121.4)	90.7 ± 20.4 (90.8; 58.5-132.9)	0.30
LV ejection fraction, %	52.6 ± 10.5 (54.3; 31.3-68.8)	52.4 ± 8.6 (52.1; 33.3-68.5)	1.0

Data are presented as mean ± SD (median; minimum-maximum).
EDV = end-diastolic volume; LV = left ventricle; PR = pulmonary regurgitation; RV = right ventricle.



adverse events were reported. With respect to the safety outcome criteria, 100% of patients were free from procedure- or device-related death, and 91% were free from serious procedure- or device-related events.

Discussion

To date, the only published series of Melody valve implantation have been from the Bonhoeffer group and demonstrate excellent short- and intermediate-term results (11,12). This study confirms that equally good acute and short-term results can be achieved by trained, experienced operators at multiple other centers. Furthermore, it is the first prospective multicenter clinical trial of the Melody valve that uses defined entry criteria, standardized implantation and follow-up protocols, independent core laboratories for assessment of outcomes, and cinefluoroscopy and CT pulmonary angiography to evaluate for stent fracture and pulmonary embolism.

Procedural success and short-term effectiveness. The procedural success rate in this series was high (29 of 30 attempts) and compared favorably with results published by experienced operators (12,15). The current system design makes Melody valve implantation simple and comparable technically to bare-metal stent implantation, a common intervention performed in most congenital catheterization laboratories. There were no device malpositions or embolizations in this series. The current delivery system, designed specifically for this application, protects the stent and preserves the balloon-stent relationship during advancement to the RVOT and may offer some advantages over conventional methods of stent implantation. The average hospital stay of just over 1 day in this study compares

favorably with both surgical conduit replacement and bare-metal stenting.

In the current study, a minimum sizing balloon waist of 14 mm was required to undergo valve implantation. Using this approach, only 1 patient had a post-implantation RV-PA gradient that was considered inadequate by pre-determined criteria. Pre-dilation of the conduit before sizing was a required component of the protocol for conduits with an angiographic diameter <18 mm, but pre-stenting was not allowed in this initial cohort (the protocol has since been modified to allow concomitant procedures, including pre-stenting of the conduit). The rationale for pre-dilation was to optimize conduit diameter before balloon sizing and Melody valve implantation and to assess compliance of the conduit and identify multiple or highly resistant stenoses. As Sugiyama et al. (16) confirmed in their series of bare-metal stenting for conduit obstruction, the smaller the achieved diameter of the conduit relative to the normal pulmonary valve size for the patient, the higher the post-intervention RVOT gradient. This may be more important with an implantable valve, in which the valve and vein segment add bulk to the implant site and may contribute to luminal narrowing and obstruction if the stent is under-expanded.

In the patient with a post-implantation peak RVOT gradient of 37 mm Hg, the obstruction was below the conduit and unrelated to the Melody valve itself. Four other patients developed Doppler mean gradients >30 mm Hg by 6-month follow-up. These outcomes highlight the importance of appropriate patient selection for the Melody valve. As more data become available, it will be important to evaluate patient-related and procedural data associated with early recurrence of conduit obstruction to improve patient selection and execution of the procedure. It will also be important to determine the role of pre-dilation and/or pre-stenting in preventing recurrent RVOT obstruction.

Consistent with prior reports, function of the Melody valve was excellent in short-term follow-up, with no or trivial PR in almost all patients, and none with more than mild regurgitation (11,12,15). RVOT gradients were significantly lower at 6 months than before implantation, and MRI demonstrated favorable RV volume remodeling. A majority of patients improved in NYHA functional class, and none declined, consistent with prior reports (12). Although symptomatic improvement was typically noted 1 month after implantation, some patients continued to improve as late as 6 months after implantation, raising the possibility that cardiac remodeling and conditioning may continue beyond the acute restoration of pulmonary valve competence (21). In the current series, we did not observe significant improvements in maximal VO_2 and anaerobic threshold, although the preponderance of patients with PR as the primary indication for valve placement may be a factor in this finding. Coats et al. (22) reported that patients with PR have minimal improvement in maximal VO_2 and anaerobic threshold after Melody valve implantation, in

contrast to patients who receive a Melody valve primarily for stenosis (22). Further examination of the physiologic mechanisms underlying changes in exercise performance and symptomatic improvement is warranted.

Stent fracture. Stent fracture, well described after both bare-metal stenting of RVOT conduits and Melody valve implantation, was an important finding in this study (19,23). Peng et al. (19) described 221 patients treated for conduit obstruction with bare-metal stenting and found a 43% incidence of stent fracture, with external compression and a substernal conduit location identified as important risk factors. In a series of 123 patients who underwent Melody valve placement, Nordmeyer et al. (23) reported a 75% freedom from Melody stent fracture at 2 years, with implantation in the native RVOT, no calcification along the RVOT, and greater recoil after balloon deflation associated with a higher risk of fracture. It is logical to postulate from these 2 studies that when excessive external loading forces are applied to stents in the RVOT, either from dynamic compression or other cyclic stresses, there is an important risk of stent fracture. The current series includes too few patients to provide robust insight into this issue, but the frequency of stent fracture appears consistent with these earlier reports. Nordmeyer et al. (24) recently reported a series of patients who underwent successful treatment of re-stenosis after Melody stent fracture, with bare-metal stenting followed by implantation of a second Melody valve. The same approach was used in 3 patients in this series, with good acute results. Further attention is needed to better understand the risk factors for, prevention of, and treatment of stent fracture in patients undergoing transcatheter pulmonary valve placement.

Safety. The procedural adverse event rate of 9% in this cohort is acceptable for a new procedure of this magnitude and compares favorably with previously published reports involving catheter or surgical intervention for conduit dysfunction (1-3,16-20). The large profile of the delivery system did not result in any obvious vascular damage or prohibit delivery of the device in any patient, including children as young as 10 years. Importantly, none of the adverse events in this study resulted in death or long-term sequelae. Aside from stent fractures and re-interventions, as discussed above, there were no device- or procedure-related adverse events reported during follow-up.

Protocol. There are challenges to developing a standardized, rigorous protocol for percutaneous pulmonary valve placement in individuals with dysfunctional RVOT conduits and a spectrum of hemodynamic disease that includes variable degrees of PR and obstruction. There are limited data from which to define rigorous, outcome-based indications for valve implantation. Moreover, the indications for implantation and metrics of success will necessarily differ for patients at different points on this disease spectrum, and there is no simple means of capturing the complexities of mixed disease. The inclusion criteria for this protocol were designed to reflect general practice on the basis of the

published literature and the experience of the participating centers and were graduated according to symptomatic status. To address the question of clinical equipoise, 2 independent physicians, 1 congenital cardiac surgeon and 1 pediatric cardiologist, reviewed prospective patients and provided written support for the decision to implant a Melody valve. Nevertheless, individuals varied within the cohort, and our population may have differed in composition from that of previously reported series (12,21). Echocardiographic assessment of hemodynamic entry criteria may be considered a limitation of the study protocol and was chosen for logistical reasons. The catheterization protocol used in this study was successful in identifying 2 patients at risk for coronary compression, a potentially fatal complication. Pre-implantation balloon inflation with simultaneous coronary angiography should be used in any case of conduit stenting or transcatheter valve implantation when coronary artery compression is suspected. Further, the protocol specified cinefluoroscopy at the 6-month follow-up visit to assess for stent fracture. The decision to use cinefluoroscopy was based on its anticipated high sensitivity for detecting even minor stent fractures.

Conclusions

This is the first multicenter prospective trial of an implantable transcatheter pulmonary valve in a population of patients with congenital heart disease and RVOT conduit dysfunction. The implantation success rate was high, the frequency of adverse events was acceptable, and short-term outcomes were encouraging, supporting the conclusion that this technology can be translated effectively to experienced, properly trained interventional cardiologists and is not highly operator dependent. Longer follow-up and a larger patient experience are needed to determine the ultimate role of this therapy in the treatment of conduit dysfunction.

Reprint requests and correspondence: Dr. Doff B. McElhinney, Department of Cardiology, Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115. E-mail: doff.mcelhinney@cardio.chboston.org.

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