A prospective 5-year study of the frequency of arrhythmias during serial exercise testing and clinical follow-up after Melody valve implant

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BACKGROUND Although percutaneous Melody valve implant has become an accepted alternative to surgical pulmonary valve replacement in patients with congenital heart disease, the benefit regarding frequency and severity of arrhythmias remains undefined.

OBJECTIVE The purpose of this study was to evaluate the impact of Melody valve implant on the type and frequency of arrhythmias during cardiopulmonary exercise testing (CPET) and subsequent clinical outcome.

METHODS As part of the phase I Melody valve clinical trial, 136 patients with congenital heart disease underwent prospective serial evaluation including CPET before implant, 6 months after implant, and annually thereafter for 5 years. Arrhythmias were defined as premature ventricular complexes (PVCs) and supraventricular or ventricular tachycardia (VT).

RESULTS Before Melody implant, PVCs occurred in 55 patients (40%) and nonsustained ventricular tachycardia (NSVT) in 1 patient during CPET. Median age at valve implantation was 19.0 years (range 7–53 years). During median follow-up of 4.9 years (range 0.8–7.3 years), there was no significant change in the proportion of patients with PVCs during CPET at any follow-up interval (40%–45%). However, postimplant, NSVT occurred in 18 patients, including 8 during CPET. Diagnoses in the patients with NSVT were tetralogy of Fallot (11), transposition (2), and post-Ross procedure (5). Improved hemodynamic status was not associated with resolution or prevention of arrhythmias.

CONCLUSION Despite improvement in hemodynamics, Melody valve implant was not associated with resolution or prevention of arrhythmias during CPET. PVCs or VT may be related to pathologic hypertrophy, fibrosis, dilation, or possible mechanical effects of the Melody device.

KEYWORDS Congenital heart disease; Valve replacement; Ventricular tachycardia; Tetralogy of Fallot; Exercise testing

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Introduction

Transcatheter pulmonary valve replacement was first reported by Bonhoeffer in 2000 with the prospective, phase I Melody multicenter trial initiated in 2007.[1,2] Although a number of studies subsequently reported improved hemodynamics and exercise functional status, the impact of Melody valve implant on the type and frequency of cardiac arrhythmias and potential reduction in the risk of late sudden death is less certain.[3–5] It has been proposed that pulmonary insufficiency and right ventricular volume or pressure overload may be critical factors in the genesis of ventricular arrhythmias in congenital heart disease (CHD); thus, correction of these hemodynamic abnormalities theoretically should reduce the frequency and risk of arrhythmias.[6,7]

The usefulness of preoperative cardiopulmonary exercise testing (CPET) in predicting the long-term prognosis in adults with CHD is supported by several studies.[8,9] Furthermore, we reported the type and prevalence of arrhythmias during CPET before Melody valve implant in this specific patient cohort in a recent publication.[10] However, prospective data regarding the long-term outcome after surgical or catheter intervention on the prevalence and types of arrhythmias during serial CPET in patients with CHD are not available. Therefore, the purpose of this study was to assess the cardiac rhythm status during serial CPET on patients enrolled in the Melody valve multicenter study before implant and then during serial evaluation for up to 5 years postimplant. Secondary analyses were subsequently performed to assess whether (1) hemodynamic status

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correlated with arrhythmia prevalence and type, and (2) arrhythmias during CPET and the overall incidence of arrhythmias correlated with patient outcomes during follow-up.

Methods

Study design

This study was 1 component of the US Melody Transcatheter Pulmonary Valve IDE trial, a nonrandomized, prospective study designed and sponsored by Medtronic, Inc., to assess the short- and long-term effects of transcatheter valve implant in patients with right ventricle to pulmonary artery conduit dysfunction. Patients were included or excluded from the study based on specific criteria.[2] Preimplant and follow-up CPET, along with echocardiograms, cardiac magnetic resonance imaging (cMRI), and cardiac catheterization, were performed at the following centers: Children's Hospital Boston, Miami Children's Hospital, Nationwide Children's Hospital, Seattle Children's Hospital, and Children's Hospital New York. Data analysis and interpretation of CPET were performed at the University of California Irvine. Pediatric cardiologists at each implanting institution and University of California Irvine reviewed individual reports after each test was completed.

The study was conducted under an investigational device exemption (No. G050186), and all versions of and amendments to the protocol were approved by the U.S. Food and Drug Administration, the Center for Devices and Radiological Health, and the institutional review board at each institution.

Cardiopulmonary exercise testing

Patients who underwent a Melody valve implant between January 2007 and January 2010 were evaluated with a standardized CPET protocol. CPET was performed on a mechanically braked cycle ergometer. Equipment was calibrated to the manufacturers' specifications, and testing was performed with standard protocols previously used in subjects with CHD.[11] Subjects pedaled in an unloaded state for 3 min. Workload was then increased continuously with a slope chosen to achieve each subject's predicted maximal work rate after 10 to 12 min of cycling. A 12-lead electrocardiogram was recorded throughout the CPET protocol to analyze cardiac rhythm, with recordings performed during baseline, exercise, and recovery phases. Leads II, aVF and V5 were also monitored continuously on an oscilloscope. The postexercise electrocardiogram was monitored and recorded every minute for at least 5 minutes. CPET was performed before implant, 6 months postimplant, and then at yearly intervals for 5 years.

Arrhythmias were defined as premature ventricular complexes (PVCs): isolated complexes or couplets during any stage of the CPET; supraventricular tachycardia or atrial flutter/fibrillation; nonsustained ventricular tachycardia (NSVT): 3 beats to 30 seconds; and sustained ventricular tachycardia (VT): >30 seconds or requiring intervention. Spontaneous VT was defined as occurring in absence of provocation (e.g., during catheterization procedure or programmed stimulation).

Hemodynamic evaluation

Concurrent with the CPET, patients underwent echocardiographic examination, cMRI, and, when indicated, cardiac catheterization at specified intervals post Melody implant. When cMRI was contraindicated because of implanted cardiac devices, by protocol, echocardiography was defined as a viable alternative. The specifics of these aspects of the testing have been previously reported.[10,12]

Statistical analysis

Basic statistical analysis was performed using commercially available software (Excel 2011 for Mac, Microsoft, Redmond, WA). Comparison of individual parameters are expressed as mean $\pm$ SD or median (range). Group comparisons were calculated on the base mean plus or minus the 95% confidence interval. Comparison of proportions was performed using the Mariscuilo procedure, Fisher exact test, χ^2 analysis, and McNemar test for significance in a matched case-control study. Kaplan–Meier and repeated measures analyses were performed by the Children's Hospital Los Angeles Saban Research Center. Comparison of proportions (e.g., incidence of arrhythmias) was performed using the generalized estimating equation with logistic regression. The Wilcoxon signed-rank test was used to assess pre- and postimplant hemodynamic data. For all analyses, $P < .05$ was considered significant.

Institutional review boards at each institution approved the study, and written informed consent was obtained from each patient or his/her parents before the baseline CPET. The Melody trial was sponsored by Medtronic, Inc. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

Study selection

A total of 171 patients were initially recruited in this study, and 164 completed the initial CPET protocol before Melody valve implant. Of that subset, 149 patients received the valve implant with serial CPET and hemodynamic evaluation completed in 136 patients, who are the primary subjects of this report (Table 1). Melody implant was not performed in 6 patients because of risk of coronary artery compression, and 13 patients did not receive the implant because specific implantation criteria were not present or the anatomy of the right ventricular outflow tract was unsuitable for implant. One subject achieved the desired hemodynamic result through balloon angioplasty, and 1 subject withdrew consent before the implant procedure. Melody valve implant was attempted in 1 other patient, but surgical explant was required because of rupture of the existing homograft and subsequent left hemothorax.