A prospective 5-year study of exercise performance following Melody valve implant

Bryant Priromprintr, MD, [a,b] Michael J Silka, MD, [a] Jonathan Rhodes, MD, [c] and Anjan S Batra, MD [d] *Los Angeles, Palo Alto, Irvine, CA; and Boston, MA*

Background The long-term benefits of Melody valve implant for right ventricular outflow tract conduit obstruction or insufficiency on exercise capacity are undefined.

Methods As part of the Melody valve clinical trial, 136 patients with congenital heart disease underwent serial cardiopulmonary exercise testing prior to, 6 months after, and annually for up to 5 years postimplant.

Results Mean age at Melody valve implantation was 22.4 ± 0.9 years (range 7-53 years). The 95 patients who completed the study protocol provide the basis of this report. An initial improvement in % predicted workload was present at 6 months postimplant; however, at the final (5 year) follow-up, sustained or further improvements in workload were not demonstrated for the entire cohort compared to baseline. By subgroup analysis, age <17 years at implant and pulmonary regurgitation as the primary lesion were variables associated with sustained improvement in exercise performance. There were sustained improvements in the ventilatory equivalents for O_2 (minute ventilation/O_2 intake, $P = .01$) and CO_2 (minute ventilation/CO_2 output, $P < .01$) at the ventilatory anaerobic threshold at the study conclusion. Improvements in forced vital capacity were also observed during the study but not sustained at the final follow-up.

Conclusions A cautious appraisal of the cardiovascular benefits of Melody valve implant on sustained improvements in exercise performance appears warranted. Although the observed changes in pulmonary function suggest improved restrictive lung physiology and more efficient gas exchange, after an initial increase in % predicted performance, neither sustained nor further improvements in exercise performance were observed, except in specific patient subgroups. (Am Heart J 2019;209:47-53.)

Following surgical repair of various congenital heart defects, residual pulmonary stenosis or regurgitation may result in progressive right ventricular (RV) dilation and dysfunction. This clinically results in fatigue, dyspnea, arrhythmias, and possibly sudden death.[1,2] One of the first clinical signs of RV dysfunction in an otherwise asymptomatic patient may be decreased exercise capacity,[3-5] as exercise testing may identify the inability to appropriately augment cardiac output in response to activity.[6,7]

The hemodynamic benefits of surgical pulmonary valve replacement in the resting state have been well

described.[8,9] However, sustained improvements in exercise capacity after pulmonary valve replacement in surgical studies have been inconsistent.[10-12]

Short-term improvements in the hemodynamic overload of the RV and short-term effects on arrhythmias and exercise function have been described following transcutaneous Melody valve implantation in patients with RV to pulmonary artery conduits.[13-15] In a prior study in this cohort, improvements in gas exchange efficiency and exercise performance as measured by cardiopulmonary exercise testing (CPET) at 6 months following Melody placement were reported.[13] However, whether the short-term benefits in gas exchange efficiency and exercise performance are sustained during serial evaluation over years is undefined. In this study, we describe the results of serial CPET performed over 5 years as part of the prospective US Melody Valve trial.

Methods

This study was one aspect of a nonrandomized, prospective study of the long-term effects of Melody placement in patients with RV to pulmonary artery outflow tract dysfunction. The study was sponsored by Medtronic, Inc, for the US Melody Transcatheter

Pulmonary Valve investigational device exemption trial. Patients were included or excluded from the study based on previously reported specific criteria.[16] Preimplant and follow-up CPETs, along with echocardiograms and cardiac magnetic resonance imaging, were performed at the following centers: Boston Children's Hospital, 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 core laboratory at 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 Food and Drug Administration, the Center for Devices and Radiological Health, and the Institutional Review Board at each institution. The trial is registered in ClinicalTrials.gov (identifier: NCT00740870). Data from this trial are confidential and locked by Medtronic Inc.

Patients who underwent a Melody valve implant between January 2007 and January 2010 were evaluated with a standardized CPET protocol commonly used in subjects with congenital heart disease.[17] CPET was performed on a mechanically braked cycle ergometer. Subjects pedaled initially in an unloaded state for 3 minutes. Workload was then increased continuously with a slope chosen to achieve each subject's predicted maximal work rate after 10 to 12 minutes of cycling.

Pulmonary function tests were performed at rest prior to the exercise studies. Expired gases were measured at rest and throughout the exercise protocol. Oxygen consumption (Vo_2), carbon dioxide production (Vco_2), and minute ventilation were measured on a breath-by-breath basis. *Peak Vo_2* was defined as the highest Vo_2 achieved by the subject during the test. Ventilatory anaerobic threshold was measured by V-slope method when it could be accurately determined. Because of the extended time interval under study and the potential for large changes in body size during this period, we chose to focus upon % predicted values (as opposed to absolute or weight normalized values) for peak Vo_2, peak workload and pulmonary function, and related parameters.[18,19] To exclude data from patients who stopped exercising for noncardiovascular reasons (ie, before approaching their cardiovascular limit), peak exercise data were excluded from analysis if the patient did not achieve a respiratory exchange ratio at peak exercise ≥ 1.05.

Concurrent with the CPET, patients also underwent echocardiographic examination at the same specified intervals and/or cardiac magnetic resonance imaging at the 6-month follow-up examination only. When cardiac magnetic resonance imaging was contraindicated because of implanted cardiac devices, by protocol, echo-cardiography was defined as a viable alternative. The specifics of these testing have been previously reported.[13,20]

Basic statistical analysis was performed using commercially available software (Excel 2011 for Mac, Microsoft, Redmond, WA; SPSS statistics v 20, IBM, Armonk, NY). Continuous variables were summarized as mean ± SD for normally distributed. Categorical variables were summarized as frequencies and percentages.

Repeated-measures analyses were performed by the Children's Hospital Los Angeles Saban Research Center. Comparison of proportions over time was performed using the generalized estimating equation with linear regression model to examine the change in ventilation and pulmonary function from preimplant to 5-year postimplant follow-up. For all analyses, a value of $P < .05$ was considered statistically significant. To allow a more accurate determination of the long-term effects of the Melody valve implant, analysis was performed to include only those patients who performed the preimplant CPET and at least 5 of the 6 prescribed follow-up evaluations.

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 population

A total of 149 patients were initially enrolled in the study protocol following Melody valve implant. One hundred thirty-six patients had matched CPET data prior to and 6 months after the initial implant. Gradual patient attrition occurred during the study, with 132 patients (97.1%), 129 patients (94.9%), 105 patients (77.2%), 89 patients (65.4%), and 82 patients (60.3%) completing the 1-, 2-, 3-, 4-, and 5-year follow-up CPETs, respectively. Ninety-five patients (70%) completed the preimplant CPET and at least 5 of the 6 prescribed follow-up studies and are the basis of this report. Reasons for attrition included death during the follow-up period (4 patients, 2.9%); surgical valve explant (7 patients, 5.1%) for endocarditis (1), conduit stenosis (5), or fracture (1); reintervention at time requiring deviation from protocol (1 patient, 0.7%); and loss to follow-up (29 patients, 21.3%) from inability to contact or moving out of the area of the implanting center. The baseline characteristics and acute changes in hemodynamics after Melody placement for this study group have been previously reported[15,20] and further are expanded in Table I to provide comparison of the initial and final study groups.

Table I. Baseline demographics

Parameter	Total sample Median (range)	Completed study Median (range)
n	136	95
Age (y)	19.0 (7-53)	19.0 (7-53)
Weight (kg)	64.0 (27.0-146.7)	63.5 (27.0-118.0)
Body mass index (kg/m^2)	23.4 (14.1-44.1)	22.9 (14.3-44.1)
Male	91 (66.9%)	64 (66.7%)
NYHA functional class		
I	19 (14.0%)	14 (14.7%)
II	96 (70.6%)	67 (70.5%)
III	20 (14.7%)	13 (13.7%)
IV	1 (0.7%)	1 (1.1%)
No. of surgical procedures	3 (1-7)	2 (1-7)
Indications for Melody valve		
Stenotic	35 (25.7%)	23 (24.2%)
Regurgitant	73 (53.7%)	52 (54.7%)
Mixed	28 (20.6%)	20 (21.1%)
Anatomic diagnosis		
Tetralogy of Fallot	68 (50.0%)	44 (46.3%)
Aortic stenosis (status post-Ross)	29 (21.3%)	22 (23.2%)
Transposition of the great arteries	14 (10.3%)	10 (10.5%)
Truncus arteriosus	14 (10.3%)	12 (12.6%)
Double-outlet right ventricle	7 (5.1%)	4 (4.2%)
Other	4 (2.9%)	3 (3.2%)

Table II. Baseline pulmonary function and CPET before and after Melody valve implant

	Preimplant	Postimplant (4 y)	P value	Postimplant (5 y)	P value
Total subjects	95	89	–	82	–
Subjects who achieved RER >1.05	62 (65.3%)	73 (82.0%)	–	67 (81.7%)	–
FVC (% pred)	77.6% ± 21.0% (77.0%)	83.1% ± 20.5% (80.5%)	.003	77.7% ± 22.5% (77.0%)	.410
$FEV_{1.0}$ (% pred)	75.8% ± 21.7% (77.0%)	79.4% ± 22.5% (79.5%)	.125	73.7% ± 24.6% (77.0%)	.402
$FEV_{1.0}$/FVC	83.1% ± 8.0% (83.0%)	80.4% ± 8.5% (81.0%)	.087	79.9% ± 12.8% (81.0%)	.043
VE/VO_2	29.4 ± 4.7 (28.0)	27.7 ± 4.8 (27.0)	<.0001	26.9 ± 5.8 (27.0)	<.0001
VE/VCO_2	30.2 ± 4.3 (30.0)	28.3 ± 5.2 (28.0)	<.0001	28.0 ± 5.2 (28.0)	.0001
Peak VO_2 (% pred)*	67.3% ± 21.1% (65.0%)	63.9% ± 18.2% (62.5%)	.472	65.6% ± 18.1% (67.5%)	.580
% Peak O_2 pulse (% pred)*	80.5% ± 21.8% (78.0%)	80.3% ± 19.5% (80.0%)	.813	82.9% ± 20.9% (82.0%)	.831
% Peak workload (% pred)*	68.8% ± 18.6% (66.5%)	71.3% ± 22.4% (71.0%)	.041	68.1% ± 22.0% (69.5%)	.816
Peak HR	154.1 ± 25.5	154.7 ± 23.9	.934	151.8 ± 30.5	.744

Data represent the patients with a preimplantation CPET and at least 5 (of the 6 possible) follow-up studies. Data are expressed as n (%) or mean ± SD (median value in parenthesis). Pulmonary function tests and ventilator measures performed prior to and during 4- and 5-year follow-up CPET. Data are presented as mean (range). P value of < .05 was considered statistically significant. *RER*, respiratory exchange ratio; *AT*, anaerobic threshold; *HR*, heart rate.
* Measures collected at peak exercise only, restricted to subjects who reached RER >1.05.

Exercise function pre– and post–Melody valve

Baseline exercise physiology data and a summary of changes in exercise function are presented in Table II. Exercise performance (% predicted workload) for the overall study group was reduced at baseline (68.8% predicted). Although there was a trend toward improvement at 4 years (71.3% predicted, P = .04), this finding was not sustained ay the conclusion of the study at 5 years (68.1% predicted, P = .82) (Figure 1).

By subgroup analysis, significant sustained improvement in % predicted workload was present for younger patients (<17 years of age) at implant (66.1% preimplant vs 78.2% at 5 years) compared to no significant improvement in patients age ≥17 years at implant (69.9% preimplant vs 68.7% at 5 years) (P ≤ .001) (Figure 2). Of note, most of the improvement in the younger patients occurred 3-5 years postimplant. Significant improvements in % predicted workload at study conclusion were also present for patients with pulmonary regurgitation as the primary indication for implant (67.2% preimplant vs 74.0% at 5 years) compared to no significant improvement in patients with conduit stenosis or mixed lesions (70.2% preimplant vs 69.2% at 5 years) (P ≤ .001) (Figure 3).

Figure 1
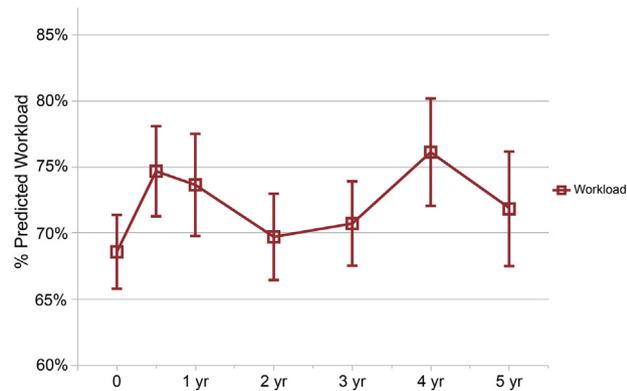
Exercise capacity. The % predicted workload during CPET following Melody valve placement. Although there was an overall trend toward improvement at 4-year follow-up (P = .04 compared to baseline), this was not sustained at 5 years. Error bars represent standard error.

Prior to Melody valve placement, peak Vo_2, and peak oxygen pulse (Vo_2 max/heart rate), a variable that provides an estimate of the forward stroke volume at peak exercise, were moderately reduced. The peak Vo_2 was lower for patients with a New York Heart Association (NYHA) functional classification III (55.3% predicted compared to 67.5% predicted for patients with NYHA I, P = .010) or if the reason for valve replacement was pulmonary regurgitation (56.6% compared to 66.1% predicted for patients with pulmonary stenosis, P = .004). These parameters did not change significantly at the 6-month or the long-term follow-up after Melody valve implant.

Gas exchange efficiency measured by ventilatory equivalents for oxygen (VE/Vo_2) and carbon dioxide (VE/Vco_2) at ventilatory anaerobic threshold were abnormal pre-Melody placement.[13] Improvements in both VE/Vco_2 (P < .0001) and VE/Vo_2 (P = .0001) at the ventilatory anaerobic threshold were noted at the 6-month follow-up and were sustained during 5 years of follow-up (Figure 4). There was no significant correlation between post-Melody improvements in VE/Vco_2 and VE/Vo_2 at the ventilatory anaerobic threshold and preimplantation catheterization, echocardiographic or magnetic resonance imaging variables (eg, initial RV volume indexed ≥150 mL/m^2), indication for Melody valve (regurgitant, stenotic, or combined), or in patients who had the largest improvement in exercise/ventilatory capacity.

Prior to Melody valve implant, the mean indexed RV area in diastole (by echo measurement) was mildly dilated (21.3 cm^2/m^2), which corresponded to a mean indexed RV end-diastolic volume of 129.5 mL/m^2 via cardiac magnetic resonance imaging[21]; 25 patients (18.4%) had indexed RV end-diastolic volume >150 mL/m^2. Although the indexed RV systolic and diastolic areas decreased progressively throughout the 5-year follow-up period, the fractional area change did not have a statistically significant improvement or correlate with changes in exercise function.

Peak heart rate during CPET did not change significantly during the follow-up study intervals (Table II). Forty-one patients (30.1%) were taking antiarrhythmic medications, 12 patients (8.8%) had a pacemaker, and 2 patients had an implantable cardiac defibrillator.[20]

## Pulmonary function testing pre— and post–Melody valve implant

Prior to Melody valve placement, pulmonary function testing revealed a mild restrictive/obstructive pattern. Forced vital capacity (FVC) and first second forced expiratory volume (FEV$_{1.0}$) were decreased at 77.6% ± 21.0% and 75.8% ± 21.7% predicted, respectively. After valve implant, there was a progressive, statistically significant improvement in FVC through 4 years of follow-up (+5.5%, P = .003), but improvement was not sustained at the fifth year of follow-up; there was not an improvement in FEV$_{1.0}$ at either the fourth- or fifth-year follow-up CPET.

Patients with NYHA classification III-IV prior to valve placement had statistically significant improvements in pulmonary function testing parameters (FVC, FEV$_{1.0}$, and FEV$_{1.0}$/FVC P < .0001) but not in measures of exercise tolerance.

Discussion

Functional limitations in exercise capacity following surgical repair for congenital heart defects involving the RV outflow tract may be related to progressive pulmonary valve or conduit dysfunction and subsequent RV dilation.[3] Patients may report being asymptomatic yet have significant abnormalities detectable on formal exercise testing that may reflect early manifestations of RV dysfunction.[22] Because resting indices of RV hemodynamics have demonstrably improved after pulmonary valve replacement,[15] one may anticipate that exercise capacity would

Figure 2
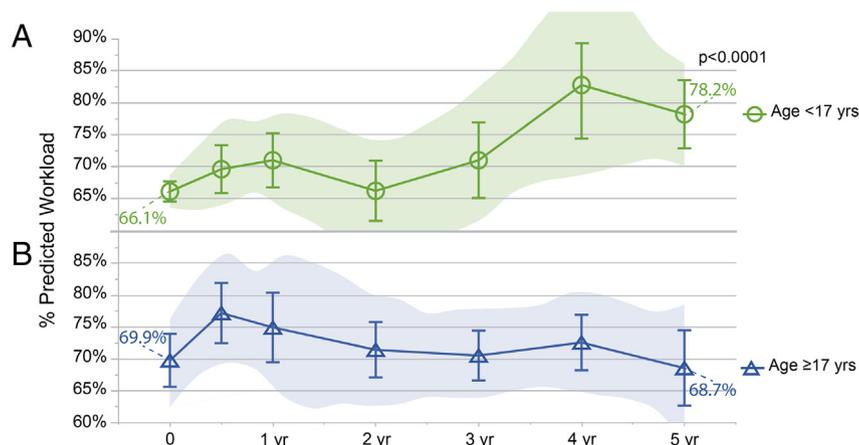
Exercise capacity at ≥ or <17 years of age. The % predicted workload during CPET following Melody valve placement by age (A) ≥17 years or (B) <17 years. There was a statistically significant improvement in exercise capacity for older patients which occurred primarily in the 3- to 5-year range. Error bars represent standard error.

Figure 3
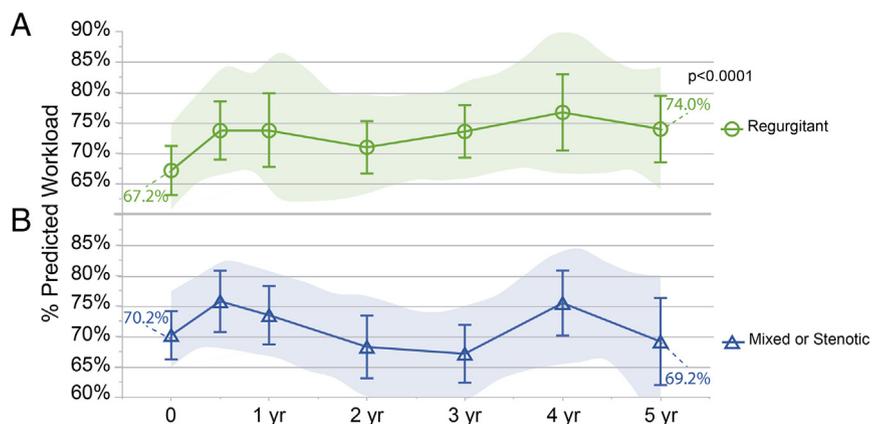
Exercise capacity by melody valve indication—conduit regurgitation versus stenosis versus mixed. The % predicted workload during CPET following Melody valve placement by device indication—(A) conduit regurgitation versus (B) conduit stenosis or mixed. There was a statistically significant improvement in exercise capacity for patients who received a Melody valve for conduit regurgitation ($P < .0001$). Error bars represent standard error.

show similar improvement. However, among patients with congenital heart defects, discrepancies between baseline hemodynamic effects of surgical/catheterization procedures and more modest improvements in exercise capacity have been encountered.[23-30] These studies using CPET have focused on workload achieved and peak Vo_2 (measures of cardiac output) and found minimal or no significant change in these parameters.[31,32] The current study is consistent with prior studies in that although hemodynamic parameters are significantly improved at baseline, a consistent, sustained improvement in peak

exercise parameters was not observed after pulmonary valve placement for the entire study group.

In the current study, sustained improvements % predicted workload were demonstrated for the subgroup of patients <17 years of age at implant and those in whom pulmonary regurgitation was the primary indication for Melody valve implant. As these changes occurred gradually 2-4 years postimplant, they suggest that improvement in CPET measurements may be due to gradual RV remodeling which occurs in young patients with pulmonary regurgitation but not in older patients with longstanding PR or in

Figure 4
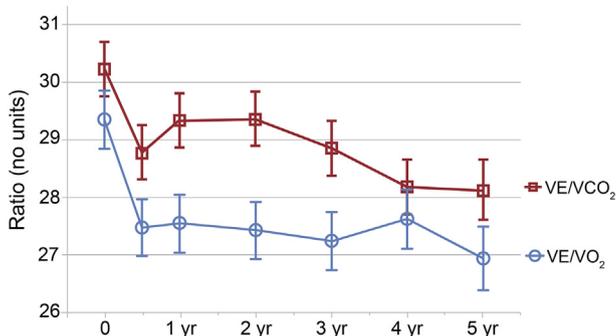
Ventilation during exercise. The minute ventilation–carbon dioxide production (VE/Vco₂) and oxygen consumption (VE/Vo₂) slopes at anaerobic threshold. Sustained improvements were present 6 months after pulmonary valve replacement, showing improved ventilatory efficiency, which were sustained through follow-up.

those with RV dysfunction secondary to RV pressure overload secondary to RV outflow tract obstruction.

The observed improvements in gas exchange efficiency (VE/Vco₂ and VE/Vo₂ at the ventilatory anaerobic threshold) at the 6-month follow-up testing persisted over the 5-year study. The improvement in the VE/Vco₂ at the ventilatory anaerobic threshold may be the result of improved pulmonary blood flow distribution (and hence improved ventilation-perfusion mismatch and gas exchange efficiency) following restoration of pulmonary valve function. A high VE/Vco₂ has been previously suggested to be related to hemodynamic inefficiency.[33] The VE/Vco₂ slope (which is closely mirrored by the VE/Vco₂ slope at the ventilatory anaerobic threshold) has been found to correlate negatively with exercise capacity and has also been identified as a marker of poor outcomes in tetralogy of Fallot.[34] Hence, the effect of Melody valve placement on the VE/Vco₂ at the ventilatory anaerobic threshold perhaps constitutes an important secondary observation in this study.

However, the findings of improved gas efficiency did not translate into overall sustained improvements in exercise capacity. This discrepancy may be related to the fact that functional aerobic capacity is determined by skeletal muscle physiology as well as cardiopulmonary function. The improvement in gas efficiency addresses only 1 component of the complex physiology of exercise capacity. Interventions such as a training program that addresses a patient's skeletal muscle system may have additional beneficial effects on improving the overall exercise capacity.

Restrictive lung volumes, a known pulmonary pathophysiology in patients with tetralogy of Fallot after surgical repair,[35,36] may be attributed, in, in part, to altered pulmonary and chest wall mechanics following thoracic surgery, cardiomegaly, differences in pulmonary hemodynamics, or lack of physical activity. Not surprisingly, patients in this series started with mild restrictive physiology. Following

Melody valve implant, they realized significant initial improvements in both FVC and FEV₁.₀. At the time of the 4-year follow-up studies, these indices averaged >80% of predicted (ie, the lower limit of normal), although these improvements were not consistent through year 5.

Limitations

One major limitation in our study is that in a long follow-up period such as ours, there is difficulty in controlling multiple variables such as exercise training. At the start of this prospective trial, there was not a standardized exercise regimen, so subjects may have had varying degrees of aerobic training. This made objective assessment of long-term changes in exercise tolerance related solely to the restoration of pulmonary valve function more difficult.

Also, within the longitudinal study, there was incomplete follow-up for various reasons. Patients were lost to follow-up or were unable to complete the follow-up because they expired, had the valve explanted because of endocarditis or stent fracture, or had reintervention for indications including conduit stenosis or insufficiency.

Conclusions

Melody valve implant was associated with initial improvements in % predicted exercise performance and gas exchange efficiency at 6 months postimplant. These initial changes tended to be variable through 4 years of follow-up. However, it is important to emphasize that further improvements in functional capacity or pulmonary function were not observed. Furthermore, by the fifth year of postimplant follow-up, the initial improvements in % predicted performance during CPET and improved gas exchange efficiency were no longer statistically significant for the entire study group.

By subgroup analysis, significant sustained improvements in exercise capacity were demonstrated for patients <17 years of age at implant and those in whom conduit insufficiency was the primary indication for Melody valve implant. Although these observations suggest a cautious appraisal of the overall benefit of Melody valve implant on exercise performance in patients with congenital heart disease, certain subgroups of patients may demonstrate significant benefit.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.12.014.

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