Pediatric Transcatheter Valve Replacement: Guests at Our Own Table?

**Running title:** Petit; Outcomes Following TPVR in Children

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Transformative advances in medical technology rarely occur in isolation, but rather may be indirectly informed, if not accelerated, by advances in related fields. Bonhoeffer et al introduced the first transcatheter valve in 2000, implanting it in a 12 year-old boy with tetralogy of Fallot\(^1\).

The report of the transcatheter aortic valve by Cribier a mere two years later suggests the interdependence of investigators on breakthroughs in related fields\(^2\). The advancements in cardiac devices are shared among pediatric and adult cardiologists, with benefits ideally befalling both patient populations when a breakthrough occurs, whether that technology was initially introduced for adults or children.

It is notable that the Melody valve implanted in 2015 is in large part the same device and delivery system as the first transcatheter valve implanted in 2000. The operator learning curve has been significant, while the device has remained for the most part unmodified. The unchanging character of the valve speaks to two issues specifically.

When considering the performance and clinical of a bioprosthetic valve, one might subscribe to the British surgeon Dr. Donald Ross’s approach: the primary consideration is the early safety and efficacy of the valve, with secondary value placed on valve durability\(^3\). In consideration of early safety and efficacy, the Melody valve has shown excellent results. As has been demonstrated in multiple studies, a significant learning curve occurred to optimize patient safety during transcatheter valve implantation – such as careful coronary artery assessment, prestenting the outflow tract, and anticipation of outflow tract tearing\(^4,5\). It is worth remembering that some of the experiences on this technical learning curve are embedded within the results of the current midterm study by Cheatham et al in this issue of *Circulation*\(^6\).

Early efficacy has also been previously demonstrated in a wide range of reports that speak to the immediate improvements in hemodynamics, the early improvement in patients’
exercise performance and the early benefits to right ventricular volume and systolic performance. Hence, within a decade of the introduction of the transcatheter pulmonary valve, there was a growing literature suggesting that transcatheter PVR would be generalizable, and that the technology would be effective at abolishing regurgitation and relieving obstruction.

Valve durability is particularly emphasized in the current study by Cheatham et al. Until this study, it was unclear how the Melody valve would perform in the long term. Conceptually, transcatheter pulmonary valve replacement (TPVR) has been thought of as a means to extend the lifespan of surgically placed pulmonary valves. Cheatham et al report that, when placed in the proper anatomic and physiologic setting, Melody valve function changed very little over midterm follow-up. That is, when right ventricular outflow tract (RVOT) obstruction is relieved at time of implantation, TPVR is associated with a very low rate of repeat intervention. In contrast to reports of surgically implanted pulmonary valves, this study indicates that the Melody valve remains non-stenotic and non-regurgitant up to 7 years after implantation.

The ramifications of such promising midterm results are important. This data allows the clinician to more confidently counsel families when considering TPVR, and likewise gives our surgical colleagues good reason to implant conduits and valve prostheses compatible with future Melody utilization.

A notable issue raised by the current study is bacterial infection following TPVR. In the current study by Cheatham et al, 14 of the 148 patients experienced either clear Melody endocarditis or persistent bacteremia. Although six of these 14 patients were treated with antibiotics alone and underwent no additional interventions, the remaining eight patients underwent repeat interventions, including repeat TPVR, Melody explantation, or redilation of the Melody valve. This study, then, suggests an unadjusted rate of infectious endocarditis (IE) post-
TPVR of 9.5%, or roughly 2% per year. Other studies have reported significant morbidity following IE in this population post-TPVR. A prospective study assessing risk factors for IE post-Melody reported 5 cases of IE among 86 patients (5.8%) over 13 months, with mortality from IE in three out of five. More troublesome to the clinician is the difficulty in assigning IE to the pulmonary valve itself. Cheung et al noted that both transthoracic and transesophageal echocardiography, owing to stent artifact, may be inadequate to detect valve degeneration or vegetations in Melody-associated IE.

Appropriate prophylaxis against TPVR-related IE requires understanding of the pathophysiology. Patel et al reported the histopathology of TPVR IE cases, finding that bacterial superinfection often accompanied thrombus residing within the cusps of the valve. The interaction between valve thrombosis and increased RVOT gradient has been invoked as potentially causative in TPVR IE in a separate prospective study; notably, lack of antiplatelet therapy was associated with development of Melody IE. Future study will hopefully assess the benefits, if any, of enhanced anticoagulation and endocarditis prophylaxis.

Of course, the issue of endocarditis following valve implantation is not unique to the Melody valve, or to the transcatheter route. Rates of surgical valve IE are similar to that reported in the current study, particularly when the surgical valve is the Contegra® bovine jugular vein. It is interesting that the bovine jugular vein – common to both the Melody valve and to the Contegra conduit – appears to be particularly vulnerable to IE. A study by Van Dijck indicated that IE following pulmonary valve replacement was nearly 8.5 times more likely in Contegra® conduits compared with homografts. However, IE exists among all bioprostheses: transcatheter aortic valve implantation (TAVI) studies have also found IE in multiple implant types, with demonstrated rates of IE post-TAVI ranging between 0.3 to 3.4%.
Finally, the report by Cheatham et al lays bare another facet of the Melody valve, and its unchanging status over 15 years. The only transcatheter pulmonary valve currently approved by the U.S. Food and Drug Administration (FDA) for implantation in children and adults remains the Melody valve. Given the significant advancements in transcatheter valve development over the past 15 years, the absence of significant modification to the Melody valve and the valve delivery system is noteworthy. It is worthwhile, yet sobering, to compare the experience of a child with tetralogy of Fallot to that of an adult with acquired aortic valve disease. In the United States, a child with pulmonary valve failure might be fortunate to be among the subset of patients with suitable anatomy for the only FDA-approved percutaneous valve option. Even so, that child would face a certain future of regular valve replacements. On the other hand, an adult in 2015 with acquired aortic stenosis may undergo implantation of one of five TAVI devices in the United States, or one of seven devices in Canada or Europe19.

The rate of progress in pulmonary valve development is no doubt linked to the wide range of anatomic complexity seen in patients with repaired congenital heart disease. And yet, the lack of transcatheter options for pulmonary valve implantation also reflects an economic reality: worldwide, there have been 8,000 Melody valve implants – with 4,500 in the United States since the original IDE study began in 2007. Between 2002 and 2012, an estimated 50,000 adults underwent TAVR20.

One is tempted to ask: where do we, the pediatric cardiology community, go from here? How will the tremendous technological advancements in adult valve technology translate into gains for children and adults with congenital heart disease? Will pediatric interventionalists participate in device trials to study efficacy of transcatheter aortic valves in children? Will future advancements in pediatric valve implantation occur under the guise of off-label use? There has
been, to date, no lack of creative off-label use of existing valves to palliate children with congenital heart disease\textsuperscript{21-23}. Such reports of “first-in-man” may be individually significant, but hold little prospect for advancing meaningful device development.

Clearly the FDA intends, rather, for future device development to occur through trials, and the Humanitarian Device Exemption (HDE) pathway makes sponsoring a pediatric device trial somewhat more attractive. It is notable that the Melody valve is one of only six pediatric cardiac devices to attain HDE approval since HDE introduction in 1997. The aim of the HDE pathway is to incentivize industry to manufacture devices for areas of unmet clinical need\textsuperscript{24}. The HDE allows a regulatory pathway, and yet the economic burden from device manufacturers and from hospitals remains significant. HDE approval is based on studies demonstrating both safety and “probable benefit” of the device (compared to normal post-market approval (PMA) in which studies establish both safety and effectiveness)\textsuperscript{25}. Unfortunately, payors are free to resist reimbursement of devices lacking efficacy data. Future device trials for pediatric populations may indeed follow the same HDE route to attain FDA-approval. But the success of the HDE pathway will be measured by the number of devices put forward on this track for FDA approval.

Thus, in 2015 the congenital heart disease community continues to lag behind the adult cardiac world, where advancements and modifications can be more quickly studied and implemented. We are currently enjoying an incredibly active and productive era of incredibly clever cardiac device development. The current study demonstrates the value of transcatheter valve implantation for treatment of congenital heart disease. One hopes that the Melody valve, despite its incredible success and durability, becomes the first of many transcatheter options for children with valve failure.

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