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Will Catheter Interventions Replace Surgery for Valve Abnormalities?

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Abstract

Purpose of Review—Catheter-based valve technologies have evolved rapidly over the last decade. Transcatheter aortic valve replacement (TAVR) has become a routine procedure in high-risk adult patients with calcific aortic stenosis. In patients with congenital heart disease (CHD), transcatheter pulmonary valve replacement represents a transformative technology for right ventricular outflow tract dysfunction with the potential to expand to other indications. This review aims to summarize 1) the current state of the art for transcatheter valve replacement (TVR) in CHD, 2) the expanding indications for TVR, and 3) the technological obstacles to optimizing TVR.

Recent findings—Multiple case series have demonstrated that TVR with the Melody transcatheter pulmonary valve in properly selected patients is safe, effective, and durable in short-term follow-up. The Sapien transcatheter heart valve represents an alternative device with similar safety and efficacy in limited studies. Innovative use of current valves has demonstrated the flexibility of TVR, while highlighting the need for devices to address the broad range of post-operative anatomies either with a single device or strategies to prepare the outflow tract for subsequent device deployment.

Summary—The potential of TVR has not been fully realized, but holds promise in treatment of CHD.

Keywords

Congenital heart disease; valve replacement; heart catheterization

Introduction

Transcatheter valve replacement (TVR) represents a potentially transformational technology for the treatment of congenital heart disease (CHD), especially for patients with right ventricular outflow tract (RVOT) dysfunction (defined as stenosis and/or regurgitation). The potential for TVR to supplant surgical valve replacement (SVR) is predicated on optimistic

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speculation at present. However, recognizing the rate at which valve technologies are evolving, we would venture that the answer to the question is a qualified “yes,” while acknowledging that technology is nascent and much remains to be determined. The pertinent questions at this time are: 1) are there current patient populations for whom TVR is a safe and effective alternative to SVR, 2) what obstacles remain in the way of an optimized TVR technology which can be broadly applied to the majority of CHD patients, and 3) what knowledge-gaps need to be addressed to help clinicians and policy-makers determine how best to choose between TVR and SVR.

To date, research and development for TVR devices aimed at patients with CHD has focused on right ventricular outflow tract (RVOT) dysfunction, and it is in this population that safety and efficacy of TVR has been clearly demonstrated. Reconstruction of the right ventricular outflow tract (RVOT) with homograft conduits is performed in patients with stenotic or atretic RVOT (e.g. tetralogy of Fallot or truncus arteriosus) and with left ventricular outflow obstruction in whom the pulmonary valve is used as a neo-aortic valve (e.g. the Ross operation). RVOT augmentation can also be performed by patch augmentation (e.g. trans-annular patch in tetralogy of Fallot). In either case, progressive RVOT obstruction and/or insufficiency can develop. Neither obstruction or insufficiency typically cause dramatic symptoms for years, but both proximal functional limitation (ascertainable on cardiopulmonary exercise testing) [1,2] and insidious, progressive detriment to the RV, including systolic dysfunction and the risk of arrhythmia and sudden death[2–4] have been demonstrated. Until the introduction of TVR, the only treatment for dysfunctional RVOT was surgical valve replacement. The presuppositions 1) that all prosthetic valves have finite lifespans and 2) that the technical complexity and associated morbidity of reoperations increase with repetition have resulted in consensus to delay operative re-intervention as long as possible[1,2,5–7]. This paradigm is reflected in observational studies which attempt to identify threshold values from imaging data that identify the point beyond which the RV is not recoverable[1–4,8–11]. TVR alters the risk-benefit calculation by providing a less invasive alternative therapy with potential reductions in morbidity and mortality. Moreover, serial re-interventions with TVR have similar or reduced complexity and morbidity, while in SVR repeat operations become increasingly complex and hazardous.

Brief history of TVR in CHD

TVR of the pulmonary valve was first reported in 2000 by Bonhoeffer and colleagues in a lamb[12], quickly followed by a report of TVR in a human patient with dysfunctional RVOT conduit[1,2,13]. The Melody transpulmonary valve (TPV) (Medtronic Inc., Minneapolis, MN) is the only available device designed for pulmonary valve TVR. A prospective nonrandomized study of the Melody TPV was completed in 2010[3,4,9,14] and in January of 2010 the Melody TPV was approved for use in the United States under a Humanitarian Device Exemption (HDE) (http://www.accessdata.fda.gov/cdrh_docs/pdf8/H080002a.pdf). The Sapien transcatheter heart valve (Edwards Lifesciences LLC, Irvine, CA), which was developed for deployment in the aortic position, has since been used for TVR in the pulmonary position but is currently only available in the United States as part of an investigational device exemption (IDE) trial.

Current indications for TVR in CHD and outcomes

Current indications for Melody TPV deployment under HDE are a circumferential RVOT conduit and either greater than moderate regurgitation or stenosis with peak-to-peak gradient 35mmHg. The IDE stated that the narrowest portion of the conduit should be at least 16 mm in diameter at the time of TPV deployment. No upper limit to conduit size was included in the HDE, but the outer diameter of the deployed valve is 1.4 mm larger than the available delivery systems (18-, 20-, and 22 mm) limiting the use of the Melody TPV in larger conduits and dilated RVOT (such as in tetralogy of Fallot). The initial IDE established a lower weight limit of 30 kg[5–7,14], but the valve has been subsequently implanted in smaller patients, and currently there are no explicit age or size limits.

Case series of TVR with Melody TPV in RV to PA conduits from the United States and Europe have demonstrated >90% technical success, procedural mortality <1%, and infrequent adverse events in appropriately selected patients[8,10,11,14–21], with uniform reductions in RV systolic pressure, RVOT stenosis, and RVOT regurgitation [12,15,17,20–23], along with subsequent improvement in RV end-diastolic volume[23–25], diastolic function[26], and strain[26] after TVR. The effect of TVR with Melody TPV on exercise capacity (measured by maximal oxygen consumption (mVO₂)) has been equivocal in studies, whether subjects with RVOT stenosis, regurgitation, or a combination of both were pooled[17,22,24,27,28] or divided into subgroups with predominant stenosis or predominant regurgitation[22–24,28]. No trials have directly compared SVR to TVR for clinical or functional outcomes. A parallel case series of a single center's experience with TVR and SVR, reported similar short-term results in both groups[29], demonstrating that, with some caveats, TVR has comparable safety and efficacy to SVR. Durability of the Melody TPV has been good in published case series, but few series have median follow-up greater than a year[15,21,30,31]. Progressive stenosis is the more commonly cited cause of reintervention after TVR. In early series, this was most commonly due to stent fracture[14,32], but implantation of a bare metal stent prior to TVR has reduced that risk[1,2,15,17,19,32,33]. Currently, freedom from reintervention is 92–95% at one year and 86–87% at 2 years[1–4,9,30,33], with most reintervention able to be accomplished via catheter-based procedure. Endocarditis has been identified as a potential adverse event[1,2,5–7,34–36], but it is not yet clear how the risk compares to that in surgical prosthetic valves.

The Sapien transcatheter heart valve is a balloon-expandable stent-mounted valve designed for implantation in the aortic position in adults with acquired calcific aortic stenosis. The range of diameters available includes 23, 26, and in some countries 29 mm, which make it potentially suitable for larger diameter conduits and native outflow tracts than the Melody TPV. Short-term outcomes are similar to the Melody TPV[1–4,8–11,37–39].

Challenge of the dilated right ventricular outflow tract

Returning to TVR for RVOT dysfunction, only a fraction of affected patients have an RV to PA conduit or bioprosthetic valve that are appropriately sized for TVR with current technology. There are reports the off-label use of both Melody and Sapien valves deployed in native outflow tracts[8,10,11,14–21,40–43], but even with pre-stenting, these are limited

to RVOT that are the appropriate size to anchor the device, usually 24mm. The dilated RVOT typical of transannular patch used in tetralogy of Fallot is simply too large in most cases for current devices, though there are case reports of TVR in larger diameter RVOT [12,15,17,20–23,44]. Deployment of transcatheter valves in the branch pulmonary arteries is one solution, which has been reported in an animal model[23–25,45] and subsequently in human patients[26,46,47]. Deploying a nested series of stents from a branch PA back into the MPA to provide a stable position for TVR has been used[26,42,43]. Thirdly, the Medtronic Native Outflow Tract device, a self-expanding trans-catheter device, has been enrolling subjects at limited centers for an IDE trial since April 2013[17,22,24,27,28,48] (clinicaltrials.gov identifier: NCT01762124). Another approach aims to reduce the diameter of the RVOT with a transcatheter device, leaving a smaller diameter internal channel in which to deploy a transcatheter valve; these devices are currently in preclinical trials[22–24,28,49–52]. Despite these novel approaches, studies with CMR have demonstrated that post-surgical anatomy is highly variable[29,53] and will likely represent a persistent technical and technological challenge.

Expanding indications for TVR in the pulmonary position (and beyond)

Innovative use of the Melody and Sapien valves has extended use beyond their original indications, demonstrating the potential breadth of applications for TVR. Pulmonary valve TVR in patients with pulmonary hypertension [12,28,54], demonstrates the capacity of current valves to function under higher pressures. The off-label use of Melody valve for failed bioprosthetic valves in the pulmonary position has also been reported with good safety, efficacy, and short-term durability[1,2,13,31,55] (Figure 1). This is a logical extension of the current TVR approach and allows for valve deployment in orthotopic position seated in the failed surgical hardware, providing a stable, uniform substrate for seating the transcatheter valve. The valve-in-valve TVR concept has been further expanded to include deployment in both tricuspid[3,4,9,14,56–62] and mitral[5–7,14,57,63] positions.

Adapting surgical practice in the face of TVR

Transcatheter approaches are less invasive with probable reductions in mortality, and almost certain reductions in morbidity, hospital stay, and recovery time. These differences are likely only increased in patients undergoing serial reoperations. How the development of TVR technologies should affect surgical and medical practice is a difficult question, but what is clear is that 1) chronic valvar dysfunction contributes to decrements in function and increased morbidity and mortality and 2) a minimally invasive approach changes the balance of risk and benefit, exerting pressure to intervene earlier on dysfunctional valves. While TVR technology evolves to address a broader range of indications, there may be an intermediate stage, where adjusting surgical technique for procedures that have high or even certain risk of reintervention to facilitate future TVR may have real benefits. The goal for any such strategy is to provide competent valve function with the minimum risk and morbidity and to minimize the number of operative procedures by providing an anatomic substrate for transcatheter valve replacement during the primary operation.

What follows are strategies that we would advocate as first steps in this process. The first would be to consider the possibility of TVR in choosing the size of bioprosthetic valves for SVR. We would advocate (within reason) maximizing the size of bioprosthetic valves to facilitate future (and multiple) valve-in-valve TVR, effectively delaying another surgical procedure. Valve replacement with larger diameter valves in younger patients both are associated with shorter time to reintervention[64]. However, reducing the number of open-heart procedures (even if replaced by multiple TVR procedures) could potentially reduce total mortality, morbidity, and economic cost. Another adjustment would be elective placement of an annuloplasty ring in atrioventricular valves during repair of dysfunctional atrioventricular valves, which could be used as an anchoring position for TVR[14,32,65–67]. At present TVR of atrioventricular valves is only used as a bailout strategy for otherwise inoperable patients with failed surgical hardware, but as technology develops transcatheter valve deployment may prove to be less morbid and costly. Finally, for RVOT augmentation in tetralogy of Fallot, use of techniques that limit the size of RVOT (e.g. monocusp technique or partial annuloplasty), which would allow for initial PVR with a transcatheter valve, may prove beneficial in spite of increased risk of residual RVOT obstruction. The common theme amongst these strategies is that they balance some potential risk of early re-intervention or “imperfect hemodynamics” in the short run to facilitate future transcatheter intervention and also reduce long-term morbidity, mortality, and cost by replacing open-heart operation(s) with transcatheter procedure(s). All of these innovations would require cooperation between interventional cardiologists and surgeons, and we acknowledge that demonstrating the benefit of this type of approach is a challenge. It requires analysis that considers a broader range of ramifications (including cost and quality of life) of clinical decisions to a more distant time horizon than is the current standard. Both of these factors represent an obstacle to testing these ideas in a conventional clinical trial. Clinical decision analysis, an objective explicit method that combines probabilities of outcomes with their various costs and benefits to model the results of a clinical decision, may help to study these problems. Combining data about probable cost, clinical outcomes, and quality of life over time into a single metric which can be compared between one or more strategy and to model those changes (even with incomplete data) over longer periods of time.

Remaining Obstacles to Broad Implementation of TVR

There remain significant obstacles to optimizing TVR technology: 1) reducing size of delivery systems, 2) maximizing the durability of the valve, and 3) the possibility of growth potential. First, the systems used to deliver the current transcatheter valves are large (22 French for the Melody TPV and 25 or 28 French for the two sizes of the Sapien valve available in the United States). Reports of major vascular complications were infrequent, with 8 events in 618 cases (1.1% with 95% CI: 0.5–2.3%)[15,17,19–21,30,40,46]. Minor vascular complications were not reported. Still, vascular complications represent a source of potentially modifiable morbidity, especially if we aim to perform multiple TVR procedures over patients' lifetimes.

Long-term durability of existent transcatheter valves remains to be determined. No studies to date have compared the long-term durability of transcatheter valves against surgically

implanted bioprosthetic valves. Recent series reporting TVR under high pressure conditions all suggest that transcatheter valves are more durable than anticipated[28,68]. Failure of analogous surgically implanted bioprosthetic valves occurs secondary to deposition of calcium resulting in stenosis and/or secondary tears resulting in progressive incompetence, in a process that combines immunologic and mechanical factors[69]. Homograft induces a humoral immunologic response, which has been correlated with the risk of failure in conduits[70,71]. The bovine-derived tissue used in Melody valves is pretreated to reduce immunogenicity, but no studies to date have assessed immunologic reaction and it is not clear whether this reaction can be modified in a meaningful fashion. Finally, current transcatheter valves have no potential for growth, which limits their utility in younger or smaller patients. Bioengineering of prosthetic valves, with biomechanical scaffolds populated with cells derived from the patient, thereby reducing immunogenicity and introducing growth potential has been an area of research in recent years and reviewed elsewhere [72,73], but remains remote at this time.

Quantifying comparative effectiveness and monitoring safety and efficacy outside of clinical trials

Technical challenges to the production of a transcatheter valve are not the only obstacles to be overcome to allow TVR to compete with SVR. Quantifying the comparative effectiveness of TVR versus SVR is a multi-faceted process. Recent studies of transcatheter aortic valve interventions (TAVR) provide a roadmap for this. The PARTNER trial demonstrated that a randomized clinical trial of SVR, TVR, and medical management is possible[74,75]. In addition, though it was aimed at assessing survival benefit, it also included measurements of morbidity and economic cost. Thus, investigators were able to demonstrate that, in addition to comparable clinical outcomes[74–76], TAVR was cost-effective and good value for subjects with severe aortic stenosis[77,78] and with inoperable aortic stenosis[79,80]. Inclusion of cost and quality of life as outcomes in studies of TVR in CHD is important because randomized clinical trials aimed at assessing mortality benefit is challenging due to low prevalence of disease, low baseline mortality, and a heterogeneous population, measurement of other relevant outcomes is important.

Another lesson from TAVR is the importance of prospective registry programs. Registries of TAVR from France, the United Kingdom, and Germany have proven invaluable in following monitoring safety and efficacy of these devices as they enter broad clinical practice[81–83]. This is especially important in congenital heart disease where the rare indications for these devices make single or small multi-center studies potentially uninformative and misleading. These registries should augment existent registries of congenital heart catheterization that collect hemodynamic data, procedural outcomes, and complications but as of yet do not provide longitudinal follow-up. The challenge of administering and funding these registries is an additional obstacle.

Conclusion

Returning to the question of whether TVR will replace SVR, we believe that the answer is “yes.” Transcatheter techniques will supplant open procedures for many indications and

have already done so for some. In adults with calcific aortic valve disease, transcatheter valve replacement of the aortic valve has been shown to be a safer and more cost-effective option for valve replacement in appropriately selected patients. In congenital heart disease patients with dysfunctional RVOT conduits or existent bioprosthetic valves, TVR appears to be safe and effective, and next-generation devices will soon be available to address dilated and distorted RV outflow tracts. Technical innovation is accelerating, and the range of devices is constantly increasing with hopes to expand beyond the context of the RVOT. A number of devices are currently being tested in animals for transcatheter mitral valve replacement[84–89], which represent another step towards supplanting SVR. Even at this early stage, the availability of TVR should reduce the threshold to intervene on dysfunctional valves and motivate change in surgical practice to facilitate future TVR. To truly supplant surgical valve replacement transcatheter valves must continue to demonstrate efficacy and safety along with improvements in delivery and durability.

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Key Points

- Transcatheter valve replacement with either the Melody transcatheter pulmonary valve or the Sapien transcatheter heart valve within circumferential conduits for RVOT dysfunction appears to be both safe and effective.
- Pre-stenting of conduit with bare metal stent reduces risk of fracture of the stent in which the transcatheter valve is mounted and may increase the functional lifespan of the valve. Other risk factors for fracture and reduced lifespan are close position to the sternum, recoil or compression of the stent, and (possibly) a residual gradient following deployment of the stent.
- Extended indications for transcatheter valve replacement have been explored. Valve-in-valve transcatheter valve replacement within failing bioprosthetic valves has been shown to be a safe and effective location for transcatheter valve deployment.
- Circumferential homograft conduits represent only a small fraction of dysfunctional right ventricular outflow tracts, and thus there is need for innovative use of current technology or development of new devices to address native outflow tracts. Alternatively, adaptation of surgical techniques, which recognizing the need for reintervention, facilitate transcatheter valve replacement may provide great benefit.
- Current obstacles to producing an optimum transcatheter valve are 1) size of the delivery system and 2) durability of the transcatheter valves.

Figure 1. Melody valve implantation in failed bioprosthetic valve

Angiograms before and after Melody valve deployment in a patient with a failing Sorin Mitroflow bioprosthetic valve (inset). Panel A shows free pulmonary insufficiency and stenosis due to calcification of the leaflets of the bioprosthetic valve. Panel B shows the Melody valve seated in the bioprosthetic valve. There is no residual pulmonary insufficiency or stenosis.