Percutaneous Pulmonary Valve Replacement

Indications, current practice, and the ongoing evolution of this technique.

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Since Bonhoeffer's original report over a decade ago,[1] transcatheter pulmonary valve replacement (tPVR) has progressed rapidly to establish itself as an acceptable therapy for right ventricular-to-pulmonary artery conduit and bioprosthetic valve dysfunction, with more than 5,500 valves implanted during this time frame. Detailed data collection through early clinical experience and clinical trials was necessary to prove the safety and efficacy of this approach. Evolving data from these studies have demonstrated the beneficial effects of tPVR in right ventricular (RV) volume reduction,[2] left ventricular (LV) filling properties,[3] exercise capacity,[4] and electrical remodeling[5]; hence, in many countries, tPVR is now preferable to surgery in selected cases.

However, ongoing challenges remain. With growing experience, practice has aimed to minimize both stent valve fractures and the potential for conduit rupture and coronary artery compression. Detailed assessments of the effects of the varied anatomy of the right ventricular outflow tract (RVOT) on potential transcatheter valve function have provided insight into the compressive forces of the chest on valve geometry and function.[6,7] Application of the technology has extended to smaller patients (< 20 kg) via hybrid approaches[8] and to native outflow tracts using a varied array of technical modifications to support valve stability.[9,10]

In the short term, extending valve longevity to ensure satisfactory outcomes must, at the very least, mimic the best surgical valve outcomes. Randomized trials are unlikely to be conducted, so periodic detailed comparisons may have to suffice. Ultimately, future aspirations should be focused on providing living autologous valve replacements with growth potential. The concept of a "living valve" delivered on a bioresorbable scaffold with the potential to grow has been explored in an animal model,[11] but much work is required before this reaches clinical application. This article focuses on current practices with tPVR, particularly in relation to indications, procedural challenges, and outcomes and touches briefly on the future potential of this technology.

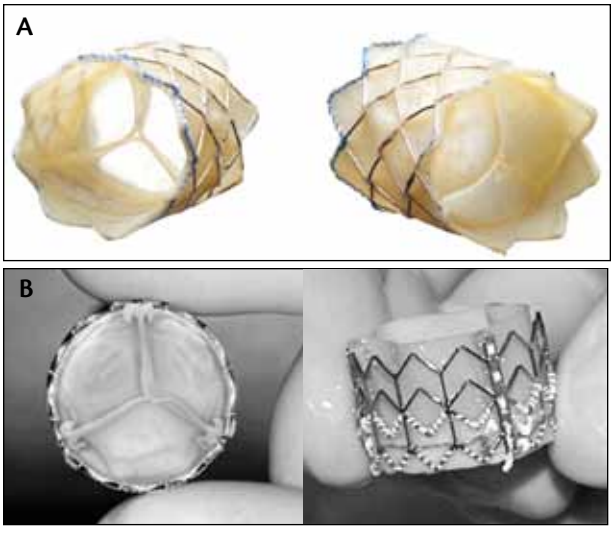

Figure 1. The Melody valve (Medtronic, Inc., Minneapolis, MN) (A) and the Edwards Sapien valve (Edwards Lifesciences, Irvine, CA) (B) each seen in two different views.

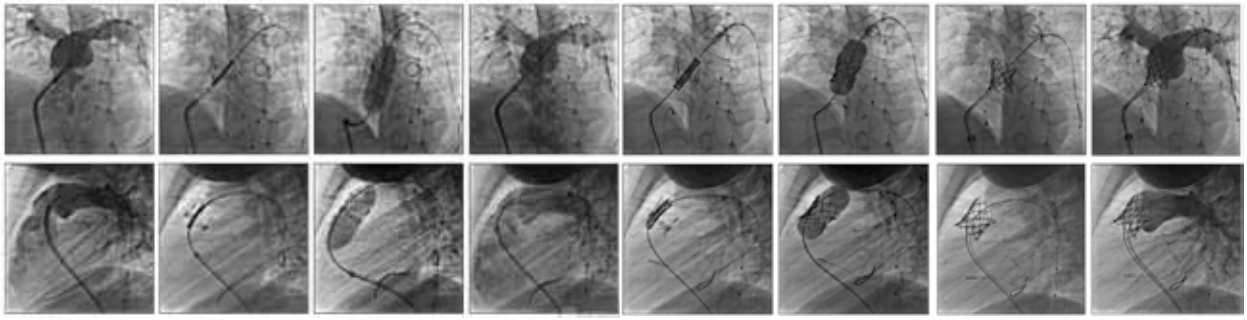

Figure 2. A series of fluoroscopic and intracardiac echocardiographic images demonstrating tPVR in a patient with a pre-existing bioprosthetic pulmonary valve (the Melody valve). Fluoroscopic images in both frontal (top panels) and lateral (lower panels) imaging planes from prestenting to valve deployment and postdeployment angiography. Reprinted from Kenny D, Hijazi ZM. Transcatheter pulmonary valve replacement: current status and future potentials. *Intervent Cardiol Clin.* 2013;2:181–193.

INDICATIONS

Defining objective parameters of when to replace the pulmonary valve in the setting of chronic pulmonary regurgitation has been difficult. Currently, surgical intervention is generally indicated with the following features:

- The patient has symptoms attributable to RVOT dysfunction;
- Indexed LV end-diastolic volumes > 150 mL/m^2 ± regurgitant fraction > 40%;
- RVOT peak instantaneous gradient > 50 mm Hg;
- RV dysfunction (RV ejection fraction < 40%);
- Moderate-to-severe accompanying tricuspid regurgitation.[12]

Guidelines for tPVR are less clear cut, with recently published guidelines for intervention in pediatric cardiac disease advocating tPVR in a patient with an RV-to-pulmonary artery conduit with associated moderate to severe pulmonary regurgitation or stenosis "provided the patient meets inclusion/exclusion criteria for the available valve."[13]

Thus, with two currently available valves (Figure 1), indications for tPVR are reflected in the inclusion/exclusion criteria of published clinical trials with these respective valves (Table 1).[14,15] In many instances, tPVR is performed in cases of mixed RVOT disease, and therefore, indexed RV volumes may not reach the previously mentioned parameters, as stenosis is the predominant factor. The contribution of outflow tract narrowing to symptoms should not be underestimated in this setting. In a study by Lurz et al,[16] patients with predominantly stenotic conduits demonstrated significant improvements in stroke volume with exercise after tPVR—changes not seen in those with predominant regurgitation.

Two other important considerations when considering intervention should be the risk for longer-term arrhythmia and progressive LV dysfunction. QRS duration ≥ 180 ms has been associated a 2.2-fold increased risk of sudden cardiac death during a 10-year follow-up study.[17] Transcatheter pulmonary valve replacement has been shown to significantly reduce QRS duration in those with predominant regurgitation and therefore may affect the arrhythmia burden in this patient group.

LV dysfunction has been seen in approximately 20% of adult patients with repaired tetralogy of Fallot, particularly in association with significant RV dysfunction.[18] The exact mechanisms underlying the LV dysfunction are not clear, but ventricular diastolic interaction, along with prolonged abnormal electrical remodeling, may be involved.[19] The impact of tPVR on LV dynamics has demonstrated small but significant increases in LV ejection fraction; however, more focused studies are required to specifically evaluate this.

PROCEDURAL CHALLENGES

Variability may exist due to operator preference, but a general assessment approach involves (1) baseline hemodynamics/angiographic assessment, (2) stiff wire positioning in the appropriate branch pulmonary artery, (3) assessment of coronary artery proximity to the RVOT, and (4) prestenting of the RVOT to prepare the conduit for valve delivery (Figures 2 and 3).

Significant RVOT morphological heterogeneity exists in relation to the original conduit size, degree of "shrinkage" and calcification, relationship of the conduit to the sternum, and proximity of the stenosis to the branch pulmonary arteries. Therefore, preprocedural preparation is essential to appropriate patient selection and determining the procedural strategy, which cannot be overstated. However, even with meticulous preparation, a number of predictable and unpredictable events warrant attention including coronary artery compression, conduit rupture, and stent fracture.

The potential for coronary artery compression by RVOT stenting or valve implantation was reported to

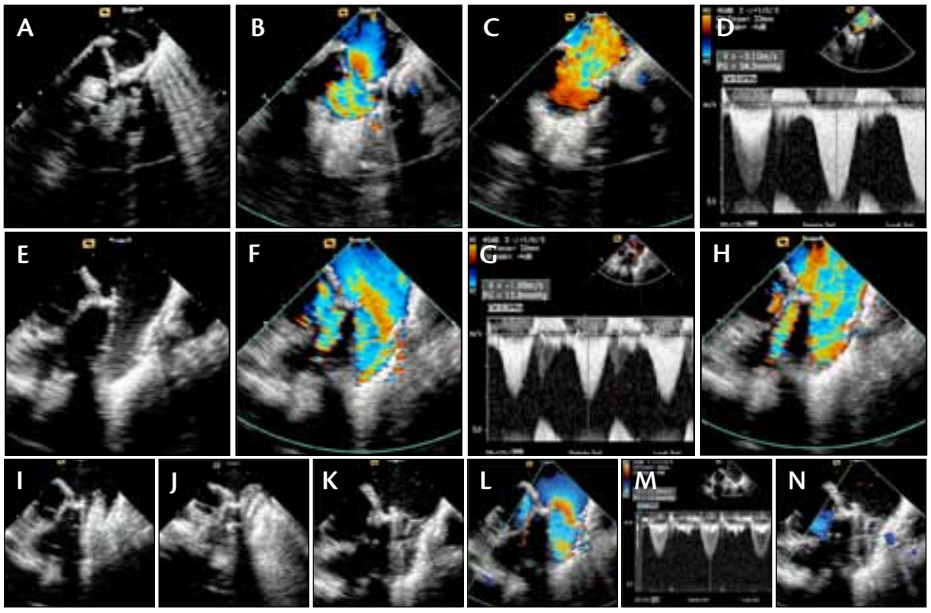

Figure 3. The lower panel of figures demonstrates the corresponding ICE images evaluating the RVOT prior to valve deployment (A through D) and following prestenting (E through H) and subsequent valve deployment (I through N). Reprinted from Kenny D, Hijazi ZM. Transcatheter pulmonary valve replacement: current status and future potentials. *Intervent Cardiol Clin.* 2013;2:181–193.

be 4.4% in the Melody US clinical trial.[14] Intraprocedural assessment of the relationship of the left coronary to the dilated RVOT is essential. This has provided challenges because aggressive balloon dilation of a heavily calcified conduit during selective coronary angiography may itself lead to conduit damage, and a staged strategy with compliant and noncompliant balloons assessing coronary artery proximity may be the most sensible approach.

The risk for conduit rupture has also been reported to be 4%, with many operators now choosing elective placement of a covered stent, if available, in patients with heavily calcified conduits. This approach is gaining momentum outside of the United States, as appropriate covered stents are freely available. However, within the United States, options are limited to self-fabrication of covered stents, emergency use of self-expanding stent grafts, and preprocedural application for use of balloon-expandable covered stents on a compassionate basis or participation in the PARCS (Pulmonary Artery Repair With Covered Stents) trial. The main challenge is that, as yet, no preprocedural predictive risk factors have been identified for conduit damage, and therefore, it is unclear when a covered stent may be necessary.

Stent fracture also remains an important event with the Melody valve, despite prestenting (5%–16%), and is the most common reason for reintervention. The extent of stent fracture is also relevant to clinical outcomes, with higher grades of stent fracture more likely to need repeat intervention. Attempts to understand the impact of the hostile environment of the stenotic RVOT conduit on valve function are ongoing, as loss of stent circularity and apposition to the anterior chest wall are also associated with an increased likelihood for reintervention.[7]

TABLE 1. PUBLISHED INCLUSION CRITERIA FOR CLINICAL TRIALS WITH BOTH THE MELODY AND SAPIEN VALVES

Inclusion Criteria for Melody[13]	Inclusion Criteria for Sapien[16]
Age ≥ 5 years/weight ≥ 30 kg	Weight > 35 kg
Original conduit diameter ≥ 16 mm	In situ conduit ≥ 16 mm and ≤ 24 mm
Echocardiographic RVOT conduit dysfunction: • Patients classified as NYHA class II, III, or IV: Doppler mean gradient ≥ 35 mm Hg or ≥ moderate PR • Patients classified as NYHA class I: Doppler mean gradient ≥ 40 mm Hg or severe PR associated with TV annulus z-score ≥ 2 or RVEF < 40%	≥ 3+ PR (TTE) or PRF ≥ 40% (MRI) With or without stenosis

Abbreviations: PR, pulmonary regurgitation; PRF, pulmonary regurgitant fraction; RVEF, right ventricle ejection fraction; TTE, transthoracic echocardiography; TV, tricuspid valve.

TABLE 2. PROCEDURAL OUTCOMES FROM CLINICAL STUDIES

Investigators	N	Success Rate	Procedural Complications	Fracture	Freedom From Reintervention (Follow-Up)
Lurz et al[20]	163	155 (95%)	7 (4.5%)	21%	70% (70 mo)
McElhinney et al[14]	136	124 (91%)	8 (6%)	22%	93.5% (12 mo)
Eicken et al[26]	102	100%	2 (2%)	5%	89% (12 mo)
Kenny et al[15]	36	33 (92%)	7[a] (20.5%)	0	97% (6 mo)
Butera et al[27]	63	61 (97%)	9[a] (14%)	16%	81.4% (30 mo)

[a]*Includes major and minor complications.*

OUTCOMES AND FUTURE DIRECTIONS

An initial clinical report from a group in London consisted of 59 patients, with successful valve implantation in all but one.[2] Three patients required acute surgical intervention due to stent dislodgment or conduit rupture. During a mean follow-up of 10 months, there was no mortality; however, device-related complications were seen in 25% of patients. These device-related complications included in-stent stenosis, referred to as the "hammock effect," in seven patients due to a lack of apposition of the valve to the stent. This observation lead to a change in device design in which the entire length of the bioprosthetic valve tissue was sutured to the stent. Stent fracture, which has continued to be clinically relevant for the Melody valve, was noted in seven patients, with one patient undergoing a second "valve-in-valve" procedure.

More recent studies with the Melody valve have demonstrated improved outcomes, with a reduction in adverse events. Further follow-up data from Bonhoeffer's group after their initial report demonstrated a reduction in procedural complications from 6% to 2.9%.[20] Recently, a multicenter United States clinical trial evaluating the Melody valve demonstrated excellent medium-term outcomes in 124 patients with dysfunctional RV pulmonary artery conduits. Freedom from Melody valve dysfunction or reintervention was nearly 94% at 1 year.[14] More recent concerns have been reported regarding the potential for endocarditis after Melody valve implantation, with reported rates of 2% to 3%.[21]

An alternative transcatheter pulmonary valve has also become available, achieving CE Mark approval in Europe and undergoing trials in the United States. The Edwards Sapien transcatheter heart valve has achieved widespread acceptance in the aortic position. A multicenter international clinical trial assessing short-term safety and efficacy in the pulmonary position demonstrated an effective reduction of RVOT gradient (27 mm Hg to 12 mm Hg; $P < .001$), with improvement in clinical symptoms and maintenance of pulmonary valvular competence at 6-month follow-up.[15] To date, stent fracture and endocarditis have not been an issue, but reported residual RVOT gradients after implantation have been higher when compared with the Melody valve.[22]

Although tPVR is rapidly evolving, much uncertainty exists because longer-term data are lacking. The initial benefits in RV remodeling occur within the first 6 months, and there are limited further changes in RV end-diastolic volumes or ejection fraction (as measured by MRI [magnetic resonance imaging]) at 1 year.[23] However, this is likely to mirror surgical data, and concerns should be targeted less toward continued RV remodeling than valve and stent durability. Potential benefits exist with a more rigid valve system in the RVOT because angular distortion of surgically placed RVOT conduits have led to not insignificant rates of early valve failure.

The largest contemporary dataset evaluating surgical valve dysfunction and reintervention in adolescents undergoing surgical PVR revealed a mean freedom from valvular dysfunction rate of 72% and a mean freedom from reintervention rate of 90% at 5 years[24]; attaining these follow-up results with tPVR is a shorter-term goal (Table 2). Another attractive option for tPVR is the potential for further valve replacement with the valve-in-valve technique, expanding the number of repeat percutaneous valve replacements to an as yet undefined number.

We believe that short-term aspirations should be focused on (1) perfecting and simplifying the current approaches, (2) further valve development to meet clinical needs, and (3) development of valves that may integrate and grow with the patient.

Consolidating and improving upon current techniques to minimize procedural risk and simplify follow-up protocols, as well as to reduce cost and inconvenience to the patient, are essential. Transthoracic echocardiography has been shown to provide a good estimate of the RV and RVOT indices in the setting of tPVR and is considerably

more accessible and less costly than postprocedural cardiac MRI, which has its limitations for imaging within an elongated stent complex in the RVOT.

The second endeavor should be aimed at further valve development to extend the technology to those with native RVOTs, as this is currently an off-label use. Although deployment of balloon-expandable stents in native outflow tracts has been described, size restriction on the currently available valves (Melody, 22-mm inner diameter [but has been delivered up to 24 mm]; Sapien, 26-mm outer diameter [29-mm Sapien valve has been implanted in Europe in the pulmonic position]) prevents deployment in more than 70% of patients in need of valve replacement. Clinical reports of a new valve sewn into a self-expanding nitinol frame have been described[25]; however, applicability of this technology within the anatomical and dynamic variability that exists within the RVOT remains questionable, and further modifications may be necessary. An early feasibility trial assessing this valve has begun in North America, and other self-expanding valve systems have been deployed in humans, but robust clinical data are required before longer-term applicability is assessed.

Other endeavors should focus on miniaturization of the delivery system, so that smaller children meeting the criteria for intervention may be treated percutaneously. The newer generation of the Sapien valve, Sapien XT, has a smaller delivery system of 16 to 18 F (NovaFlex). However, this system has not yet been tested for deployment in the pulmonary position. Also, newer lower-profile pulmonary valves are being evaluated in animal models. One such valve is the Colibri transcatheter heart valve system (Colibri Heart Valve, LLC, Broomfield, CO). This valve has been tested in a swine model, and it has a 12- to 16-F delivery system for valves ranging in size from 20 to 30 mm.

CONCLUSION

Although tPVR is preferable to surgery in a number of circumstances, significant device development is necessary before this approach becomes the dominant choice for pulmonary valve replacement in all patient groups. Ultimately, future aspirations must include efforts to merge these approaches with tissue engineering technologies to provide living autologous valve replacements with growth potential. The concept of a "living valve" delivered on a bioresorbable scaffold with the potential to grow with the patient is one of the final destinations of this exciting journey, although whether this goal is achievable in the near future is unclear. ■

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