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REVIEW

# Unmet Clinical Needs for Transcatheter Pulmonary Valves

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**Abstract**
A common feature of congenital heart disease is the presence of right ventricular outflow tract (RVOT) obstruction that can range from mild to severe and can lead to atresia of the pulmonary valve, in extreme conditions. RVOT abnormalities can frequently be corrected surgically or via interventional means. However, most of these patients will ultimately develop pulmonary valve insufficiency and eventual right ventricular dilation, which will require a pulmonary valve replacement at some point in their life to mitigate the detrimental effects of pulmonary valve regurgitation (PVR) on the right ventricle (RV). The evolution from the studies done by Philip Bonhoeffer to implant a pulmonary valve via transcatheter means, have provided a bedrock for transcatheter pulmonary valve replacement (TPVR). Yet, several areas of unmet need for a demographic of patients still exist. Here, we discuss the clinical unmet needs in children under 20 Kg and expand the use of hybrid and other TPVR approaches along with the current indications and contraindications for pulmonary valve replacement. The constraints and limitations from commercially available pulmonary valves will be discussed from a clinical standpoint. Finally, we explore the use of hybrid and periventricular delivery of transcatheter pulmonary valves in younger patients.

**Keywords** TPVR · RVOT · Melody valve · SAPIEN valve · Harmony valve

## Introduction

One percent of newborns in the U.S. and Europe are born with a congenital heart defect (CHD) [7, 15, 23, 47]. Among those, it is estimated that over 80% survive infancy, owing to improved medical and surgical care [42]. Thus, it is believed that at least 1 million children are currently living with some type of CHD in the U.S [18]. A common feature of cyanotic CHD is the presence of right ventricular outflow tract (RVOT) obstruction that can range from mild to severe and in its most severe form can present as pulmonary valve atresia. RVOT abnormalities can frequently be rectified by balloon valvuloplasty, RVOT stenting, surgical pulmonary valvotomy, and or transannular RVOT patch plasty [14, 51]. Most if not all of these patients will ultimately develop pulmonary valve insufficiency and eventual right ventricular dilation, which will require a pulmonary valve replacement at some point in their life to mitigate the detrimental effects of pulmonary valve regurgitation (PVR) on their right ventricle (RV) [31].

If not treated in time, correction of RVOT abnormalities in patients with tetralogy of Fallot (TOF), pulmonary valve atresia (PVA), truncus arteriosus communis (TAC) and double outlet right ventricle (DORV) may lead to PVR-induced RV failure [59]. It is a generally accepted fact that PVR should be addressed when it becomes clinically significant to avoid irreversible RV dysfunction [12, 21]. In infants born with severe RVOT obstruction, the stenosis often needs to be relieved within the first few days of life by either transcatheter or surgical means. The initial intervention ranges from balloon valvuloplasty of the pulmonary valve in patients with critical or severe pulmonary valve stenosis, RVOT stenting in patients with tetralogy of Fallot or radiofrequency perforation of an atretic pulmonary valve in patients with pulmonary atresia. Surgical pulmonary valvotomy or transannular RVOT patchplasty is also routinely performed in patients with tetralogy of Fallot in the neonatal period. Regardless of the initial transcatheter or surgical procedure,

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most if not all of these patients will develop PVR that can lead to progressive RV dilation, and ultimately RV failure.

As an attempt to address post-repair PVR, by transcatheter pulmonary valve replacement (TPVR), was first introduced in early 2000 to avoid the detrimental effect of progressive PVR. Philipp Bonhoeffer for the first time reported successful TPVR in an ovine model [9] and subsequently in a child suffering from concurrent PVA and ventricular septal defect (VSD) [26].

The rights to Bonhoeffer's valve were later acquired by Medtronic Inc. (Minneapolis, MN) and further developed to complete the design/development process and clinical studies to obtain regulatory approval [36]. This resulted in the Melody Transcatheter Pulmonary Valve™, which is delivered using the Ensemble Transcatheter Delivery System™, a 22 French-catheter (Fr) delivery system. Since receiving FDA approval in February 2010, thousands of patients around the world have benefitted from TPV placement. Despite the success of the currently available TPV, there are still many limitations present today, which we aim to discuss here.

## Indications and Contraindications

The indications for TPVR in children after relief of RVOT obstruction by either transcatheter or surgical repair are well described, but optimal timing of the procedure is not as clear cut when considering patient's age, weight, and the currently available TPV options. It a well-known fact that successful relief of RVOT obstruction in infants by either transcatheter intervention or surgical means eventually results in long-term morbidity due to RV volume overload secondary to progressive PVR [17, 38]. RV and LV dysfunction, in addition to potential life-threatening atrial and ventricular arrhythmias, and exercise limitation are among the most common consequences of RV volume overload [60]. In most cases, patients do not show any PVR-related symptoms until severe RV dilation and diminished RV function are established. For the above reasons, timely implantation of a prosthetic pulmonary valve is crucial to prevent the detrimental effects of long standing PVR. Prior to the availability of TPVR, surgical pulmonary valve replacement was the only option to remedy severe PVR in children [30, 58]. Today, TPVR exists as a minimally-invasive option to address clinically significant PVR. However, there are currently several limitations. Both existing FDA approved TPVs are delivered through a true 22 French Ensemble sheath (Melody valve) and a true 24 French Dry Seal long sheath (SAPIEN TPV), as their outer diameter profile [48, 57]. These delivery systems mandate a minimum weight of 20-25 Kg to minimize the risk of vessel injury. Another limiting factor is the size of available TPVs, with the 20 mm Melody valve and 20 mm SAPIEN S3 being the smallest commercially available valves. There have been cases where Melody valve has been used in children as small as 17 Kg but these cases were the exception given that the size of the femoral vein was a concern [34]. In general, there is currently no TPV available smaller than 20 mm for the patients between 8 and 20 Kg.

The ideal anatomy for current TPVR systems is a main pulmonary artery segment of at least 16 mm with a uniform diameter from the RVOT to its bifurcation (Fig. 1) [6]. This will avoid impinging of the stent into the pulmonary artery bifurcation. Pediatric patients generally have shorter main pulmonary artery segment and the distance from the pulmonary valve to the pulmonary artery bifurcation may not be long enough for placing a TPV. Waiting for the patient to achieve the desired weight can result in worsening of the PVR and increasing RV dilation and dysfunction.

Current contraindications for TPVR are mainly dictated by the patient's size (weight), which limit the passage of a relatively large delivery system [34]. Other situations in which a TPVR is contraindicated include a dilated RVOT and short main pulmonary artery segment [4].

## Commercially Available Devices

Three bioprosthetic valve systems have been approved for TPVR, the Melody transcatheter pulmonary valve by Medtronic, SAPIEN-3 valve by Edwards Lifesciences (Irvine, CA), and Harmony™ transcatheter pulmonary valve by Medtronic [43].

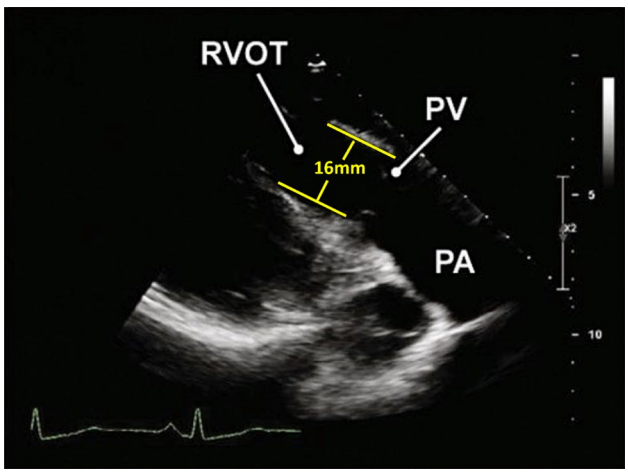


**Fig. 1** Echocardiographic image of RVOT showing the ideal minimum diameter for TPVR before bifurcation. This view is the parasternal short view

## Melody™ TPV

The Melody valve includes an intact bovine jugular vein fixed in glutaraldehyde and sutured into a Cheatham platinum Stent (NuMED, Inc.; Hopkinton, NY) (Fig. 2). Melody valve retains different leaflet morphology that are not all axisymmetric tri-leaflet as in the bioprosthetic valves, but it has been shown that the difference in variations does not affect function [8]. The stent measures 34 mm in length in its crimped configuration and 28–29 mm in length when expanded in full [36]. The valve diameter can expand from 16 to 20 mm for one size and 18 mm to 22 mm in the second size. The valve is delivered by a 22-Fr Ensemble® Transcatheter Teflon Delivery Sheath (Medtronic). A balloon-in-balloon (BiB) angioplasty system integrated within the Ensemble® has an outer diameter of 18, 20, or 22 mm. The concentric balloon system allows the valve to be repositioned after the inner balloon has been inflated. The tip of the balloon catheter is equipped with a blue nose cone acting as an introducer. Its proximal end interacts with the distal end of the sheath for a smooth contour.

Along with some limitations, several studies have shown that Melody valve is effective in relieving stenosis and in delaying surgical intervention to mitigate PVR [10, 27, 35, 40]. A well described complication is stent fracture [35] whose incidence was initially as high as 21% in patients who did not require pre-stenting [35]. The risk of bacterial endocarditis with an incidence rate of 2.3% per year per person is another major complication [40]. The incidence of endocarditis is significant at least during the first 3 years post-TPVR [1]. Overall, bovine jugular grafts are associated with a significantly greater risk for late endocarditis compared to the use of homografts [37] or pericardial leaflet tissue, as commonly used in transcatheter aortic valve replacement (TAVR) [32, 46].

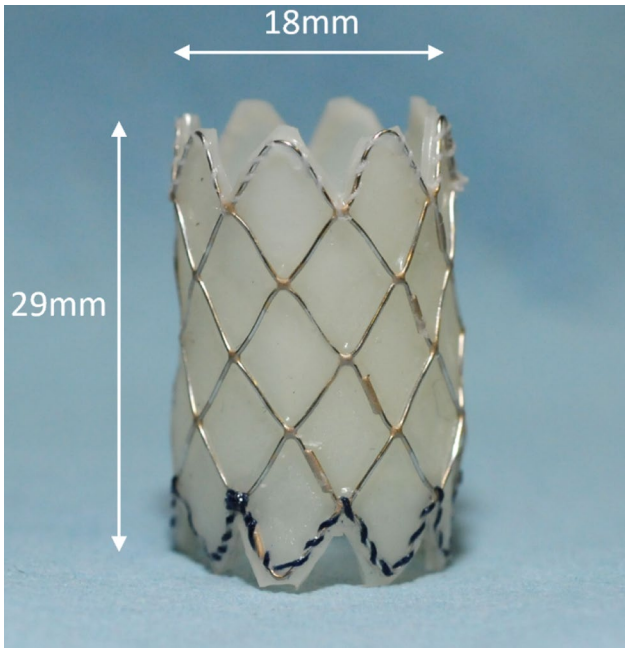


**Fig. 2** The Melody valve. The valve is hand crimped over the Ensemble II delivery system and can be viewed under fluoroscopy given its radiopaque markers

## SAPIEN XT and S3 Valves

SAPIEN valve was originally designed to mitigate aortic valve stenosis. The SAPIEN family includes balloon-expandable valves made of bovine pericardial leaflets sewn into a cobalt chromium alloy stent. The SAPIEN XT as in Fig. 3 is available in 4 different diameters of 20, 23, 26, and 29 mm. The valve is delivered with the Novaflex delivery system comprising of a sheath and a deployment balloon. Similar to Ensemble™, Novaflex contains a nose cone for smooth navigation through the vasculature.

Multiple groups have studied SAPIEN XT's safety and efficacy for treating RVOT obstruction [16, 19, 20, 29]. A 46-patient pilot study found a 93.5% procedural success rate with periprocedural complications and adverse events of 6.5% and 10.9%, respectively [20]. The rate of moderate or severe PVR had decreased from 76.1% at baseline to 5.0% in 30 days, and the calculated peak systolic gradient had decreased from 45.2 (SD ± 21.3) mmHg to 16.4 (SD ± 8.0) mmHg, with these values remaining low for up to 2 years [20]. After a follow-up of 4.6 ± 1.8 years, another study on 62 patients found a freedom of reintervention at 5 years in 89% (95% CI 74.8–95.6%) of the subjects. They found that reintervention was associated with the young age, a smaller tube-graft, a higher pulmonary valve gradient after

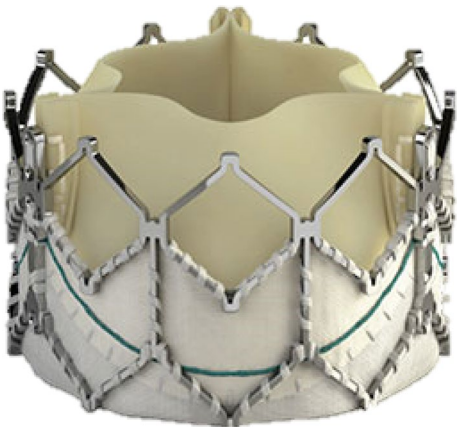

**Fig. 3** The SAPIEN XT. This valve has a low frame height to minimize damage and interference with the conduction system. It is mounted on the Novaflex system with radiopaque markers for determining valve positioning. Provided by Edwards Lifesciences

the procedure and a ratio of largest implanted stent diameter to invasive balloon conduit diameter over 1.35 [29].

The SAPIEN-3 (S3) (Fig. 4) is the third generation of the SAPIEN family approved by FDA in August 2020 for TPVR within a native RVOT, a RVOT conduit, or a bioprosthetic valve [39]. Similar to SAPIEN-XT, S3's stent is made of cobalt chromium with polyethylene terephthalate (PET) skirt and bovine pericardium leaflets sewn within. The S3 valve is available in sizes of 20, 23, 26 and 29 mm and can be over-dilated to fit a larger diameter landing zone, as needed. The S3 is delivered using the Commander™ delivery system with true outer shaft delivery sizes of 18 Fr for 20–26 mm valves and 20 Fr for 29 mm valve [48].

The S3's smaller sheath size of 24 Fr (14 Fr eSheath ID) for TPVR allows implantation in children as small as 20 Kg. Although Edwards Lifesciences states the size of the delivery catheter as 14 Fr expandable sheath, this is indeed the inner diameter [48, 57]. The pre-expanded outer diameters are 6 mm (18 Fr) for the 14 Fr expandable OD sheath and 6.7 mm (20 Fr) for the 16 Fr expandable OD sheath, respectively [48, 57]. The outer diameter of the expandable sheaths can be expanded to 24 Fr and 27 Fr based upon the circumstances and situations of the procedure. Yet, one of its drawbacks is the potential for damaging the tricuspid valve due to the S3 valve's delivery system and/or uncovered state during delivery [54]. Additionally, given that the Commander delivery system is designed for TAVR to maneuver the single curve of the aortic arch, the winding path to the RVOT for stent placement can be challenging [49]. For the above reasons, most interventionalists deliver the SAPIEN S3 TPV through a Gore Dry Seal Sheath (22–24 French sheath) that limits its use in patients smaller than 25 Kg. Despite these challenges, the S3 valve has seen positive outcomes in TPVR space. A 2-year follow up study of 82 patients found good short-term hemodynamics and functional outcomes with only one case of prosthesis dislodgement, one conduit perforation, and two cases of valve thrombosis [22]. Shahanavaz et al., studied 601 patients implanted with the SAPIEN 3, and found 10% experienced serious procedural adverse event, with 1.7% experienced tricuspid valve injury, and 4.5% experienced valve or stent embolization or significant malposition [52].

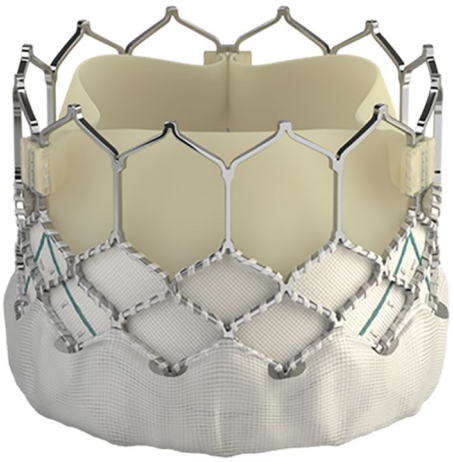

**Fig. 4** The SAPIEN-3 valve (S3) before mounting on the Commander™ delivery system. The valve includes three radiopaque markers indicating the middle of balloon deployment. Its integrated Flex Catheter has improved operator's navigation given the increased flexibility of the catheter. Provided by Edwards Lifesciences

## Harmony Valve

Introduced by Medtronic in 2021, Harmony valve is a self-expanding Nitinol stent with sutured polyester cloth covering and porcine pericardium valve (Fig. 5). The device received FDA approval TPVR in March 2021 for treating pediatric and adult patients with severe pulmonary valve insufficiency who have a native or surgically repaired RVOT. Harmony valve is available in 22 mm and 25 mm diameter sizes with flared inflow and outflow ends to conform and secure the valve to the RVOT. The Harmony valve is equipped with a fully sheathed Harmony Delivery Catheter,


**Fig. 5** Harmony Valve in 25 mm (**A**, **B**) and 22 mm (**C**), each with flared inflow and outflow ends. The large, flared inflow and outflow ends allow for a range of pulmonary artery sizes

which delivers the stented valve in one step without the need for pre-stenting with a balloon-in-balloon.

An analysis of 12 patients showed 100% acute success with no paravalvular leak according to echocardiography 1-month post-TPVR [5]. Three-year outcomes from the Harmony Native Outflow Tract Early Feasibility Study on 20 patients found no mortality, stable Harmony position, good valve function and absence of moderate to severe paravalvular leak [5]. The FDA recalled the Harmony valve in 2021 due to the possibility of the bond holding the capsule at the end of the Harmony Delivery Catheter breaking during TPVR. The capsule bond break could result in embolization or occlusion or other damage to the blood vessels at the time of the procedure [13]. Modifications have been made to the Harmony valve, specifically to its outer shaft assembly manufacturing process [44, 45]. By the end of February 2023, Medtronic relaunched Harmony valve within the U.S. Market. Clinical studies with the updated changes to Harmony valve are currently underway.

## Constraints and Limitations of Current Generation of TPVR

The leading commercial valves, Medtronic's Melody Valve and Edward Lifesciences' SAPIEN 3 Valve, each completed their FDA-mandated clinical trials detailing their complication rates. The Melody IDE trial was a long-term trial from 2007 to 2020 in which 150 patients received the valve with 6% complications and 11 deaths in total [24]. Five deaths were due to endocarditis, respiratory failure, acute hydrocephalus cerebral edema, arrhythmias and septic shock unrelated to endocarditis [24]. The COMPASSION trial for SAPIEN 3 enrolled 69 patients with a complication rate of 5% with no deaths [25]. Here, we discuss the important adverse consequences of the current TPVR systems. This information is also summarized in Table 1.

### Infective Endocarditis

Endocarditis is an inflammation of the heart valves and heart chamber lining usually due to presence of bacteria. Implantation of a bioprosthetic TPV within the pulmonary valve annulus increases the possibility of endocarditis. The Melody valve has had an annual endocarditis rate at 2% per patient-year [24]. The leading cause of mortality in the Melody IDE trial was reported as endocarditis in 5 out of the 11 deceased patients, making it the most common cause of death at the 10-year evaluation period [24]. SAPIEN 3 has had a 2.9% incidence at 3 years [25]. The clinical trial for the S3 valve involved the use of the ongoing COMPASSION S3 trial studying the safety and effectiveness of S3 in patients with RVOT conduits. Three patients within 3 years of the COMPASSION S3 trial experienced endocarditis [25]. It should be noted that the Melody valve has had a longer follow-up period and many more patients have received this valve compared to the SAPIEN 3. Therefore, it is necessary to consider more time for endocarditis risk before drawing any conclusion comparing the two valves.

### Stent Fractures

Stent fractures may occur to valves post implantation and is a common reason for reintervention. The pulmonary annulus and RVOT are muscular structures, which may exert extensive radial force capable of fracturing a stent. Risk factors for stent facture are higher pre-and post-procedural RVOT gradient, smaller angiographic conduit diameter, and stent compression and deployment [2]. These situations occur more frequently in valves positioned under or proximal to the sternum. The use of pre-stenting to provide stable housing for the TPV has been shown to reduce the incidence of stent fracture [11].

The Melody valve has a known issue with stent fracture with an incidence of 4.4 per 100 patient-years [50], which can lead to re-intervention. In a 10-year follow-up for Melody IDE trial, 23 patients had a major stent fracture in which 20 having no pre-stent placement and the remaining 3 had pre-stent [24]. Given that the SAPIEN 3 is made of cobalt-chromium and is shorter than Melody's platinum-iridium frame, the clinical trial data shows that SAPIEN 3 is less prone to fracture. Thus far, no case of stent fracture has been reported for SAPIEN 3 [25].

### Migration

Migration or embolization of the valve is rare, but few cases were reported for both the Melody and SAPIEN 3

**Table 1** Summary of incidence rate of adverse effects with the current TPVR devices within the U.S market

| Summary of incidence rates in pulmonary valve | | |
|---|---|---|
| Adverse events | Melody rate | SAPIEN 3 rate |
| Infective endocarditis | 2% per patient-year [24] | 2.9% at 3 years [25] |
| Stent factures | 4.4% per 100 patient-year [50] | No report cases [25] |
| Migration | 4% [33] | 3.2% [52] |
| Tricuspid valve injury | No reported cases | 3% [52] |

valves. If during placement the valve recoils or if it is not correctly implanted within the pulmonary annulus, its movement may affect blood flow. For Melody valve, pre-stenting is used to minimize the risk of migration and stent fracture. However, SAPIEN valve does not require pre-stenting [55]. Some studies have argued that the outer surface of the SAPIEN valve provides a secure grip for the valve to remain in pulmonary annulus position and prevent paravalvular leak [55]. Though, COMPASSION trial reports migration in 2 patients [25]. Shahanavaz et al. have found a 3.2% rate of valve embolization with the SAPIEN valve [52]. Martin et al, reports a 4% embolization rate for Melody valve, which necessitated surgical stent retrieval or repositioning. [33].

### Injury to the Tricuspid Valve

Injuries and damage to the tricuspid valve may occur during TPVR commonly due to the delivery catheter or uncovered stents [52, 54]. Damage to the valve typically requires surgical intervention and repair. It has been reported that S3 valve predominately leads to tricuspid valve injuries due to its uncovered delivery system, which is its most significant adverse event [52, 54]. A study by Shahanavaz et al. found a 3% incidence rate for tricuspid injury due to both SAPIEN S3 and XT valves' implantation [52].

### Predicting Coronary Artery compression

Pre-procedural CT to determine coronary artery anatomy and relationship to the RVOT conduit can be performed to aid in decision making for TPVR. The distance from the right coronary artery to the pulmonary tract is measured to calculate the risk of coronary artery compression (CAC). Thresholds of less than 2 mm were evaluated to be high risk, between 2 mm and 5 mm was intermediate risk, and greater than 5 mm was low-risk [56]. An evaluation of 52 candidates for percutaneous pulmonary valve implantation (PPVI) where 30 underwent pre-procedural CT found intermediate to low coronary artery compression risk [56]. Balloon inflation testing was conducted on 25 patients to verify the risk of coronary artery compression using CT in the right coronary artery (RCA). The size of the inflated balloon deployed during pre-procedural CT was compared to the final size of the deployed valve in PPVI. The balloon in pre-procedural CT was found to be the same size in 14 patients, smaller in 9 patients and larger in 2 [56]. Six patients who underwent CT for PPVI were found to be high risk and excluded from PPVI [56]. Performance of the above procedures reduced the risk of coronary compression by preventing PPVI [56].

## Unmet Clinical Need

The SAPIEN family, Melody Valve and Harmony Valve have provided a minimally invasive treatment for pulmonary valve dysfunction in adults and children. Yet, these products cannot be used in all patients with native or surgically repaired right ventricular tract obstruction. These valves are designed for patients weighing 20 Kg or greater. Waiting for the patient to gain enough weight to be eligible for a TPVR only increases the possibility of RV dilation. Although there is not a recommended consensus for when to perform a TPVR, the rate of TPVR in children in the U.S. has dramatically increased between 2004 and 2012 [41]. Placement of a Melody TPV at a younger age has been associated with shorter time to reintervention. As well, it was found that the Melody valve durability was comparable to surgical conduits [3]. TPVR procedures studied in children under 20 Kg have been successful in 84% of cases. However, vascular injury and compromise due to the 22 Fr delivery system is unknown [35]. Berman et al. concluded that similar acute and short-term hemodynamic outcomes in older and larger populations can be achieved in patients smaller than 20 Kg [7]. They recommended a vessel size requirement to be defined for smaller patients [7]. These studies show that TPVR can safely be performed in patients less than 20 Kg. Despite the higher reintervention rate in pediatric patients, there may be important advantages to early intervening on conduit stenosis and regurgitation given that the higher risk of reintervention in children has been found multifactorial [3].

With the increase in rate of TPVR, there is clearly an unmet need for TPVR in smaller children weighing less than 20 Kg. These children have small vasculatures that may not accommodate the current large delivery systems. Additionally, given that children will continue to grow, an implantable pulmonary valve must accommodate for the child's growth.

Two developing TPV solutions addressing this need are the Low-force Expanding/Adaptable Pediatric (LEAP) valve and IRIS valve. Developed by Draper Labs, the LEAP valve is implanted to grow with the patient with the ability to passively expand from 7 to 14 mm in diameter [28]. The valve uses mechanical adhesion to tissue (MANTIS) technology to reduce the complexity of soft tissue and metal interaction [28]. A multicenter study is ongoing to determine the safety and efficacy of the valve in an animal model. The IRIS TPV is being developed by our group, which offers a growth accommodating valve solution through one time balloon expansion. The IRIS valve size accommodates growth in a diameter range from 12 to 20 mm. The valve's leaflet design derives from origami

for improved coaptation and uses a 12 Fr delivery catheter system to minimize damage to the small vasculatures. The IRIS Valve is currently undergoing animal studies, with computational and in vitro hemodynamic studies to follow.

### Hybrid and Periventricular Delivery of TPV in Smaller Patients and Children

Alternative methods of TPV delivery for smaller patients and children should also be considered when standard methods of TPV delivery are not possible. While surgical pulmonary valve replacement remains the gold standard, there are advantages to TPVR that could provide benefit to smaller patients. The hybrid delivery approach entails cooperation between the cardiothoracic surgeons and interventional pediatric/adult congenital cardiologists to help identify patients who are generally smaller and who have size limitations that preclude use of the larger delivery sheaths required for standard TPVR. In addition, these patients may have access limitations from prior catheterization procedures including femoral and internal jugular vein obstruction or challenging anatomy (markedly dilated RVOT) that can prevent successful delivery of TPVR. The hybrid approach is usually performed through a small median sternotomy incision after which purse strings are applied in the right ventricular anterior wall. Together, the interventional cardiologist and the cardiothoracic surgeon will then utilize a percutaneous approach to puncture the RV and pass a guidewire under fluoroscopic guidance across the RVOT into either the right or left pulmonary artery. A delivery sheath is then advanced into position through which the TPVR is delivered. The advantages of this approach are bypassing of the tricuspid valve thereby minimizing injury to the tricuspid valve and ease of delivery without having to traverse either a severely dilated or stenotic RVOT. After confirming proper position of the valve, the delivery sheath is removed and the stay sutures are tightened and the puncture site in the RV anterior wall is repaired. The advantage to this procedure is avoiding cardiopulmonary bypass and shorter procedure and hospital stay times [53]. The use of the hybrid approach should be part of the armamentarium of all congenital heart disease programs that take care of patients of all ages with congenital heart disease.

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