Transcatheter Valve Replacement for Right-sided Valve Disease in Congenital Heart Patients ☆

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ABSTRACT

Pulmonary and/or tricuspid valve dysfunction is common among individuals with congenital heart disease, and surgical intervention often carries prohibitive risks. Transcatheter valve replacement (TVR) of the right-sided cardiac valves has become a viable treatment option over the past two decades, while continued technological development aims to broaden its applicability to an even larger portion of those with repaired congenital heart disease. To date, two transcatheter valves have been approved for use in patients with dysfunctional right ventricular to pulmonary artery conduits as well as those with failing pulmonic bioprosthetic valves, and are also used off-label in the "native" RVOT and within surgically repaired/replaced but failing tricuspid valves. TVR has demonstrated comparable safety and short-term outcomes to that of surgical valve replacement. This article aims to review current available devices, focusing on their safety, efficacy and on and off label usage, while briefly describing some of the emerging devices and novel procedural techniques that will likely lead to significant expansion of transcatheter treatment of right sided valve disease in the future.

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Introduction

Congenital heart disease (CHD) is the most common congenital malformation, with an incidence of nearly 1%.[1] Dysfunction of right-sided heart valves is common in CHD patients, but unfortunately these patients are often challenging surgical candidates because of extensive prior surgical interventions. Technology is rapidly advancing in the field of transcatheter valve replacement (TVR) and repair, giving greater numbers of patients alternative therapeutic options. This paper will review the current state of transcatheter valve replacement for the pulmonic valve and transcatheter repair/replacement of the tricuspid valve (TTVR) as it pertains to patients with CHD. It will focus on patient selection, outcomes and complications, as well as potential new developments that will likely expand its applicability.

Pulmonic valve disorders

Dysfunction of the pulmonic valve or right ventricular outflow tract (RVOT) is not uncommon among patients with CHD. Early surgical intervention may be required including pulmonic valve dilatation or replacement, RVOT muscle bundle resection and transannular patch, or construction/implantation of a right ventricular to pulmonary artery (RV-PA) conduit.[2] Long term durability of these surgical repairs is variable and largely dependent upon both patient-specific (e.g. age at repair and underlying pathology) and intervention-specific (e.g. type of operation and material used) factors.[3–5]

RVOT dysfunction classically manifests as pulmonary valvular regurgitation, stenosis or a combination of the two, which ultimately leads to complications including right sided heart failure and cardiac arrhythmias.[6,7] Dysfunction usually results from structural growth secondary to somatic outgrowth, bioprosthetic stenosis, conduit anastomosis stenosis, conduit external compression, neointimal hyperplasia, calcification and aneurysmal degeneration.[8] The need for recurrent surgical correction has been linked to increased morbidity and mortality among this group.[9,10] Classically, reoperation was delayed if possible, but this approach risks the development of irreversible right ventricular dilatation and dysfunction.

Transcatheter pulmonary valve replacement (TPVR) was initially developed as a non-surgical alternative for the treatment of RVOT conduit dysfunction, to reduce the number of necessary open-heart surgeries. Since its first reported use by Bonhoeffer and colleagues in 2000, utilization has rapidly grown, and studies have demonstrated safety, clinical outcomes and costs that compares favorably to surgical intervention.[11,12] Currently approved indications for TPVR include functional limitation or symptoms in the context of a conduit with at least moderate stenosis or moderate pulmonic regurgitation. Recently, implantation within previously placed bioprostheses was also approved and new approaches continue to expand the eligible population[13] Most notably missing from approval are patients with "native" RVOTs following a surgical transannular patch and patients following surgical valvotomy or balloon pulmonic valvuloplasty, even though this group of patients represents the largest number of patients with RVOT dysfunction, far outnumbering patients with circumferential RV-PA conduits. In fact, it is estimated that only ~15% of all patients with RVOT dysfunction are currently able to be treated with TPVR. Consequently, newer, off-label use of these valves with modified implantation techniques tailored to the "native" RVOT have been reported, and newer devices designed specifically for the "native" RVOT are currently being studied in U.S. clinical trials or are already available for use in some countries.

Clinical presentation, indications, and patient selection

Long term pulmonary valve dysfunction results in progressive functional limitation, increased occurrence of both supraventricular and ventricular arrhythmia, and ultimately right sided heart failure with systemic consequences of venous congestion. Chronic pulmonary valvular insufficiency, resulting from either surgical conduit or bioprosthetic valvular degeneration, results in progressive volume overload. Compensatory right ventricular dilation leads to eventual systolic dysfunction. The presence of significant pulmonic regurgitation is a strong predictor of adverse outcomes within this group.[14,15] Stenosis of a surgical RV-PA conduit or bioprosthetic pulmonary valve results in compensatory ventricular hypertrophy ultimately leading to diastolic and eventually systolic dysfunction. Tricuspid valvular regurgitation (TR) often coexists, secondary to annular stretch produced by right ventricular dilation and remodeling. The arrhythmogenic substrate and end organ damage resulting from these changes place these patients at increased risk for morbidity and mortality, both from cardiac and non-cardiac causes.[16–18] Timing of surgical pulmonary valve replacement has historically reflected a careful balance between procedural risk and the consequence of irreversible dysfunction.[19,20]

Among the most recent major cardiovascular professional society guidelines, the authors of the recently revised 2018 American Heart Association (AHA)/American College of Cardiology (ACC) Guideline for the Management of Adults with Congenital Heart Disease provide the most specific recommendations for TPVR.[21–24] In individuals with repaired Tetralogy of Fallot, TPVR carries a Class I recommendation for relief of symptomatic pulmonary regurgitation that is at least of moderate severity (Level of Evidence B). TPVR also carries a Class IIa recommendation for preservation of ventricular size and function in asymptomatic patients with ventricular dysfunction or enlargement and at least moderate pulmonary regurgitation. Class IIb recommendations for TPVR are made in the setting of ventricular arrhythmia and at least moderate pulmonary regurgitation. TPVR may also be reasonable in patients with at least 2 of the following: mild or greater RV or left ventricular (LV) dysfunction, indexed RV end-diastolic volume (RVEDVi) ≥ 160 mL/m^2 or indexed RV end-systolic volume (RVESVi) index

≥80 mL/m², RVEDVi ≥ twice the indexed LV end-diastolic volume, stenosis with RV systolic pressure (RVSP) ≥ 2/3 of systemic pressure, and progressive objective reduction in exercise capacity. In patients with RV-PA conduits, TPVR carries a Class IIa recommendation when there is ≥moderate pulmonic stenosis or regurgitation with reduced functional capacity or arrhythmia. A Class IIb recommendation in favor of TPVR exists for patients with an existing RV-PA conduit who remain asymptomatic despite severe stenosis or regurgitation but have RV dysfunction or dilation.

Prior to these new recommendations, patient selection for TPVR mirrored the inclusion criteria of published clinical trials, which largely drew upon the available surgical pulmonary valve replacement literature.[25–28] The recommendations for surgical pulmonary valve replacement have largely guided those for TPVR; however, the generalizability of these criteria to the more heterogeneous group of patients whom may benefit from TPVR remains unclear. The 2008 AHA/ACC and the 2010 European Society of Cardiology (ESC) guidelines regarding surgical pulmonary valve replacement among those with repaired Tetralogy of Fallot have proven the most influential upon TPVR clinical trial design.[21,29] The two differ in some respects, but both consider 3 major categories of risk factors 1) historical elements such as patient age at repair, 2) electrophysiological markers, and 3) hemodynamic sequela of severe pulmonic regurgitation. The guidelines focus on right ventricular volumetric criteria and systolic function, significant tricuspid regurgitation (TR), significant RVOT obstruction, occurrence of arrhythmias, QRS duration and the presence of significant residual intracardiac defects.

Symptomatic severe pulmonic stenosis and/or pulmonic regurgitation are class I indications for surgical replacement. Both the AHA/ACC and ESC make specific recommendations for timing of surgical PVR in asymptomatic patients as there are identified threshold levels of dysfunction beyond which improvement following PVR may be limited.[30] These parameters have largely been determined via echocardiography, cardiac magnetic resonance imaging, and right heart catheterization. The 2008 AHA/ACC guidelines on management of adult congenital heart disease recommends surgical PVR in the asymptomatic patient with ≥ moderately increased RVEDVi, ≥moderate reduction in RV ejection fraction, peak pulmonary valve gradient (PPG) ≥50 mm Hg or RV/LV pressure ratio ≥ 0.7, severe pulmonic regurgitation, ≥moderate TR, symptomatic atrial tachycardia or ventricular tachycardia, and significant residual ventricular septal defect or aortic regurgitation defect.[29,31] The ESC recommends surgical PVR for RVEDVi ≥ 160 mL/m², progressive decrease in RV ejection fraction, PPG ≥80 mm Hg (4.3 m/s transvalvular velocity), severe pulmonic regurgitation, ≥moderate TR, QRS duration ≥180 msec, sustained atrial or ventricular tachycardia, or objective decrease in exercise cardiopulmonary functioning.[21]

There are currently two valves that are FDA approved for TPVR in the US, the Medtronic Melody Valve (Medtronic Inc., Minneapolis, MN) and the SAPIEN XT Valve (Edwards Lifesciences, Irving, CA). Both valves are currently approved for use within an existing circumferential conduit, and the Melody Valve was recently also approved for use within failed bioprosthetic valves.[32] Indication for use of both valves includes ≥ moderate PR ± mean RVOT gradient >35 mm Hg by transthoracic echocardiogram. The Melody Valve and its delivery system (the Ensemble Delivery System) were developed specifically for use in the pulmonary position, whereas the SAPIEN XT and its delivery system were originally developed for use in the aortic position, with expanded approval to the RVOT following completion of the COMPASSION Trial.[33] The newest generation SAPIEN S3 Valve and the Commander Delivery System are currently being evaluated in the COMPASSION S3 Trial for use in both RV-PA conduits and within bioprosthetic valves in the pulmonary position.

TPVR is not currently recommended for surgical RVOT conduits smaller than 16 mm in diameter or "native" right ventricular outflow tracts, including those who underwent previous surgical repair with a trans-annular patch. Off-label uses in each of these situations have been safely demonstrated in the literature and formal studies are currently ongoing.[34] Specific studies will be discussed later in this manuscript. Contraindications to TPVR include active infection, lack of appropriate central venous access, evidence of coronary artery compression or aortic compression resulting in aortic insufficiency during pre-deployment balloon dilation. Other relative contraindications include a history of recurrent infectious endocarditis and active intravenous drug use.

Comprehensive patient assessment is performed to identify the optimal timing of intervention and should include a thorough history and physical examination, electrophysiologic evaluation, functional imaging, and cardiopulmonary exercise testing to determine appropriate timing of intervention. Increased QRS duration in patients after Tetralogy of Fallot repair is independently associated with sudden death risk and is a useful adjunct in determining the need for intervention.[35] Ambulatory ECG monitoring allows for detection of sustained or non-sustained arrhythmias. Echocardiography is used for assessment of ventricular systolic functioning and determining severity of regurgitation/stenosis using Doppler. Quantitative echocardiographic measures of right ventricular function and size have been shown to be insensitive, and cardiac magnetic resonance imaging (MRI) has become the preferred method for this evaluation.[36] Cardiac MRI has increasingly been utilized in pre-intervention assessment given its ability to provide accurate quantitative information on biventricular size and function, blood flow measurements, myocardial viability, valvular functioning, and cardiovascular anatomy. Surrogate markers of right ventricular dysfunction including RV ejection fraction, both end diastolic and end systolic volumes, and regurgitant fraction have been widely adopted in both clinical decision-making and procedural prognostication.[19,35,37,38] Continued advancements in cardiac MRI will likely make it an even more invaluable part of pre- and post-procedural monitoring. As a complement to cardiac MRI, cardiopulmonary exercise testing (CPET) has proven to be a valuable tool for non-invasive evaluation of diminished myocardial reserve and early ventricular dysfunction.[39] This information has proven useful in determining the need for valvular replacement, as CPET measures can indicate whether observed hemodynamic and anatomic abnormalities contribute to reduced aerobic capacity. Additionally, CPET measures such as peak VO2, E/CO2 slope (ratio of minute ventilation to carbon dioxide production), and heart rate reserve have been shown to be predictive of post-operative mortality and freedom from re-intervention in the surgical PVR population.[40]

Available devices

Melody valve

The Melody Transcatheter Pulmonary Valve (Medtronic Inc., Minneapolis, MN) was developed from the initial device used by Bonhoeffer et al. for the first-in-human transcatheter pulmonic valve implantation (Fig. 1 panel A).[11,41] It was FDA approved with a Humanitarian Device Exemption in 2010, with pre-market approval in 2015. The device consists of a bovine jugular vein segment manually sewn to a bare metal platinum-iridium stent (NuMED INC., Hopkinton, New York). The Melody Valve is delivered using Ensemble Delivery System, which is a 22Fr delivery sheath, and is available with a 18, 20, or 22 mm diameter (see Fig. 2). It has also been reported to work effectively when delivered on a modified delivery system using a 24 mm balloon or when post dilated with a 24 mm balloon.[42]

SAPIEN valve

The Edwards SAPIEN XT Transcatheter Heart Valve (Edwards Lifesciences, Irving, CA) received FDA approval for use in failing pulmonary conduits in 2016 (Fig. 1 panel B). It is a tri-leaflet bovine pericardial tissue valve hand-sewn in a balloon-expandable, radiopaque, stainless steel stent available in 23 mm, 26 mm, and 29 mm diameter sizes
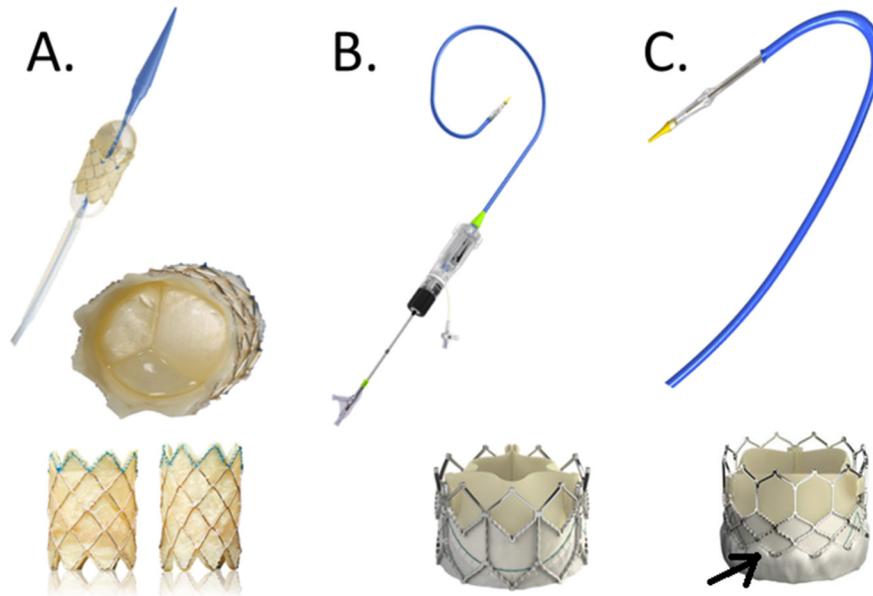
Fig. 1. A. Medtronic Melody valve and the Ensemble Delivery system. B. Edwards SAPIEN XT Valve and the NovaFlex Delivery System. C. SAPIEN S3 Valve and the Commander delivery system. The SAPIEN S3 Valve has the addition of a "skirt" (arrow) to prevent paravalvular leak.

(Fig. 2). It is delivered via the Novaflex Delivery System, which has an 18Fr profile, from a femoral approach. It can also be delivered via per-ventricular approach with the Ascendra Delivery System, and has a guiding catheter and a single balloon catheter. The valve must be manually crimped over the valvuloplasty balloon prior to deployment.[43] The third generation Edwards SAPIEN Valve, the S3, is currently being studied for approval for use within dysfunctional RV-PA conduits and bioprosthetic valves (see Fig. 1 panel C). It is deployed via the Commander delivery system, with a 14Fr or 16Fr profile, and offers an additional 20 mm diameter valve (see Fig. 2) (Compassion III trial; ClinicalTrials.gov Identifier: NCT02744677).

Outcomes

Procedural success

Procedural success with TPVR, defined as deployment of a transcatheter pulmonary valve with acceptable gradient (<30 mm Hg) and regurgitation (≤mild) without need for surgical conversion prior to discharge, has been shown to be favorable. A systematic review and meta-analysis of 19 observational studies by Chatterjee et al. included pooled patient data from 1044 cases and reported a mean valve deployment success rate of 96%.[44] Early and intermediate outcomes with both the Melody and SAPIEN Valves are similar, although outcome data of the SAPIEN Valve is limited, as the final results of the COMPASSION trial have not yet been published. Need for reintervention was noted at a rate of 4.4 cases per 100-person years of follow up (95% CI, 3.0–5.9).[44] Need for catheter-based reintervention was 2.7 events per 100-person years follow up (95% CI, 1.7–3.7), while surgical reintervention occurred in 1.7 cases per 100-person years (95% CI, 1.2–2.2). The most common reason for reintervention was re-stenosis of the implanted valve due to stent fracture (a complication that has been reduced substantially with pre-stenting stenotic conduits using bare metal stents), while 15% were for explantation and valve replacement due to infectious endocarditis.

Hemodynamic and functional outcomes

Favorable early outcomes have been consistently reported with immediate relief of RVOT pressure gradient and valvular insufficiency.[25,27,43] Other markers of hemodynamic improvement include measures of RV size and systolic function, TR, and left ventricular filling.[27,45–48] Various studies have shown significant functional improvement in New York Heart Association functional class and peak VO$_2$ during cardiopulmonary exercise testing following TPVR.[32,49] Although complete results of the

	Medtronic Melody®	Edwards SAPIEN XT™	Edwards SAPIEN S3™
Stent	Platinum iridium	Cobalt chromium	Cobalt Chromium
Valve	Bovine Jugular	Bovine pericardium	Bovine pericardium
Implant Diameter	18, 20, 22mm	23, 26, 29mm	20, 23, 26, 29mm
Expanded height	23-26mm	14, 17, 19mm	16, 18, 20, 22.5mm
Profile for delivery	22Fr (OD)	18Fr Sheath	14-16Fr esheath
Balloon for delivery	BiB balloon-pressure	Volume controlled balloon	Volume controlled balloon
Delivery system	Ensemble	NovaFlex, Ascendra*	Commander

*Ascendra sheath is for per-ventricular delivery

Fig. 2. Currently approved transcatheter pulmonary valve characteristics.
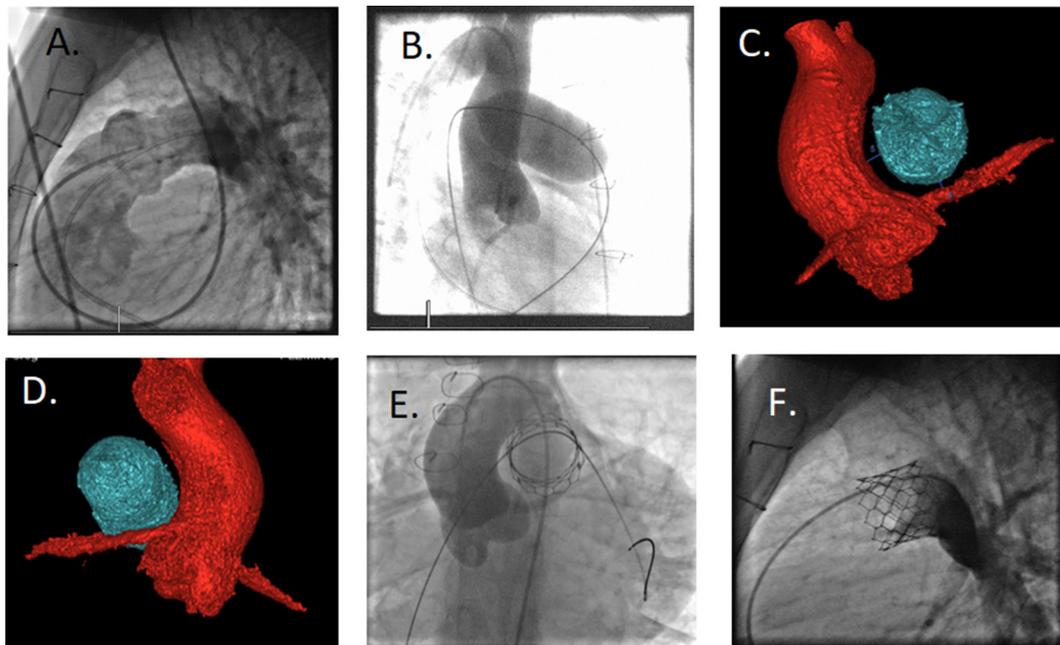
Fig. 3. Angiogram in lateral projection shows severe pulmonary insufficiency (A). Rotational angiogram of the aorta is performed during balloon inflation across the RVOT (B). 3-D modeling using GE AW Server 3.2 software allows for immediate bedside 3-d assessment that showed no evidence of coronary or aortic root compression (C-D). Following placement of a 26 mm SAPIEN S3 valve, there was no evidence of coronary compression (E) and no residual pulmonary insufficiency (F).

prospective COMPASSION trial have not yet been published, a retrospective analysis of a multicenter registry by Haas and colleagues demonstrated significant improvements in pulmonary insufficiency, RVOT stenosis, hemodynamics and functional status out to two year follow up after TPVR with the SAPIEN XT Valve.[50] Longer term outcomes out to 7 years following Melody Valve implant in 148 patients from the US Melody Valve IDE trial were reported in 2015.[26] Five-year freedom from reintervention was 76% with no significant change in RVOT gradient and no more than mild pulmonary regurgitation in all but one patient. Functionally, almost all patients remained NYHA Class I or II. Changes in procedural practice over the study period were noted with regards to use of a smaller delivery system, increased frequency of pre-stenting and post deployment dilation, all of which were associated with lower rates of stent fracture, recurrent stenosis, and need for reintervention among later recipients. Although favorable outcomes have been demonstrated beyond the early and intermediate periods, additional long-term outcomes are required, especially since procedural improvements will likely continue to improve outcomes.

Randomized trials comparing transcatheter and surgical pulmonary valve replacement do not exist. In a single center retrospective analysis, Sharma and colleagues [12] reported similar procedural success and freedom from re-intervention between surgery and TPVR. Surgical patients had longer lengths of hospitalization following procedure; however, transcatheter patients had higher total costs, attributed to the high cost of the device. Randomized trial data is needed to make any definitive comparison, as the surgical and transcatheter patient populations remain distinct based upon demographic and hemodynamic parameters, however these trials wo3be difficult to implement given the contrasting nature of the two procedures.

Complications

The Melody Valve IDE and post approval studies have shown that TPVR is a safe procedure, having a low procedural mortality of 1.5%.[51] Reported procedural-related deaths most frequently have been attributed to coronary compression, pulmonary artery obstruction, and/or ventricular arrhythmia.[44] Periprocedural complications have included surgical conduit rupture (3.2%), access site complication (2%), guidewire pulmonary

artery perforation (1.2%), and coronary artery compression (0.4%).[51] Rare serious adverse events reported include ventricular arrhythmia, device embolization, immediate device failure and complete heart block. Surgical conversion has been required in 3.4% of cases.[44]

Coronary artery and aortic root compression

Due to variability in cardiovascular anatomy among patients with CHD, approximately 5–7% of candidates are at risk for coronary compression after valve deployment.[52] Given the frequency of this potentially catastrophic complication, characterization of the coronary anatomy is required prior to valve deployment. Pre-procedural imaging via CT angiography or cardiac MRI may be utilized to identify individuals at high risk for coronary compression, including those with a single coronary artery origin or those with transposition of the great arteries. Furthermore, selective coronary angiography and/or aortic root angiography is performed with simultaneous balloon inflation in the RVOT at the intended landing zone for the transcatheter valve prior to placing the valve or a pre-stent. Three-dimensional rotational angiography and/or three-dimensional overlay using a previously performed cardiac MRI or CT angiogram are now frequently used to assist in assessment of coronary compression during balloon inflation across the RVOT (Fig. 3), as well as during valve deployment.[53] Evidence of coronary compression is a contraindication to TPVR, and these patients will require surgical management. Despite careful screening, post-marketing surveillance identified rare cases of late coronary compression up to three months post-procedure.[51] Additionally, aortic root compression resulting in significant aortic valvular dysfunction has been documented after TPVR in conduits and is an even more significant problem that needs to be screened for prior to off-label TPVR in the "native" dilated RVOT.[54,55]

RVOT/conduit tear

Surgical RV-PA conduits are prone to calcification and structural degradation over time, putting them at significant risk for tear or rupture during balloon and stent angioplasty. The incidence of conduit tear or rupture is 4.1% of reported cases, most of which are contained tears and not associated with hemodynamic compromise. Conduit
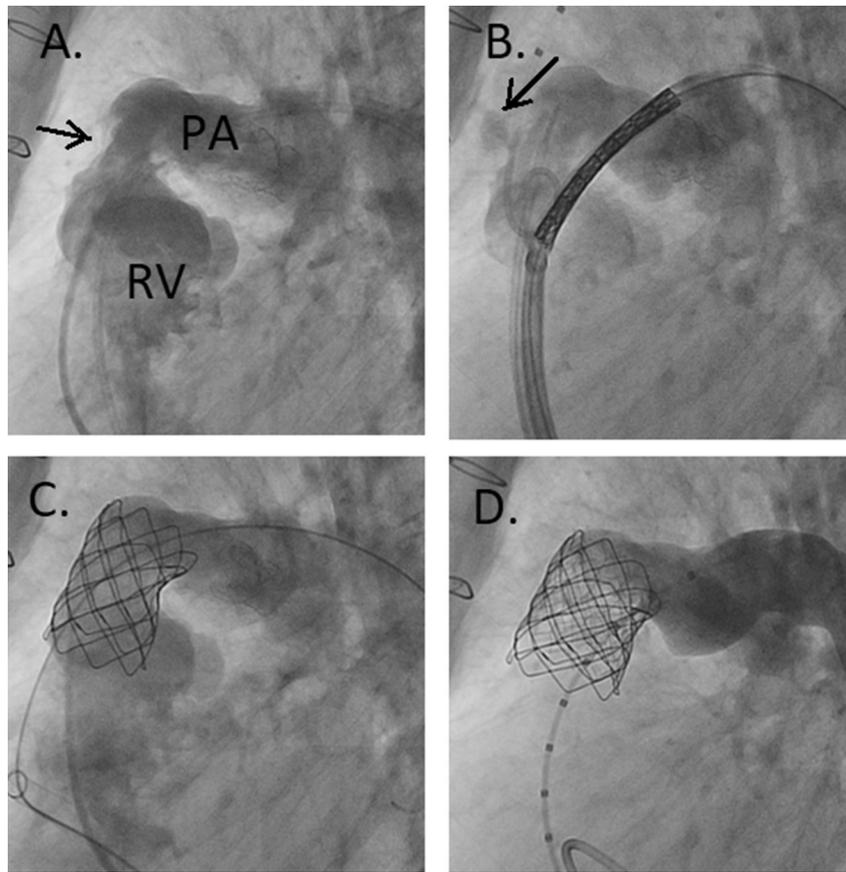
Fig. 4. Lateral projection right ventricular angiogram demonstrating severe RV-PA conduit stenosis (arrow) (A). Following balloon dilation to assess for coronary compression, there is a contained conduit tear (arrow) in the conduit (B). The conduit tear is completely covered after implanting a NuMed Cheatham Platinum Covered Stent and an additional Palmaz XL stent (C). Pulmonary angiography after implantation of a 26 mm SAPIEN S3 valve shows resolution of the conduit stenosis and no pulmonary insufficiency (D). PA = pulmonary artery; RV = right ventricle.

tears can usually be managed with the placement of covered stents (Fig. 4); however rare cases have required surgical intervention.[44] The use of covered Cheatham-Platinum stents for repair of tears that occur in the pulmonary artery during surgical conduit dilation is being formally evaluated in the Pulmonary Artery Repair with Covered Stents (PARCs) Trial (ClinicalTrials.gov Identifier: NCT01824160).

Stent fracture

Stent fracture was the most common indication for reintervention among the initial Melody Valve clinical trials, reported in 23.4% of cases.[51] Risk factors associated with stent fracture include younger age; higher pre- and post-procedural outflow tract gradient; smaller angiographic conduit diameter; stent recoil or compression after deployment and valve position directly below the sternum.[56] Nordmeyer and colleagues created a classification for stent fracture to better determine which events pose the greatest risk for eventual valve failure and need for reintervention.[57] Type I stent fractures indicate fracture of ≥1 strut without loss of stent integrity. These are most commonly observed early after the procedure and are not usually associated with adverse events.[57] Type I stent fractures may be managed conservatively with routine monitoring for progression. Type II stent fractures indicate loss of overall stent integrity. Type III stent fractures are those associated with separation of device fragments or distal embolization. Type II and III stent fracture often require re-intervention, either by surgical replacement or repeat transcatheter intervention, as they are associated with early conduit restenosis and valve failure.[57] Pre-stenting with one or more bare metal stents in the RVOT or conduit to serve as a landing zone for valve deployment has been shown to decrease incidence of stent fracture and prolong freedom from reintervention.[44,58] To date, no stent fracture has been reported with use of the Edwards SAPIEN Valve, although more follow up data is needed for this device.

Endocarditis

Bacterial endocarditis is a concern for both the Melody and SAPIEN Valves, and numerous articles have reported and evaluated this complication after TPVR. The pooled incidence rate of infectious endocarditis was 1.4 cases per 100 patient years (95% CI, 0.9–2.0) in a 2017 meta-analysis.[44] Cases with vegetation involving the implanted valve or new valvular dysfunction, cases requiring reintervention or device explanation, or cases causing death cumulatively occurred at a rate of 0.6 per 100-person years (95% CI,0.3–0.9). McElhinney and colleagues reported the combined results of 3 prospective trials and noted that most endocarditis cases did not involve the prosthesis and were responsive to medical therapy.[59] The organisms isolated have been diverse, representing both common (e.g. Streptococcus viridians and *Staphylococcus aureus*) and atypical (e.g. Coxiella burnetti) pathogens. Suspected risk factors include discontinuation of antithrombotic therapy, prior history of infectious endocarditis, smaller valve size, stenotic lesions, non-compliance with antibiotic prophylaxis, balloon post-dilation, interval non-cardiac surgery, and interval dental procedure.[60] The incidence of endocarditis after TPVR appears comparable to what is seen with surgical RV-PA conduits and bioprosthetic valves, although this has been debated.[61]

Emerging devices

Asymmetry and compliance of the "native" RVOT among CHD patients results in poor landing zones for valve placement. Poor device

apposition to the RVOT may result in significant paravalvular leak or device embolization. Several self-expanding stent valves have been developed to overcome these obstacles.[62,63] In 2010 Schievano and colleagues reported the first implantation of a self-expanding percutaneous pulmonary valve into a dilated pulmonary trunk, which would ultimately result in development of the Medtronic Native Outflow Tract Transcatheter Pulmonary Valve, later rebranded as the Medtronic Harmony Valve.[64] This device features an hourglass shaped design with larger diameters at the proximal and distal ends and a narrowed central portion containing the valve. The use of nitinol and its temperature-dependent shape memory properties aids in stabilizing the device within varied anatomies. The Harmony Delivery System is a 25Fr coil-loading catheter delivery system. Initial results of the Investigational Device Study involving 20 patients demonstrated excellent procedural success and safety with favorable acute device performance.[65] The Harmony Valve is currently undergoing a premarket efficacy trial (clinicaltrials.gov identifier: NCT02979587).

The Venus P Valve (Medtech, Shanghai,China) is a self-expanding stent valve available for TPVR in China and currently undergoing initial trials to support CE mark approval in the European Union and FDA approval in the United States. It is composed of a trileaflet porcine pericardial valve mounted on a covered nitinol stent frame, similar in design to the Harmony Valve, with valve diameters ranging from 18 to 34 mm and delivered via a 20-22Fr system. Early reports describe excellent procedural success in restoring short term pulmonary valvular functioning within the" native" RVOT, though these are limited to small case series.[66–69]

The Pulsta Valve (TaeWoong Medical Co., Ltd., Gimpo-si, Gyeonggi-do, South Korea) is another self-expanding, transcatheter stent valve designed for the "native" RVOT. It is comprised of a porcine pericardium valve hand-sewn to a porcine pericardium-covered nitinol stent. It has been successfully implanted in humans[70,71] and is currently in clinical trials to further assess safety and efficacy (Clinicaltrials.gov Identifier: NCT03110861).

The Altera Adaptive Pre-Stent (Edwards Lifesciences, Irving, Ca) was introduced in 2018 and was designed to internally remodel native RVOTs.[72] By internally remodeling the native RVOT, the device creates a rigid landing zone for eventual implantation of a standard balloon expandable, transcatheter pulmonary valve. The device has a symmetrical frame design with inflow and outflow diameters of 40 mm and a central diameter of 27 mm to create a landing zone for the 29 mm SAPIEN S3 Transcatheter Heart Valve, and fits through the 16Fr eSheath (Edwards Lifesciences, Irvin CA).

Given the larger patient population requiring transcatheter aortic valve intervention, developments in that field have far outpaced those within the pulmonary valve. Advancements in transcatheter aortic valve devices should lead to further improvements in pulmonary valve technology, such as the development of low profile delivery devices which may allow for more precise deployment and facilitate device recapture, subsequent repositioning or removal.[73] Similarly, new flexible delivery systems such as the Nucleus Balloon have allowed for oversizing of the SAPIEN XT Valve.[74]

The long-term durability of transcatheter bioprosthetic valves remains to be seen. Device longevity is largely limited by progressive degradation secondary to host immune response and dystrophic calcification. The use of tissue-engineered stent valves may overcome these limitations. Use of autologous stem cells to develop and successfully implant a tissue engineered pulmonary valve has already been demonstrated in a preclinical study.[75] Advances in tissue engineering and adaptive materials design may allow for pediatric prosthetic valves capable of adapting to surrounding cardiac structures as children age.

Expanding indications

Since the labelled indications for TPVR currently apply for <20% of CHD patients with RVOT dysfunction, off-label use has become widespread in patients with native RVOT that are aneurysmal as well as in

RV-PA conduits <16 mm at implant.[76] Meadows and colleagues reported the outcomes of TPVR following creation of a rigid landing zone for deployment via pre-stenting in 31 native RVOT patients.[77] Despite high procedural success (demonstrating the potential utility of TPVR for native RVOT dysfunction), stent fracture was common and posed a significant risk for developing RVOT obstruction. Successful TPVR in patients after tetralogy of Fallot repair with a transannular patch has been reported by several groups.[76,78] The development of hybrid procedures for surgical RVOT plication prior to TPVR and the development of new technologies including self-expanding nitinol stents, lower profile, large diameter valves, and transcatheter RVOT remodeling devices promise to further expand TPVR. Use of TPVR in the pediatric population has also been limited by the size and rigidity of the delivery systems, which risk development of vascular access complications. Given the trend towards earlier intervention, expanded use of TPVR in the pediatric patient population is desired. Several groups have now demonstrated appropriate safety and efficacy in small diameter right ventricular outflow tracts (<16 mm) and low weight patients (≤20 kg).[79–81] Additionally, more advanced techniques to address highly complex RVOT anatomies, such as pulmonary artery bifurcation stenosis, have been reported.[82]

Hybrid procedures

Advances in catheter-based technology may now facilitate improvements in conventional surgical valve implantation; utilizing smaller surgical exposures, limiting the use of cardiopulmonary bypass, and possibly decreasing associated morbidity. Efforts to percutaneously reduce the RVOT diameter prior to TPVR deployment have been successfully demonstrated.[83,84] Sonoski and colleagues compared conventional surgical pulmonary valve repair with a hybrid procedure where open pulmonary artery plication was followed by TPVR. Early surgical outcomes were similar and hybrid cases were able to be performed off of cardiopulmonary bypass.[85] Similarly, Phillips and colleagues utilized pre-procedural 3D modeling of the RVOT to perform individualized, hybrid off-pump procedures utilizing a limited sub-xiphoid incision and per-ventricular approach to modify the RVOT morphology and allow for successful TPVR.[86] While the long-term outcomes from these and similar hybrid procedures is unclear, the hope is that they can be used for individuals at high operative risk for whom TPVR is otherwise not possible.

Remaining obstacles

Transcatheter pulmonary valve technology has been demonstrated as a safe and effective non-surgical alternative in a subset of CHD patients with RVOT dysfunction. Delivery systems with lower profile and greater flexibility will surely expand the eligible population. Remaining obstacles include reduction of complications that require reintervention (e.g. stent fracture), increased long term durability of devices and defining appropriate timing for intervention. If TPVR represents a safer, cost-effective, and equally efficacious option in comparison with surgery, earlier timing of intervention will likely continue to be the trend. More study of emerging technologies including cardiac MRI and 3D CT modeling will be required to determine the appropriate clinical parameters for deciding on timing of intervention. Finally, ongoing advancements within the fields of tissues and materials engineering will be needed to improve device longevity and minimize thrombogenicity. Lastly, further study will be required to develop devices that may adapt within the growing pediatric patient, obviating the need for future reinterventions.

Tricuspid valve disorders

Tricuspid valve dysfunction is a frequent primary and secondary problem in CHD. Once an underappreciated phenomenon, the growing

recognition of its adverse physiologic effects has prompted a concurrent increase in surgical intervention.[87] It has historically received less attention than the other three cardiac valves in terms of research and guidelines for management.[88] Long considered the "forgotten valve," new data suggests severe TR is independently associated with poorer clinical outcomes and there has been increasing interest in percutaneous intervention.[89,90]

The prevalence of significant TR in the US is estimated at 1.6 million individuals[91] with 9% of these cases attributed to congenital disease,[92] although the true prevalence of tricuspid dysfunction among patients with CHD has likely been under-reported due to the heterogenous underlying etiologies, limitations in diagnostic assessment and uncertainty regarding impact on overall outcome. There are numerous causes of TR in patients with congenital heart disease. Primary dysfunction of the valve occurs with Ebstein anomaly of the tricuspid valve, but secondary causes of TR are considerably more common. These include postsurgical TR after AV canal or VSD repair, congenital heart disease resulting in a systemic right ventricle and consequent valvular dysfunction, right ventricular dilation due to right heart failure or chronic pulmonary insufficiency, and pulmonary hypertension due to left heart disease or pulmonary vascular disease.[93]

Surgical repair of severe TR is generally preferred to replacement owing to prosthesis durability issues, and is comprised of ring annuloplasty or banding to facilitate leaflet coaptation. Despite the poor prognosis associated with untreated severe TR, current guidelines favor valvular repair only in the setting of concurrent left sided cardiac surgery[31] and surgical intervention for isolated tricuspid valve disease remains uncommon.[94] Guidelines and criteria for intervention remain more subjective and less uniform across the major professional societies.[31,95] This trend has been preserved in patient selection for transcatheter interventions as well. Although most patients will benefit initially from tricuspid valve repair, the longevity appears limited. Twenty-five percent of patients experience recurrent, progressive valvular dysfunction within 5 years of repair.[96] Patients with recurrent tricuspid valve dysfunction following initial surgical intervention often have complex anatomy and multiple comorbid conditions, making them high risk surgical candidates. Although re-operative data is limited, perioperative morbidity and mortality are as high as 30% and 11% respectively.[97,98] Unlike tricuspid stenosis, for which percutaneous intervention were demonstrated over 25 years ago, catheter-based treatment of TR has been slow to develop. Given the advances in transcatheter valve replacement and the high risk of surgery, off-label use of current transcatheter valve technology for TTVR within failed bioprosthetic valves and annuloplasty rings has become an attractive option. The transcatheter approach to tricuspid valve replacement is typically performed from either the femoral vein or right internal jugular vein with a guidewire typically positioned in the distal pulmonary artery. Transesophageal or intracardiac echo can be used to assist in positioning and assessing valve function before and after implantation.

Valve-in-ring TVR

Tricuspid valve repair is associated with improved mortality compared to tricuspid valve replacement and is the preferred method of surgical management whenever feasible.[99] Repair is most commonly achieved through implantation of an annuloplasty ring or band to reduce the size of the annulus and improve leaflet coaptation. Ring annuloplasty has demonstrated overall good long-term outcomes[100]; however, one quarter of these patients will develop recurrent moderate to severe TR by five years.[97] The annuloplasty ring can serve as a rigid landing spot for bioprosthetic valve deployment. Mazzitelli and colleagues were first to demonstrate the feasibility of transcatheter valve placement with a SAPIEN XT Valve into a previously repaired tricuspid valve through a trans-atrial surgical approach, while Fassa and colleagues were first to demonstrate feasibility via transvenous approach, also with a SAPIEN XT Valve.[101,102] Subsequently, multiple small case

series have documented procedural success and favorable early outcomes with TTVR using the Medtronic Melody Valve and the Edwards SAPIEN XT Valve.[103–105] The largest series of transcatheter valve in ring replacement to date included 20 patients,[106] 10 of which had an underlying congenital heart defect. An Edwards SAPIEN XT Valve was implanted in 17 patients and a Medtronic Melody Valve in 3, with very good procedural success and safety. There was one valve embolization with successful retrieval and one valve malposition requiring placement of second valve, and all patients were free from significant residual regurgitation or stenosis post-procedure. However, some degree of paravalvular leak was a significant problem in this series, and was seen in 15 of 20 patients, requiring reintervention in 7 patients. During a median follow up of 12 months, there was one nonprocedure related mortality and one patient required surgical valve replacement. At final follow up, functional capacity (as assessed by NYHA class) remained improved in 70%, while initial post-procedural hemodynamic improvements persisted in all surviving patients. The high incidence of paravalvular leak highlights a limitation of TTVR within a ring, presumably caused by the incomplete circular structure of the semi-rigid annuloplasty ring. The incomplete portion of the annuloplasty ring is placed at the apex of the triangle of Koch to minimize atrioventricular node trauma. Unfortunately, this creates a distensible landing zone for the valve and predisposes to medial paravalvular leak. This open-ended structure may also predispose to future tricuspid annular dilation, given the absence of structural support at that location.

Valve-in-valve replacement for bioprosthetic tricuspid valve degeneration

Surgical tricuspid valve replacement is indicated in cases where the valvular apparatus morphology is unfavorable for surgical repair or in patients who have failed prior repair. Bioprosthetic valves are typically preferred over mechanical valves, as they do not require anticoagulation. Long term need for reintervention after surgical TV replacement is estimated at 1.5% per patient year, but this likely underestimates the true burden of bioprosthetic valve dysfunction, as reoperation for isolated tricuspid valvular dysfunction is rarely performed due to procedural risk.[107] Common reasons for bioprosthetic valve failure include structural degradation, calcification, pannus formation, endocarditis, and thrombus formation.[108,109] Due to low number of cases being performed at individual centers, most reports of transcatheter tricuspid valve-in-valve replacement have been limited to case reports and small single center series.[110–115] However, a recent report from the ViVid Registry, an international multicenter registry created to collect data on tricuspid valve-in-valve cases,[116] provides the largest patient experience to date with 152 cases of transcatheter tricuspid valve-in-valve procedures (94 patients with Melody Valves and 58 with Edwards SAPIENSAPIEN Valves). One hundred and five cases were performed via trans-femoral approach and 42 cases were performed via trans-jugular access. Eighty-seven (56%) of these patients had CHD, with most (47) having Ebstein anomaly. Procedural success occurred in 99% (150 of 152) of cases with good hemodynamics, significant improvements in TR and/or tricuspid stenosis and marked reduction in right atrial pressure. Five patients had residual valvular dysfunction immediately post-procedure and there was one procedure-related death due to hemopericardium. There were 17 late deaths that were not felt to be procedure-related or caused by valve dysfunction, reflecting the severity of illness in many of these patients. Ten cases required repeat intervention during follow up, 9 had surgical tricuspid valve replacement and one had a second transcatheter valve implanted. At a mean follow-up of 13 months, only 8 patients developed recurrent tricuspid valvular dysfunction, with most due to endocarditis (N = 4) (observed only following Melody Valves) or valve thrombosis. An additional report from the ViVID registry described transcatheter tricuspid valve-in-valve outcomes among only individuals with Ebstein's.[117] In this cohort of 81 patients, procedural success,

safety, and efficacy were similar compared to the more heterogenous registry population, with freedom from re-intervention of 80% at 36 months. In this study, risk factors for valvular dysfunction or need for reintervention included older age at implant and the presence of bi-directional cavopulmonary anastomosis reducing tricuspid inflow. Successful transcatheter tricuspid valve in valve replacement has also been reported with the Edwards SAPIEN S3 Valve.[118] An illustrative case of tricuspid valve-in-valve implantation with a Melody Valve using 3-D CT overlay guidance is demonstrated in Fig. 5. In summary, TTVR for failed annular rings or bioprosthetic valves seems to be a safe and effective alternative to surgical management of these patients and may be associated with improved outcomes, though no direct comparisons have been made. There have been no prospective trials assessing safety of the procedure, and therefore it remains an off-label use of transcatheter valves in the U.S.

Implantation within native tricuspid valve

TTVR within a native tricuspid valve presents several challenges including morphology, spatial orientation, character of the surrounding myocardium and proximity to conduction tissue. The large size and asymmetric, oval, non-planar shape of the annulus makes it difficult for existing circular bioprosthetic valves to achieve satisfactory apposition, and furthermore the valve shape is dynamic throughout the cardiac cycle.[119] The fragile, narrow tissue comprising the tricuspid annular shelf is also less favorable to valve deployment than the mitral valve, and the angulation of the valve annulus in relation to both the inferior and superior vena cava make catheter-based manipulation of the valve more difficult. The inter-patient variability in anatomy of the chordae tendineae, papillary muscles and the ventricular muscular bands also poses a procedural challenge in the absence of clear radiographic markers. Proximity of the atrioventricular nodal tissue, right coronary artery, and coronary sinus pose substantial risk for injury to these structures. Additionally, the thin walled right ventricular free wall is at risk for perforation by guide-wire or valvular strut. Furthermore, the presence of pacemaker or defibrillator leads, which are present in ~18% of this population, create another impediment.[120] Despite these challenges, Kefer and colleagues have reported successful TTVR within a native tricuspid valve using a 26 mm SAPIEN XT Valve within two covered CP stents that were first placed to create a landing zone.[121] Extra-corporeal membrane oxygenation support was required for the procedure due to patient hemodynamic instability during balloon inflation. There was a severe paravalvular leak initially, that resolved after a second SAPIEN XT Valve was implanted proximal to the first. At repeat echocardiography five months post-procedure, valve function remained intact without significant transvalvular gradient or regurgitation. There have been no other reports of transcatheter valve replacement within a native tricuspid valve; and until better options are available, this will likely remain a procedure used only for patients who are not considered to be candidates for surgical management.

Future valvular devices

Although TTVR with the current existing technology has shown promise, long-term data will be necessary to demonstrate its safety and durability. In the meantime, development of novel devices and adjunct technology remains ongoing. The GATE Tricuspid Atrioventricular Valved Stent (Navigate Cardiac Structures Inc., Lake Forrest, California) is a self-expanding nitinol stent containing an equine pericardium trileaflet valve made specifically for use in the tricuspid position. Its large outer diameter (sized 36 mm to 52 mm) and short profile (21 mm) provide better apposition than currently existing systems. Its design features a truncated conical shape to reduce valvular protrusion into the atrial and ventricular chambers, and its 12 annular winglets allow for enhanced radial force.[122] The first in human demonstration was reported by Navia and colleagues in 2017.[123] To date 16 devices have been implanted without early procedure-related mortality and have demonstrated good valvular function at 12 months follow up.[124,125] The GATE Tricuspid Atrioventricular Valved Stent is currently in use for compassionate care cases as sanctioned by Health Canada, European Health agencies and the U.S. FDA. While the initial results from this device are encouraging, clinical trials will be needed to determine efficacy and safety.

Heterotopic caval valve implantation

The first ever percutaneous valve implantation to address severe TR was one heterotopically placed into the junction of the right atrium and vena cava.[126] Instead of implanting a prosthetic valve into the anatomically correct position to restore the functional separation of the right atrium and ventricle, this approach places a valve or valves into the central venous system. Valves may be placed in the inferior vena cava alone or in the superior vena cava as well, depending upon anatomic factors and clinical symptoms. This approach does not seek to correct a dysfunctional tricuspid valve, but to alleviate the effects of the systemic venous congestion resulting from it. This approach is attractive, as it easier to navigate and avoids possible injury to structures of the right heart. However, it fails to improve right ventricular volume overload and systolic dysfunction. Caval valve implantation has been demonstrated with use of existing balloon expandable and novel self-expanding systems. The existing percutaneous valves that have been utilized in this fashion for off-label use are the Edwards SAPIEN XT and S3 Valves. The large diameter of the inferior vena cava precludes the use of the smaller diameter Melody Valve. Pre-stenting with a self-expanding stent is required
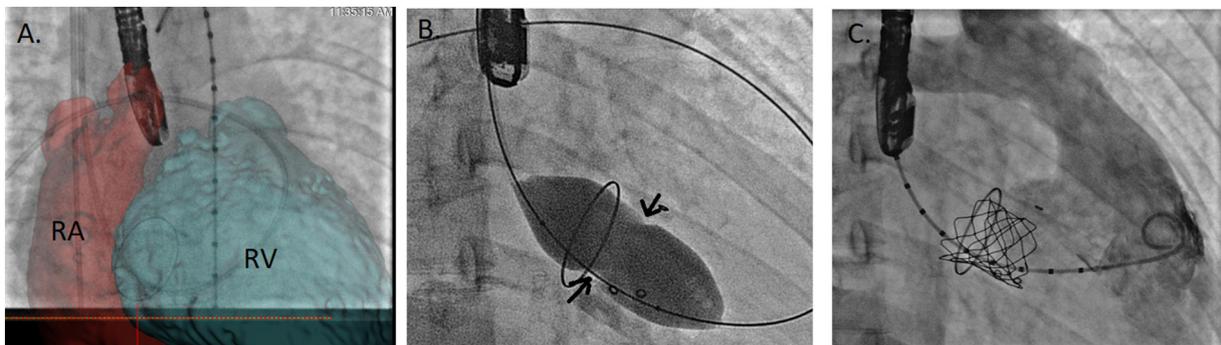
Fig. 5. Valve in valve transcatheter tricuspid valve replacement from right internal jugular approach. Pre-intervention evaluation with TEE showed moderate to severe tricuspid insufficiency and severe tricuspid stenosis. Pre-procedural CTA allowed for 3-D modeling and overlay to assist with placement of the valve (A). Balloon inflation across the bioprosthetic valve demonstrated a waist measuring 19 mm (arrows). A Medtronic Melody valve was successfully deployed on a 22 mm BiB balloon with the Ensemble II Delivery System and follow up right ventricular angiography shows no tricuspid insufficiency (C). TEE showed trace tricuspid insufficiency and trivial stenosis. RA = right atrium; RV = right ventricle.

to create a safe and semi-rigid landing zone prior to valve deployment. The SAPIEN XT Valve is currently the subject of study in two ongoing studies. First is the HOVER (Heterotopic Implantation of the Edwards-SAPIEN Transcatheter Aortic Valve in the Inferior Vena Cava for the Treatment of Severe Tricuspid Regurgitation) trial which is currently recruiting 15 patients into a prospective registry assessing procedural safety and short-term efficacy (clinicaltrials.gov; NCT02339974). The second is the TRICAVAL (Treatment of Severe Secondary Tricuspid Regurgitation in Patients with Advance Heart Failure with Caval Vein Implantation of the Edwards SAPIEN XT Valve) Trial, a randomized, open label study assessing cardiopulmonary exercise outcomes at 3 months of follow-up in those undergoing heterotopic SAPIEN XT caval implantation (clinicaltrials.gov: NCT02387697). Deployment of the larger diameter and latest generation Edwards SAPIEN S3 Valve has also been successfully demonstrated.[127]

The TricValve (P&F Products and Features GmbH:Vienna, Austria) is a novel, dedicated caval valve implant comprised of two self-expandable bioprosthetic valves designed for deployment into the superior and inferior vena cava. Its self-expanding design obviates the need for pre-stenting to create a landing zone. The device is comprised of two bovine pericardial valves mounted on a nitinol stent with sleeves covering the inside down to the leaflet to prevent paravalvular leak. The valve within the inferior vena cava protrudes into the right atrium with the valve located above the diaphragm in order protect against hepatic vein occlusion,[128] while the superior vena cava valve is mounted on a funnel shaped stent to fit the cavo-atrial landing zone. Lauten and colleagues reported a 92% success rate in implanting 6 patients with the TricValve and 18 patients with SAPIEN XT/S3 Valves.[129] Complete reduction of reverse caval flow was seen in all patients following successful valve implant. This was a study of compassionate use only in very sick patients, and mortality was high (24% during the index hospitalization); however, there were no reported procedure-related deaths. Valve migration occurred in two cases, which required surgical intervention. Symptomatic functional improvement, as measured by improvement by at least one NYHA heart failure class, was observed in 84% of patients at 12 months of follow up.

The early success of these devices has prompted development of other stented valves for use in the tricuspid position, such as the novel Tricentro System.[130] Although this method has clear benefits, it also has significant limitations. This includes the need for lifelong anticoagulation, given the low flow nature of the central venous location. Additionally, uncertainty regarding the long-term hemodynamic effect of this method has tempered enthusiasm and its widespread adoption. Hemodynamic concerns include the effects of ongoing right heart volume overload and lack of attempt to preserve right ventricular systolic function.

Emerging nonvalvular percutaneous technologies

Since current transcatheter valve technology has been inadequate for the native tricuspid valve, exciting emerging technologies are also aimed at tricuspid valve repair with development of devices that target the leaflets and tricuspid annulus. Transcatheter annuloplasty devices aim to address primary dilation of the tricuspid annulus with normal leaflet morphology. They include the TRIALIGN Device (Mitralign, Inc.: Tewksbury, Massachusetts), which addresses TR through reduction of tricuspid annular diameter by tissue plication and obliteration of the posterior leaflet. Encouraging initial results on its efficacy and safety were reported by Hahn and colleagues among 15 patients in the prospective, multicenter, single-arm study, the Early Feasibility of the Mitralign Percutaneous Tricuspid Valve Annuloplasty System, also known as Trialign (SCOUT) Trial (ClinicalTrials.gov Identifier: NCT02574650).[131] The ongoing Safety and Performance of the Trialign Percutaneous Tricuspid Valve Annuloplasty System (SCOUT-II) is currently underway to further assess the safety and performance of the system (ClinicalTrials.gov Identifier: NCT03225612). Another annuloplasty

device that acts to reduce the diameter of the tricuspid annulus is the Tricinch System (4Tech Cardio Ltd.; Galway, Ireland). This device acts to reduce the septo-lateral distance by placement of a coiled anchor into the tricuspid annulus. This anchor is then attached to a large diameter stent placed within the inferior vena cava. The tension placed upon the tricuspid annular component by the inferior vena cava stent reduces annular diameter. Two active prospective registries are underway to generate safety and performance data; the Clinical Trial Evaluation of the Percutaneous 4Tech TriCinch Coil Tricuspid Valve Repair System (ClinicalTrials.gov Identifier: NCT03294200) and the Percutaneous Treatment of Tricuspid Valve Regurgitation with the TriCinch System™ (PREVENT) (ClinicalTrials.gov Identifier: NCT02098200). The Minimally Invasive Annuloplasty System (Micro Interventional Devices; Newton Pennsylvania) reduces the tricuspid annular diameter through placement of self-tensioning anchors into the annular shelf. A thermoelastic polymer connects the two anchors to provide a retroactive force and thus reduce valve circumference. The Study of Transcatheter Tricuspid Annular Repair clinical trial is currently underway at multiple European centers.

The Cardioband Device (Edwards Lifesicences; Irvine, California) features an adjustable Dacron band implant delivered via 24-Fr transfemoral system. The band is affixed through the use of tissue anchors and novel tool to cinch the band and allow for a controlled reduction in annular area.[132] Initial safety and efficacy data was reported in the Tricuspid Regurgitation Repair with Cardioband Transcatheter System (TRI-REPAIR) (ClinicalTrials.gov Identifier: NCT02981953). Preliminary 30-day outcomes were reported at the 2017 *Transcatheter Cardiovascular Therapeutics Conference* and were comparable to the device's initial outcomes at the mitral position.[133,134] The Miipede IRIS system (Boston Scientific; Malborough, Massachusetts) is a similar device that features a retrievable, collapsible nitinol frame supporting a complete, semi-rigid annuloplasty ring. It has been demonstrated via surgical implantation and a transcatheter delivery system is currently under development.

Current leaflet coaptation devices include the Forma Repair System (Edwards Lifesicences; Irving, California), MitraClip (Abbott Vascular; Santa Clara, California), and the PASCAL System (Edwards Lifesicences; Irving, California). The MitraClip has been widely adopted for percutaneous treatment of mitral regurgitation, with a growing body of literature demonstrating comparable efficacy to surgery.[135,136] Given its widespread availability and established operator familiarity, it has become the most widely adopted percutaneous tricuspid valvular intervention, with demonstrated efficacy in multiple prospective registry trials.[137–139] Two clinical trials are currently underway to prospectively assess its utility. The Evaluation of Treatment with Abbott Transcatheter Clip Repair System in Patients with Moderate or Greater Tricuspid Regurgitation (TRILUMINATE), a prospective, single arm, multi-center study is aimed to evaluate safety and efficacy and effectiveness among 85 patients in Europe, Canada and the United States. Outcomes include echocardiographic TR reduction at 30 days and major adverse events at up to 5 years duration. A second trial, the MitraClip for Severe TR (TV repair) Trial has yet to begin recruiting, but will investigate procedural feasibility and 30-day outcomes in selected, highly symptomatic patients with severe TR. Advancements in device design and procedural technique, such as edge-to-edge repair and the use of advanced imaging techniques, hope to improve outcomes and overcome the system's limitations at the tricuspid location.[140,141]

According to Edwards Lifesicences, the FORMA system is designed to reduce TR by occupying the regurgitant orifice area and providing a surface for the coaptation of the valve's native leaflets. The device consists of a foam-filled polymer balloon "spacer" and a rail that is anchored at the RV apex. Implantation is performed via left axillary vein access. The FORMA system has been designed to be fully retrievable during all stages of the procedure until sheath removal. It was first successfully deployed in 2015 and has since demonstrated good clinical and echocardiographic results at one year follow up.[142,143] A multi-center,

prospective, early feasibility study is currently recruiting participants and is expected to follow-up 60 cases over three years duration (ClinicalTrials.gov Identifier: NCT02471807). The PASCAL system by Edwards Lifesciences utilizes a spacer device which clasps each valve leaflet independently and approximates the valve for improved coaptation. It is currently being studied for use in the mitral position and has now been successfully implanted at the tricuspid location as well.[144] The spacer device utilized allows for large coaptation gaps to be treated, that would otherwise not be amenable to rival coaptation devices.

Future directions

Recent advances in transcatheter technology aimed at tricuspid valvular intervention have demonstrated it is no longer the "forgotten valve." Expanded use of existing transcatheter devices and development of novel systems will likely expand the number of patients eligible for treatment. Further clinical trials will be required to demonstrate the safety and efficacy of these devices and provide longer term follow up, and head-to-head comparison with both surgery and among different devices may also be necessary. In addition to device design, advances in tissue engineering, cardiovascular imaging and catheter-based techniques will hopefully expand the ability to percutaneously repair and remodel the tricuspid valvular apparatus.

Conclusion

Right sided cardiac valve disease is a common problem among individuals with CHD and has historically received less attention than its left-sided counterpart. Due to the significant risks of surgical repair, transcatheter interventions have become an attractive treatment option for these patients. The safety and efficacy of transcatheter pulmonary valve replacement has now been well established, and increasing clinical experience and technological development is slowly expanding the indications for transcatheter intervention in both the pulmonic and tricuspid positions. Transcatheter valve replacement looks to provide clinical outcomes comparable to that of surgical repair with an improved safety profile. As technology improves, we may see expanded indications for earlier transcatheter intervention in order to prevent the development of irreversible right-sided cardiac dysfunction, reduce the need for repeat sternotomy and improve long term clinical outcomes.

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