Percutaneous Pulmonary Valve Implantation—Clinical Context

For many congenital heart defects treated in infancy (e.g., tetralogy of Fallot, transposition of the great arteries, double outlet right ventricle), long-term right ventricular outflow tract (RVOT) dysfunction, in the form of pulmonary stenosis and regurgitation, is a common finding as patients become older (older children, adolescents, and adults). This dysfunction can lead to right ventricular (RV) dilatation, progressive dyspnea, arrhythmia, and sudden cardiac death.1,2

Patients are often treated with RV to pulmonary artery (PA) conduits or homograft, which have a finite lifespan and may require replacement every decade or sooner, with pulmonary valve replacement at open-heart surgery.3,4 Medical management has a limited role,5 and although conduit/homograft stenosis can be managed percutaneously with balloon dilatation and bare metal stent insertion6 to prolong conduit/homograft life, this has the inevitable consequence of inducing free pulmonary regurgitation.

During the last decade, however, percutaneous pulmonary valve implantation (PPVI) has been developed to provide a minimally invasive, transcatheter-based approach to prolong conduit/homograft life by treating stenosis and regurgitation without the need for open-heart surgery, thereby reducing procedural risks, hospital stay, and the time it takes to return to normal daily activities.

Since the first pioneering human PPVI in 2000 by Bonhoeffer et al,7 the technique has gained acceptance, with >4000 procedures performed to date. Several studies have now demonstrated the short-term efficacy of PPVI8–13 and defined the potential complications of the procedure, including device migration and fractures,14 coronary compression,15 and infective endocarditis. Sustained relief from stenosis and regurgitation has also been demonstrated in the medium term, with freedom from reintervention of 93%, 86%, 84%, and 70% at 10, 30, 50, and 70 months, respectively, with similar freedom from redo interventions 95%, 87%, 73%, and 73% at the same intervals. Survival at 83 months was 96.9% (Figure 1).16 Short-term data from several studies documented similar complication rates. McElhinney et al9 reported in 124 patients freedom from reintervention of 93% at 1 year, freedom from stent fracture of 77% at 14 months, 1 death, and 1 explant. Vezmar et al11 reported in an adolescent cohort freedom from reintervention at 12 and 36 months of 91% and 80%, respectively, and a stent fracture rate of 10.8%. Eicken et al10 reported in 102 patients 5% stent fracture rate, 1 death because of coronary artery compression, 1 reported episode of endocarditis, 7% reintervention by balloon dilatation, and valve-in-valve procedures. McElhinney et al17 reported 16 cases of infective endocarditis, with 6 meeting the criteria for transcatheter pulmonary valve endocarditis in a large series of 311 patients, 4 of whom had the replacement valve explanted. This equates to a freedom from prosthetic valve endocarditis of 97% at 4 years after intervention.

PPVI has also been demonstrated to be hemodynamically favorable to bare metal stent intervention in the acute setting because it avoids iatrogenic free pulmonary regurgitation after relief of RVOT obstruction.18 In the medium term, PPVI reduces RV pressure, causes favorable RV remodeling,19,20 increases exercise tolerance,21 and induces electric remodeling,22 thereby reducing arrhythmic risk.

Despite its success, PPVI presents several technical challenges because of the function and anatomy of the RVOT. RVOT, pulmonary trunk, branch PA size, and morphology are unique to each patient,23–25 and this morphology is a major determinant of device suitability (Figure 2). The proximity of coronary arteries may also influence device positioning or exclude patients from eligibility. Currently, the Melody PPVI device (Medtronic Inc, MN) is limited to a maximum, 22 mm, whereas the Edwards Sapien PPVI device (Edwards Lifesciences, CA) is available to fit a 26-mm diameter lumen, and thus, device sizing limits suitability in the majority of referred patients (Table 1). This interplay of RVOT morphology and size necessitates detailed preintervention assessment for which we recommend a minimum data set (Table 2).

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Indications for Pulmonary Valve Replacement
There is no general consensus about the indication for re-intervention in RVOT dysfunction, despite the publication of some guidelines. However, the following can act as guidelines:

Patients With Predominantly Pulmonary Stenosis
- Right ventricular pressure exceeds 75% of systemic pressure in the absence of symptoms, or
- Right ventricular pressure exceeds 65% of systemic pressure in symptomatic patients.

Patients With Severe Pulmonary Regurgitation
Patient has a regurgitant fraction >35% at cardiovascular magnetic resonance (CMR) imaging in the setting of the following conditions:
- Severe RV dilatation (indexed volume >150 mL/m² or RV/left ventricular (LV) ratio ≥1.5 in the presence of symptoms or ≥2 without symptoms);
- Severe RV dysfunction;
- Reduced exercise capacity (peak oxygen uptake is <65% of predicted at cardiopulmonary exercise testing using a bicycle and a ramped protocol);
- Significant cardiac arrhythmias or marked QRS prolongation (QRS duration>180 ms, or delta QRS prolongation ≥4 ms/yr) on ECG (or nonsustained ventricular tachycardia on 24-hour Holter ECG monitoring); or
- Significant cardiovascular symptoms (according to New York Heart Association classes).

Many of these factors can be assessed with imaging. Echocardiography remains the first-line tool to determine RVOT gradient and to semiquantitatively assess the severity of pulmonary regurgitation. Echocardiography can also be used to estimate the RV pressures (tricuspid valve regurgitant jet) and the RV to systemic pressure ratio (noninvasive blood pressure measurements). However, echocardiography can be difficult in patients who have had multiple operations and in whom the RVOT sits directly behind the sternum. For many adolescents and adult patients, cross-sectional imaging with...
CMR and computed tomography (CT) imaging are essential for selecting patients for pulmonary valve replacement.

CMR and CT techniques each differ in terms of spatial, temporal resolution, and radiation dose. Cardiac CT offers the advantages of high spatial resolution and fast acquisition times at the expense of poor temporal resolution and ionizing radiation, excellent anatomic assessment (particularly of the coronary arteries, and the possibility of 4D data [Movies I and II in the Data Supplement]) but limited functional assessment (in particular no data on quantitative flow measurement). CMR has higher temporal resolution without a radiation dose, but 4D MR sequences are relatively sparse and may not cover the full translational motion of the pulmonary trunk (Sample CMR sequences are presented in Table 3). Hence, CMR provides good 3D anatomic assessment and excellent functional assessment, definition of biventricular volumes, valvular regurgitation of both pulmonary and tricuspid valves (including peak tricuspid regurgitation jet velocity), and peak RVOT gradient (Figure 3). After implantation, imaging artifacts are generally less problematic with CT than CMR, and therefore, both conventional X-ray and CT imaging are generally used for stent fracture surveillance, although particular CMR sequences (high-flip angle gradient echo and MR angiography sequences) have been validated in vitro for adequacy of stent stenosis assessment.

Taking all these advantages and disadvantages into account, CMR is best placed for the initial assessment and routine follow-up of patients being selected for PPVI, whereas CT is best placed if there is already a bare metal stent in situ or the case is a redo PPVI. Once a decision has been made for pulmonary valve replacement in any given patient, imaging can then be used to assess suitability for either PPVI or surgery (Figure 4).

### Use of Imaging to Select Patients for PPVI—Crucial Issues

Whether PPVI is technically possible for an individual patient depends on 3 factors:

- **Size and distensibility of the RVOT/pulmonary trunk,**
- **Morphology of the RVOT/pulmonary trunk,** and
- **The position of the coronary arteries.**

#### Size and Distensibility of the RVOT/Pulmonary Trunk

The current Melody® can be implanted into pulmonary trunks or conduits sized between 14 (≥16 mm in the United States) and 22 mm in diameter. Small dimensions preclude sufficient opening of the device, resulting in residual stenosis, whereas bigger dimensions inhibit sufficient valve leaflet coaptation and cause regurgitation and, more worryingly, if the pulmonary trunk/conduit is considerably larger, then device embolization into the pulmonary circulation or device dislodgement into the RV can occur. For the Sapien Edwards® device, 2 sizes are currently available: a 23-mm device, for 18- to 22-mm implantation, and a 26-mm device, for 21- to 25-mm implantation, with a 29-mm device soon available in some countries.

Because conduit sizes can change dramatically (either larger or smaller) during the years after their implantation, sizes documented in the operation notes should not be relied on; the actual size should be measured at CMR. During the CMR investigation, this is performed using both 3D data from gadolinium contrast-enhanced MR angiography or ECG-gated whole-heart imaging, combined with 2D cine sequences, on which the maximal dimensions during the cardiac cycle can be established. This is important because most MR angiography and whole-heart CMR acquisitions are acquired predominantly in diastole, and because of cyclic expansion and translational motion, these dimensions may increase by up to 20% in systole (Figure 5). If in doubt, balloon sizing can be performed at the start of the PPVI.

Of note, highly mobile and distensible pulmonary trunks/conduits bear a higher risk of stent fractures and dislodgement. A calcified conduit provides a stable anchoring site for the PPVI device, whereas outflow tracts that have been treated with transannular patches are often mobile and distensible, which makes them unsuitable for PPVI. These characteristics of the RVOT should be described on the imaging.

### Morphology of the RVOT/Pulmonary Trunk

There are significant variations not only in size but also in the 3D geometry of different RVOTs, pulmonary trunks, and conduits. Some of these morphologies are more suitable to
serve as implantation sites for PPVI than others. A classification has been devised that comprises 5 different types of RVOT morphology based on 3D CMR (Figure 6). In short, parallel walls of the outflow tract or a narrower midsection are ideal because they provide a good anchoring area for the device. In contrast, an outflow tract that is pyramidal in shape

| Table 3. Example of the Standard Sequences and Views of a Routine Cardiovascular MR Scan, in the Order of Workflow |
|-------------------------------------------------|-------------------------------------------------|
| Sequence                                      | Purpose                                                                 |
| Scout                                          | Isocentering of the heart in the scanner                              |
| Axial stack                                    | (1) Provides a map of thoracic anatomy, relationship of RVOT to sternum. |
|                                               | (2) Planning subsequent cine imaging planes                           |
| Ventricular long-axis (RVLA, LVLA)             | Assessment of anterior and inferior myocardium, AV valves, ventricular sizes. |
| AV valves                                      | (1) Subjective evaluation of AV valve function.                       |
|                                               | (2) Planning the 4-chamber and LVOT images                            |
| 4-Chamber view                                  | Subjective assessment of atrial volumes, biventricular volumes and function, ventricular wall motion, AV valve regurgitation. |
|                                               | (2) Planning SA stack                                                  |
| SA stack                                       | Assessment of the ventricular septum, ventricular myocardial morphology and wall motion abnormalities, outflow tracts. |
|                                               | (2) Provides the images required for segmentation of RV and LV ventricular volumes |
| MR angiogram                                    | Angiographic views of large and small thoracic vessels. Images less subject to artifact caused by low velocity or turbulent flow. Predominantly diastolic image. Used for RVOT sizing, in conjunction with 3D bSSFP and RVOT cine images. |
|                                               | (2) The second pass acquisition allows assessment of systemic and pulmonary venous anatomy. Subjective determination of preferential blood flow. |
| 3D bSSFP                                       | (1) Provides high-resolution images of intracardiac anatomy, including coronary arteries. Allows multiplanar reformatting. Used for RVOT sizing, in conjunction with MR angiogram and RVOT cine images. |
|                                               | (2) Planning further imaging planes in patients with complex anatomy |
| RV and LV outflow tract                        | Outflow tract morphology, subjective assessment of semilunar valve function. Used for RVOT sizing, in conjunction with MR angiogram and 3D bSSFP. |
|                                               | (2) Planning phase contrast velocity mapping. Planning enface view of pulmonary and aortic valves |
| Great vessel flow                              | (1) Vessel flow volume.                                               |
|                                               | (2) Calculate regurgitant fractions (RF, %).                           |
|                                               | (3) Validate ventricular stroke volume measurements.                  |
|                                               | (4) Calculate pulmonary blood flow to systemic blood flow ratio (Qp:Qs). |
|                                               | (5) Evaluate presence and location of shunts.                         |
|                                               | (6) Calculate peak flow velocity                                       |

AV indicates atrioventricular; bSSFP, balanced steady-state free precession; LV, left ventricle; LVLA, left ventricular long-axis; LVOT, left ventricular outflow tract; MR, magnetic resonance; Qp, pulmonary flow volume; Qs, systemic flow volume; RV, right ventricle; RVLA, right ventricular long-axis; RVOT, right ventricular outflow tract; SA, short axis; and TSE, turbo spin-echo.

Figure 3. Cardiovascular magnetic resonance (CMR) of right ventricular outflow tract (RVOT) dysfunction. A, Volume-rendered 3D images of the whole-heart view from the front. B, Volume-rendered 3D images of the whole-heart view from the pulmonary circulation viewed from above. C, Modulus images through pulmonary trunk. D, Phase contrast images through the pulmonary trunk (pulmonary artery [PA]) to assess pulmonary regurgitation. E, Right ventricle (RV) and left ventricle (LV) cine images (4-chamber) for assessing ventricular function. F, RV and LV cine-images (short axis) for assessing ventricular function.
and gets narrower toward the bifurcation poses a high risk of device dislocation, and therefore is not suitable for PPVI. This type was seen in 61% of patients with a history of transannular patch surgery during previous primary repair and in patients who had a conduit. Thus, a patient’s previous surgical history does not provide sufficient information about likely RVOT morphology, and appropriate imaging is crucial.

Position of the Coronary Arteries

Expanding a stent in the pulmonary trunk/conduit can induce compression of the coronary arteries and lead to myocardial ischemia and infarction. In some cases, cross-sectional imaging may define coronary positions that preclude PPVI (e.g., anomalous coronary running between aorta and conduit implantation site). However, in the majority of cases, cross-sectional imaging cannot completely rule out the risk of coronary artery compression and is used to alert the interventional cardiologist to its potential because of the close proximity of the implantation site to a coronary artery. In this setting, the coronaries should be assessed with an aortic root angiography at the time of PPVI, and if potential for coronary compression remains, coronary angiography should be repeated while simultaneously inflating a high-pressure balloon catheter in the pulmonary trunk.15

Does Patient Selection for PPVI With CMR Make a Difference?

It is difficult to say whether preintervention planning with CMR makes a difference to PPVI success. However, in our own practice, there was a marked improvement (learning curve) during our first 50 PPVIs in terms of the need for surgical pulmonary valve replacement and reinterventions (Figure 1). This corresponded not only with improvements in the device, the delivery system, and the growing experience of actually doing the cases but also with the introduction of protocolized pre-PPVI CMR imaging after the first 50 cases.24

Modeling RVOT Anatomy

In cases with complex RVOT morphology, patient-specific modeling with finite element method (FEM) techniques enables virtual implantation of devices (Figure 7). PPVI strut location, dimensions, and deformation characteristics are integrated with great vessel diameter and distensibility data to suggest optimal position and sizing. Clinicians may advance the simulation further by physically attempting trial implantation using the rapid prototype 3D printed polymer model to assess approach, feasibility, and safety, which has been shown to increase the accuracy of patient selection over and above MR imaging alone.23 This approach can be particularly useful in borderline cases, in which the pulmonary trunk/conduit dimensions are at the upper limit in terms of size or have a morphology that might not be considered suitable for PPVI.

In our practice, 3D CMR data sets are reconstructed from the DICOM (Digital Imaging and Communications in Medicine)
format data with Mimics software (Materialise; Ann Arbor, MI). FEM is performed with ABAQUS (Simulia; Providence, RI) to simulate patient-specific dynamic stent–graft interactions. The Mimics data are subsequently segmented to highlight the RVOT as the region of interest. Semiautomated reconstructions of blood volumes without RVOT wall are first generated, and then a virtual 2-mm thick wall is built before digital subtraction of the luminal blood volume. Subsequently, a standard stereolithograph solid-to-layer triangulated RVOT model is exported to the rapid prototyping system.

The rapid prototyping system comprises a computer-aided manufacturing system that can fabricate physical objects directly from simulated design data, of which the ultimate output is a 3D printer prototype object (P1500 polyester; Stratatis, Eden Prairie, MN). The accuracy of physically printed 3D models was reported as a tolerance of ±0.75 mm at the typical RVOT threshold diameter of 22 mm, which would be deemed clinically acceptable.

Moving Forward—Preprocedural Planning for New Generation Devices

Currently only ≈15% of patients referred for pulmonary valve replacement will be suitable for PPVI because of size and morphological limitations. This leaves a sizable population of referred patients with no readily available percutaneous valve to treat RV dysfunction, who still require open-heart surgery.

Recently, however, larger devices have been developed (29-mm Edwards Sapien PPVI). Although this widens the range of patients who can be treated, even a larger device (eg, 40–45 mm) is required to deal with patients who have free pulmonary regurgitation and dilated outflow tracts (particularly patients with tetralogy of Fallot repaired with transannular patches). To address this issue, Medtronic developed a covered PPVI (constructed from 6 Nitinol rings and interwoven polyester fabric) that was first implanted in 2009 and is due to undergo preliminary clinical investigations in the near future.

Schievano et al reported the first-in-man implantation of this transcatheter pulmonary valve device for the native outflow tract in a 42-year-old symptomatic patient who had undergone 4 previous open-heart procedures, had residual severe pulmonary regurgitation because of a dilated RV conduit, and was considered too high an operative risk for further surgery. Preintervention imaging with 4D CT data was used to define the patient’s anatomy, confirming that the currently available PPVI devices would not fit the dilated pulmonary trunk (mid-pulmonary trunk of 37 mm; Figure 5). This 4D CT information was then used by the device manufacturer to create a bespoke, patient-specific device; 40 mm at the proximal and distal ends, with an hourglass configuration centrally of 22 mm. Further, the patient-specific anatomy and the new device were incorporated into FEM analysis and generated a 3D rapid prototype model (Figure 8). The FEM analysis and 3D rapid prototyping were then used to demonstrate that device anchoring and positioning were possible. This process was essential to show the following to the interventional cardiologist: (1) that implantation was possible and safe; (2) the route required to achieve optimal positioning (guidewire in the left PA, device partially uncovered in the left PA, then pulled back into the pulmonary trunk for full deployment); and (3) the final position and configuration of the device after successful implantation.

The device was implanted successfully after regulatory approval on humanitarian grounds. Postintervention imaging (serial echocardiograms, 4D CT at 3 days and 3 months after the procedure, and biplane fluoroscopy at 1, 3, and 6 months after the procedure) demonstrated the success of the procedure, with dramatic, sustained clinical improvement for the patient. To date, surveillance has shown no stent fractures and a patent,
incorporating a multimodality imaging protocol and integrated software and manufacturing tools. Despite the promise of this integrated approach, patients and their caregivers need to understand that although percutaneous therapies prolong conduit life span and delay future surgical procedures, stent fracture and redo interventions remain a real possibility.

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