The future of transcatheter pulmonary valvulation

Le futur de la valvulation pulmonaire percutanée

Zakaria Jalal\textsuperscript{a,b}, Jean-Benoit Thambo\textsuperscript{a,b,c}, Younes Boudjemline\textsuperscript{a,d,e,*}

\textsuperscript{a} Groupe de cathétérisme interventionnel pédiatrique et congénitale (GCIPC), filiale de cardiologie pédiatrique et congénitale de la Société française de cardiologie, 75015 Paris, France
\textsuperscript{b} University Hospital of Bordeaux, Department of Paediatric and Adult Congenital Heart Defects, 33604 Pessac, France
\textsuperscript{c} Université Victor-Segalen, 33076 Bordeaux, France
\textsuperscript{d} Centre de référence malformations cardiaques congénitales complexes, M3C, Necker Hospital for Sick Children, Assistance Publique des Hôpitaux de Paris, Paediatric Cardiology, 75015 Paris, France
\textsuperscript{e} Université Paris Descartes, Sorbonne Paris Cité, 75006 Paris, France

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**Summary** Percutaneous pulmonary valve implantation now has a key role in the setting of dysfunctional right ventricle-to-pulmonary artery conduits or failing bioprosthetic pulmonary valves. However, despite the excellent results obtained with the two devices available currently (the Melody\textsuperscript{®} valve [Medtronic Inc., Minneapolis, MN, USA] and the Edwards SAPIEN\textsuperscript{®} valve [Edwards Lifesciences, Irvine, CA, USA]), many patients eligible for pulmonary valve replacement remain unsuitable for percutaneous pulmonary valve implantation, mainly because of large native outflow tracts. Accordingly, one of the major challenges for the future is to expand percutaneous pulmonary valve implantation to a broader population of patients. Moving forward, there is important ongoing research that is intended to improve patient outcomes, expand percutaneous pulmonary valve implantation therapy and continue to reduce the number of open-heart surgeries in this population. In this review, we underline the limitations and issues

**KEYWORDS**
Congenital heart disease; Percutaneous pulmonary valve implantation; Melody\textsuperscript{®} valve

**Abbreviations:** MRI, Magnetic resonance imaging; PPVI, Percutaneous pulmonary valve implantation; PVR, Pulmonary valve replacement; RVOT, right ventricular outflow tract.

* Corresponding author. Service de cardiologie pédiatrique, hôpital Necker–Enfants-Malades, 149, rue de Sèvres, 75015 Paris, France.
E-mail address: younes.boudjemline@nck.aphp.fr (Y. Boudjemline).

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associated with the devices available currently, and we focus on the development of new strategies (such as hybrid approaches or magnetic resonance-guided procedures), new devices (such as right ventricular outflow tract reducers or the novel Native Outflow Tract valved stent from Medtronic) and new technologies (such as tissue-engineered valves), which may help to take up these challenges and represent the future of transcatheter valve implantation.

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### Introduction

Patients with complex congenital heart defects are subject to numerous open-heart surgeries, usually performed to relieve right ventricular outflow tract (RVOT) abnormalities, with incremental risks and significant morbidity. In September 2000, the first successful percutaneous pulmonary valve implantation (PPVI) was performed, using a bovine jugular vein sutured on a platinum stent [1]. Since this first-in-man report, catheter-based valve implantation has evolved rapidly over the last decade. This novel treatment option has changed the culture of paediatric cardiology, adult cardiology and cardiovascular surgery. Moreover, it has modified the way in which the expectant family of a foetus likely to undergo several RVOT surgeries is counselled [2].

Currently, there are two devices used for PPVI: the Melody® valve (Medtronic Inc., Minneapolis, MN, USA), a bovine jugular vein valve sutured within a platinum and iridium stent; and the Edwards SAPIEN® valve (Edwards Lifesciences, Irvine, CA, USA), made of bovine pericardium mounted in a rigid stainless steel stent, although the SAPIEN valve is not widely available. Multiple studies have demonstrated that PPVI with the Melody valve is safe and effective, with a high rate of procedural success, and durable in short- and medium-term follow-up in properly selected patients [3,4]. The SAPIEN transcatheter heart valve is an alternative device with similar safety and efficacy in limited studies [5,6]. PPVI with these revolutionary devices provides a nonsurgical alternative in the treatment of dysfunctional RVOT and allows a reduction in the number of open-heart surgeries in these patients.

However, despite these excellent results, the heterogeneity of this population and the wide variety of implantation site morphologies, sizes and dynamics, limits the suitability of PPVI to approximately 15% of patients who require pulmonary valve replacement (PVR), indicating surgical PVR in 85% of patients [7]. Accordingly, one of the major challenges for the future is to expand PPVI to a broader population of patients, including those with large and/or patched RVOTs or complex lesions with a vulnerable neighbourhood, and small children.

Several authors have described advanced techniques or device modifications to make these patients suitable for the transcatheter technique [8–10]. The hybrid approach, including strategies to surgically and/or percutaneously prepare the outflow tract for subsequent transcatheter valve deployment, is another key area of pulmonary valvuloplasty development.

Furthermore, extensive research and development is being conducted to design a suitable transcatheter valve for patients with a dysfunctional native or patched RVOT, typically with significant pulmonary regurgitation rather than obstruction, which is too large for the devices available currently. The first-in-human implantation of a large RVOT transcatheter valve developed by Medtronic was reported in 2010 [11].

In this review we aim to: underline the limitations and issues associated with the Melody and SAPIEN valved stents; focus on the alternative techniques and approaches that
allow effective PPVI with these valves; and describe the ongoing research into and design of new transcatheter pulmonary devices.

**Percutaneous pulmonary valve implantation in large right ventricular outflow tract**

Current transcatheter pulmonary valves have demonstrated a high rate of procedural success with acceptable safety profiles and favourable outcomes. However, of the patients with a clinical indication for PPVR, only 15% can be treated with the devices available currently, indicating surgical PVR in 85% of patients, as they have a history of transannular patch reconstruction of the RVOT, leading to distortion and dilation of that region and precluding PPVI because of the absence of an appropriate landing zone (16–24 mm for the Melody valve; 21–27 mm for the SAPIEN valve) [7, 12, 13].

To extend PPVI indications, some authors started to propose valve implantation in selected native outflow tracts with stenotic and/or non-distensible physiology [14]. Other reports described advanced techniques to make those patients suitable for the transcatheter technique (i.e. the use of two Melody valves implanted in respective pulmonary arteries in a single patient; jailing and/or Russian doll techniques) [9, 15–17]. Cheatham et al. showed that PPVI using a 24 mm balloon catheter for the deployment of the Melody valve was feasible, without impairment of valvular function (RVOT diameter of 26 mm) [18]. The SAPIEN valve diameters are 23, 26 and 29 mm, which makes it potentially more suitable for PPVI in large-diameter conduits and native outflow tracts (up to 27 mm) than the Melody valve, but the device is not widely available.

Nevertheless, most patients with transannular patch repair have a dilated and distensible RVOT, making device embolization a concern in this population. Accordingly, there is worldwide interest in developing new strategies with the current devices and/or a new design of transcatheter heart valve to make these patients suitable for PPVI, avoiding the risk of surgical PVR.

**A new transcatheter pulmonary valve**

The first-in-human implantation of a new self-expandable transcatheter pulmonary valve was reported in 2010 [11]. This was done under compassionate use in a 42-year-old man with pulmonary insufficiency. The device design was tested in animals and modified to fit the patient’s anatomy and to allow safe implantation. The authors did computed tomography of the patient’s RVOT to create prototyping models to customise and test the device, which was successfully implanted into the patient with a satisfactory result. No stent fracture and only trivial paradivice leak were observed at 6-month follow-up. This new prosthesis is called the Native Outflow Tract device (Medtronic Inc., Minneapolis, MN, USA). Besides the use of porcine pericardium to make the valve, the main modifications to this valued stent, compared with the Melody and SAPIEN valves, are an hourglass geometry (i.e. larger diameters at the proximal and distal end; smaller diameters in the central portion holding the valve) and the use of a self-expanding nitinol stent with a polymeric graft, which should help the stability of the device in various RVOT anatomies (Fig. 1).

An Investigational Device Exemption trial of the Native Outflow Tract device has been enrolling subjects since April 2013 (clinicaltrials.gov identifier: NCT01762124; 10 patients enrolled so far). Given the limitations in the animal model regarding confirmation of device boundary conditions, this feasibility study aims to characterize that information as well as to evaluate safety, procedural feasibility and performance data, which will be used in the future development of the device. This innovative device may be the future of PPVI. However, regarding the wide anatomical variability of the RVOT and the frequently associated pulmonary artery disease encountered in this patient population, alternative techniques allowing valve replacement are still being explored by investigators [19]. Another device (Venous P Valve; Medtech, Shenzhen, China) is presently under investigation; 18 patients have been implanted in China, India and Thailand, but no data have been published so far. A European study should start before the end of 2015.

Finally, one major innovation in PPVI may be the development of repositionable valued stents and low-profile devices. The Lotus Valve System® (Boston Scientific Corporation, Natick, MA, USA), a bovine pericardial valve attached to a braided nitinol stent used for transcatheter aortic valve replacement, features this specific function. The braided nitinol frame has a locking system that allows controlled precise deployment, recapture and subsequent repositioning or removal, as necessary [20].

**RVOT reducers**

Patients who underwent surgical repair of tetralogy of Fallo during infancy using a transannular patch can have large pulmonary trunks that often exceed 30 mm in diameter, making PPVI technically unfeasible with the current valves. To extend the indications of PPVI, the use of percutaneously implanted RVOT size reducers has been described. Boujemline et al. designed and developed several versions of a preshaped self-expandable stent, forming a covered double cylinder, with the internal diameter calibrated to authorize implantation of available valued stents. The device is available with various external diameters (30–40 mm; Fig. 2). This device was implanted in sheep (n = 30) that had previously had surgical RVOT enlargement. During the same procedure, a valved stent (bovine jugular vein) was subsequently deployed in the central part of the filler. The main complications were device embolization (n = 1) and para-prosthetic leaks (6/24 animals; 25%). The leak was related to undersizing of the device. Indeed, 5/6 leaks (83%) occurred in animals where the size of the device was less than 5 mm larger than the pulmonary artery diameter (P < 0.05), which confirms that oversizing the device is mandatory for stent anchoring and ultimately for definitive fixation to the vascular wall [21–23].

Other authors have reported on the development of a self-expandable nitinol stent, inside which is attached a specifically designed polyurethane graft (a central tube, 20 mm in diameter, with two flared extremities), which has been successfully implanted in sheep (n = 6) [24]. During the same procedure, a 20 mm nitinol valved stent (bovine
pericardium) was implanted within the deployed size reducer. These devices seem very promising, but they have not been tested for human application so far. Indeed, the applicability of these devices to the human anatomy with calcified RVOT or non-circular cross-sectional shape remains to be proven.

Percutaneous pulmonary valve implantation in small children and those with a low body weight

The transcatheter valves available currently (the Melody and SAPIEN valves) require a large delivery sheath (22 and 24 Fr, respectively), limiting the use of this technology in patients weighing > 30 kg. A recent study focused on PPVI results with the Melody valve in this specific population [25]. Twenty-five children (median age, 8 years; median weight, 21.4 kg) were scheduled for PPVI in conduits ranging from 12 to 23 mm, using a standard technique and devices. Vascular access was by means of the femoral vein ($n=17$), the right internal jugular vein ($n=6$) or the left subclavian vein ($n=2$). PPVI was feasible in all but two patients (risk of coronary compression in one; inability to advance the delivery sheath through the common femoral vein in the other). Post-PPVI results showed good valve function. This report underlines that PPVI is feasible in children weighing > 30 kg with good procedural and haemodynamic results. However, the population sample size and short follow-up limit the statistical significance of such results. Furthermore, procedural adverse events were relatively common, although they had already been reported.
in the same proportions in studies with larger patients [4]. Nevertheless, it is probable that small patients are at risk of some complications related to the size and stiffness of the delivery system and vascular access issues.

Although the optimal timing for intervention in RVOT conduit dysfunction remains unclear, there is a trend towards earlier intervention in the paediatric population, to minimize deleterious effects of conduit failure on right ventricular function [26,27].

As technology continues to advance, minimizing the delivery sheath and valve size, and developing mini-invasive hybrid approaches should be prioritized, so that this technology can be used in younger patient populations. New devices with reduced delivery systems are under development at the moment. The most advanced device is based on a dry valve mounted on a stent. The whole system comes prepared, already mounted in the delivery system and in the same package. The valve being dry, the delivery system is only 14Fr, making the use of this device possible in small children.

‘Think hybrid’

Hybrid procedures

Hybrid procedures involving the use of surgical and transcatheter techniques are increasingly common in the field of congenital heart diseases, leading to optimized efficacy and safety when conducting at-risk procedures [28]. Hybrid approaches need a collaborative relationship between cardiac surgeons and interventionists, especially during the preprocedural work-up to assess patient suitability and choose the appropriate technique. Furthermore, while the advantage of PPVI is to avoid repeated open-heart surgeries, the ideal hybrid procedure should be as minimally invasive as possible.

In the field of transcatheter PVR, animal and human hybrid procedures mostly aimed to perform valve implantation in large RVOTs. A few years after the first PPVI, the Necker Hospital for Sick Children group (Paris, France) reported off-pump PVR using a combined approach in ewes. A left thoracotomy was first performed, then the main pulmonary artery was banding using two radiopaque rings of nitinol, giving a reduction in RVOT diameter from 30 to 17.6 mm. Subsequent PVR through a percutaneous or transventricular approach was then performed without extracorporeal circulation, using an 18-mm bovine jugular venous valve mounted in a balloon-expandable stent [29]. In line with these trials on valve implantation into the pulmonary position, first results described modified valve delivery into the aortic or mitral position [30].

Furthermore, Schreiber et al. published another approach, which allows implantation of a Shelhigh valve (Shelhigh inject, Shelhigh Inc., Union, NJ, USA) – a porcine pulmonic valve mounted inside a self-expandable stent covered with porcine pericardium, with a diameter as long as 31 mm – without the use of cardiopulmonary bypass, in 6 patients operated on with a transannular patch [31]. The valve was introduced just beneath the RVOT. One patient exhibited paravalvular leakage and the valve was replaced by a homograft 2 days later. After 6–12 months’ follow-up, the remaining patients had good valvular function. However, this approach requires complete dissection of the heart after full sternotomy.

Dittrich et al. published a report on an 8-year-old boy in whom transverse mini-thoracotomy through the third intercostal space was used to implant an injectable 29 mm stented porcine valve directly into the pulmonary artery bifurcation [32]. The procedure was performed during rapid ventricular pacing and right ventricular unload by a short running femorally implanted cardiopulmonary bypass.

More recently, some authors have reported an interesting subxyphoid hybrid approach as a first-line method for implanting a Melody valve in a 3-year-old boy (12 kg), in whom venous access using the Ensemble® 22 Fr delivery system (Medtronic Inc., Minneapolis, MN, USA) was not feasible [33]. PPVI was uneventful, with excellent valve function on echocardiography, and the patient was discharged 2 days after the procedure. Other authors have reported the use of perrventricular pulmonary valve implantations, but only in the setting of complications with the transfemoral approach in adults or larger children [34,35]. One concern is the creation by this percutaneous approach of a right ventricular scar, which might lead to an increased incidence of ventricular arrhythmias by the creation of re-entry circuits, especially in tetralogy of Fallot patients [36]. Despite these limitations, hybrid procedure results are very encouraging and this approach may be used increasingly for PVR, whether in small children or in patients with large RVOTs.

Anticipating percutaneous pulmonary valve implantation during first surgery

Another collaborative approach between surgeons and interventionists is the adjustment of the surgical strategy to further facilitate PPVI. By providing an anatomical substrate for PPVI during the first or second operation, the surgeons may minimize the number of subsequent open-heart procedures. In tetralogy of Fallot, the use of pulmonary valve sparing techniques (i.e. recycling the pulmonary valve or the Y-PLASTY technique) should be encouraged, not only to prevent RVOT enlargement and pulmonary insufficiency, but also to allow subsequent PPVI if/when necessary [37,38]. The placement of a GORE-TEX® band (W.L. Gore & Associates, Newark, DE, USA) on the main pulmonary artery to avoid major enlargement is another strategy to consider. Furthermore, surgeons should consider the possibility of PPVI when choosing the size of a bioprosthetic valve or conduit for PVR. Finally, in case of early catheterization procedures in operated children, the placement of a stent in the RVOT may be used to fix the size of the outflow tract for subsequent PPVI.

Durability of devices

Long-term durability of PPVI devices has not been evaluated so far. Indeed, recent reports have only described medium-term outcomes with these valves [3,4]. To date, no authors have compared the long-term durability of PPVI devices with surgical valves. However, considering its behaviour under high-pressure conditions, the Melody valve seems to be more durable than initially expected [39].
Failure of analogous surgically implanted bioprosthetic valves occurs secondary to deposition of calcium, leading to progressive dysfunction of the valve. Furthermore, it is known that homografts induce a humoral immunological response, which has been correlated with the risk of failure [40,41]. The use of tissue-engineering valved stents may overcome these current limitations. Indeed, tissue-engineered heart valves require no anticoagulation and have the ability to grow and remodel without immunological reaction. Tissue-engineered valves with autologous cells have already been used clinically [42]. In this human study, the authors isolated cells from children’s peripheral blood, seeded those cells on a decellularized human pulmonary valve (acellular allograft matrix), placed it into a bioreactor and surgically implanted the new tissue-engineered valve into the children. In the following 3.5 years, the pulmonary valve annulus diameter increased and the valve regurgitation decreased slightly; no signs of valve degeneration have been observed so far.

More recently, Metzner et al. implanted percutaneously similar bioengineered valves sutured on a nitinol self-expanding stent in sheep pulmonary valves. Gross morphology confirmed excellent opening and closure characteristics of all leaflets after 4 weeks, although a mammmogram of the stent showed mild annular calcification (n = 4/7) [43]. One limitation of this method is the absence of valved stent growth ability, although the use of biodegradable stents might solve that issue.

Thin-film nitinol has favourable biological properties as well as elastic properties, which make it an ideal material for use in transcatheter heart valves. Because nitinol also has shape memory, complete heart valves (the leaflets and support structure) can be made entirely from this material. A thin-film nitinol heart valve could be the ideal hybrid valve: it could have the biological compatibility and non-thrombogenicity of tissue valves, and the longevity of a mechanical valve (nitinol has very impressive fatigue properties).

A semilunar thin-film nitinol heart valve has been designed and tested in animals. This eNitinol membrane—PercValve® (Advanced Bioprosthetic Surfaces, Ltd., San Antonio, TX, USA)—has leaflets made from 10 μm membranes of thin-film nitinol, which is made to be very flexible by incorporation of multiple regularly-spaced small fenestrations. It is a self-expandable valve that can collapse into a 10-Fr sheath. These valves could have very unique advantages for improving valve durability, as they endothelialize rapidly and could certainly be made to be sufficiently low profile for use even in small infants [44].

In 2010, Tzifa et al. reported the first-in-man solely MRI-guided pulmonary valvuloplasty [47]. Cardiovascular MRI characteristics of both transcatheter heart valves currently commercially available for transcatheter aortic valve implantation (SAPIEN; CoreValve® [Medtronic Inc., Minneapolis, MN, USA]) were assessed in vitro [48].

Clinical translation for PPVI would require further development of the devices to enhance procedure safety. However, MRI-guided PPVI seems promising because of the lack of radiation and additional data provided for soft tissue characterization.

**Conclusion**

PPVI has emerged as a safe and effective procedure for the treatment of RVOT dysfunction. Despite the dramatic modifications in the management of patients with dysfunctional RVOT induced by this technology, there are some issues that continue to limit its indications and some unanswered questions regarding its long-term outcome. The development of new PPVI strategies (such as hybrid approaches or MRI-guided procedures), new devices (such as RVOT reducers or the novel Native Outflow Tract device from Medtronic) and new technologies (such as tissue-engineered valved stents) may help to take up these challenges and represent the future of transcatheter pulmonary valve implantation.

**Disclosure of interest**

Y. Boudjemline acts as a proctor for Medtronic. The other authors declare that they have no conflicts of interest concerning this article.

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