Original Studies

Off-Label Use of Percutaneous Pulmonary Valved Stents in the Right Ventricular Outflow Tract: Time to Rewrite the Label?

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Introduction: Percutaneous pulmonary valve implantation is now considered feasible and safe. "Native" right ventricular outflow tract (RVOT), small diameter conduits (<16 mm) and relatively large RVOT with a dynamic outflow aneurysm are currently considered off-label uses. Extending indications creates concerns of safety, ethics, reimbursement, and liability. _Aim of study:_ To report the safety and feasibility of off-label application of percutaneous pulmonary valve implantation. _Design:_ Retrospective analysis of prospectively collected data. _Patients and Methods:_ Off-label indications: conduit-free RVOT or patients with an existing but undersized conduit. _Results:_ Twenty-one Melody® valves and two Sapien® valves were successfully implanted in 23 patients (16.9 years; range 6.1–80.5 years). In 22 patients, prestenting was performed 4.8 months (range 0–69.2) before valve implantation (15 covered and 13 bare stents). Stent endothelial ingrowth was allowed for at least 2 months prior to implantation of the percutaneous valve if stent stability or sealing by the covering was presumed to be insufficient. Group 1 patients (_n_ = 8) had a "conduit-free" RVOT after transannular/infundibular patch and after prestenting underwent percutaneous pulmonary valve implantation (PPVI), with a final RVOT diameter of 21.5 mm (range 16–26 mm). Group 2 patients consisted of two elderly patients with pulmonary valve stenosis and severe RVOT calcifications. Group 3 (_n_ = 13) had an existing conduit (nominal 15.9 ± 3.2 mm; range 10–20 mm). The conduit was augmented from 14.7 ± 3.5 to 20 ± 1.6 mm with PPVI. The RVOT preparation and valve implantations were uneventful. _Conclusions:_ PPVI is safe and feasible in selected patients with an off-label indication. Creating an adequate "landing zone" by prestenting makes the procedure safe and predictable. Updating the indications for PPVI should be considered. © 2012 Wiley Periodicals, Inc.

Key words: right ventricular outflow tract; pulmonary stenosis/regurgitation; percutaneous pulmonary valve; stenting

INTRODUCTION

The first successful percutaneous pulmonary valve implantation (PPVI) was described in 2000 with a device comprising a valved segment of bovine jugular vein sewn within a balloon-expandable stent [1]. Currently two balloon expandable transcatheter valves are available for PPVI: the Melody® valve (Medtronic, Minneapolis, MN) and the SAPIEN™ THV (Edwards Lifesciences LLC, Irvine, CA). The label for both

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valves describes the "official" substrate for PPVI: a dysfunctional surgical conduit in the right ventricular outflow tract (RVOT) with some limitations on conduit diameter [2,3]. This indeed describes the ideal patient to undergo PPVI, but growing experience with more than 3.500 implants worldwide, has shown that these criteria are often too narrow. Off-label indications such as "native" RVOT dysfunction, small diameter conduit (absolute size <16 mm, or relative small nominal conduit size for the patient), and large RVOT with an aneurysm after transannular patch repair, constitute the majority of patients needing PPVI. Techniques have been developed that may extend the use of PPVI beyond the current indications, so that more patients can benefit from this elegant technology. The issues that arise with off-label use of devices are concerns about safety, ethics, reimbursement and liability. However, a decision-making strategy that severely restricts clinical choice to "on-label" use may deprive patients of a beneficial treatment [4]. In this article, we report our early experience with the off-label application of PPVI.

METHODS
Study Subjects

A retrospective analysis of our institutional congenital cardiology database was performed to identify patients who underwent off-label PPVI. Off-label indications were defined as valve implantation in patients with a native or "conduit-free" RVOT (pulmonary valve or patch), conduits smaller than 16 mm in diameter, or final percutaneous implanted valve diameter 2 or more mm larger than the original nominal diameter of the surgical conduit. Indications for PPVI were based on data previously published [5]. Patient records were used to obtain catheterization and follow-up data. Patients were selected based on noninvasive screening including clinical assessment, transthoracic echocardiography, and cardiovascular magnetic resonance imaging in most cases. Valve dysfunction was categorized echocardiographically as predominantly stenotic [RVOT peak instantaneous gradient (PIG) > 50 mm Hg with less than moderate pulmonary regurgitation (PR)]; predominantly regurgitant (more than moderate PR with RVOT PIG < 50 mm Hg); or mixed (RVOT PIG > 50 mm Hg and more than moderate PR). The severity of PR was classified on color flow Doppler as $0 =$ none, $< 1 =$ trivial, $1 - 2 =$ mild (no retrograde diastolic flow in pulmonary trunk), $3 =$ moderate (retrograde diastolic flow in main pulmonary artery), and $4 =$ severe (additional retrograde diastolic flow in branch pulmonary artery). Patients were divided into three groups: group I with a "conduit-free" RVOT after transannular/infundibular patch or pulmonary val-

voplasty, group 2 with a native stenotic pulmonary valve, and group 3 in whom valve implantation was performed in an existing conduit, which would be too small for the patient even when re-expanded to its nominal value. Digital measurements of catheterization data were performed using an IMPAX® viewer (Agfa Heartlab®, Mortsel, Belgium). The study was conducted in accordance with local Ethical Committee guidelines.

Cardiac Catheterization and PPVI

All procedures were performed under general anesthesia with biplane fluoroscopic guidance. The catheterization procedure and valve implantation were similar to that previously described [3,6,7]. Conduit or pulmonary valve calcifications were assessed on pre-procedural chest X-rays and on fluoroscopy images during the implantation. Hemodynamic and angiographic assessment was performed and the minimum RVOT diameter estimated.

Group 1: Conduit-free RVOT. In patients with a conduit-free RVOT, balloon-interrogation at low-pressure was performed using a flexible, semicompliant, mildly oversized balloon (typically Tyshak® balloon; NuMED, NY) to delineate the potential zone of retention (careful observation of the balloon during submaximal inflation and deflation). Simultaneous coronary angiography was performed to exclude coronary compression [8]. Prestenting was performed in all patients; in the large RVOT, we typically used a bare stent with a hybrid open cell design to provide sufficient anchoring at the retention zone. The stents were delivered on a Balloon in Balloon® BIB dilatation catheter (NuMED, NY) with diameters 2 – 4 mm larger than the retention zone. Stents were deployed using hand inflation, allowing maximal control during deployment, aiming for full deployment of the proximal and distal ends, but only approximation to the wall at the retention zone, typically leaving some indentation centrally (Fig. 1). When stent stability was presumed insufficient to withstand additional pushing and pulling, valve implantation was postponed for about 2 months to allow endothelial tissue ingrowth to fix the stent to the heart and vessel wall. Care was taken at the subsequent catheterization to cross the stent through the central lumen opening, either by using a J-tipped guiding wire or a balloon-catheter. If we anticipated difficulty directing the PPVI delivery system through the prestented RVOT, the proximal stent end was flared with a balloon, or a second "smooth" covered stent was implanted to facilitate valve positioning.
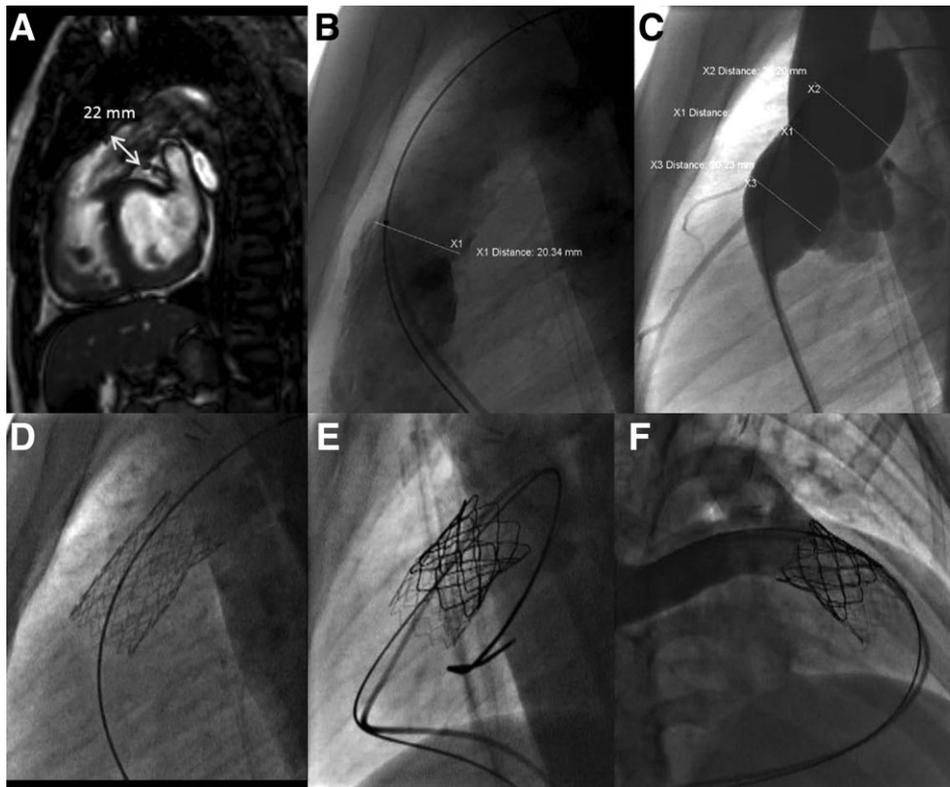
Fig. 1. Twelve-year-old symptomatic boy after infant repair of tetralogy of Fallot with a transannular patch. (a) MR showing dilated infundibulum estimated at 22 mm; PR 31%; (b, c) angiogram of RV: the annular region is estimated at 20 mm; balloon interrogation of RVOT with 25 mm balloon shows indentation at valvular level down to 18 mm; (d) 39 mm Andramed stent (open cells) was deployed with a 22 mm BIB; the hybrid open cell design provides multiple "hooks" to anchor; end of first procedure; (e) 2 months later, a Melody valve was implanted with a 22 mm Ensemble; (f) pulmonary angiogram shows no pulmonary regurgitation.

Group 2: Native pulmonary valve stenosis (PS). This group consisted of patients with native PS resistant to balloon dilation: the lesion was expandable but with significant recoil or showed extravasation due to fracture of a calcified annulus.

Group 3: Dysfunctional conduit (small for patient size). Fig. 2. In patients with an existing undersized conduit in the RVOT, we anticipated the need for significant expansion of the conduit beyond nominal value in order to get adequate gradient relief. Balloon interrogation was done using moderate inflation pressures to determine the distensibility of the conduit without causing graft rupture. Inflation was typically done by hand using a 20 ml syringe; this automatically limits the inflation pressure. As in group 1 patients, a standard coronary angiography with simultaneous balloon inflation at the target implantation site was performed to assess the danger for coronary artery compression; full dilation to the final anticipated size was typically not performed to avoid graft tearing or rupture [8]. To allow a controlled expansion without blood extravasation, prestenting was performed typically with covered Cheatham Platinum stents^{TM} (CCP stent^{TM}, NuMED, NY); we aimed to cover the full length of the conduit overlapping the proximal and distal anastomosis. Early in our experience two stents were deployed telescopically when required, but later we obtained longer (55 and 65 mm) covered stents. As in group 1 patients, stents were deployed using mildly oversized BIB dilatation catheters and hand inflation; we concentrated on stent delivery and flaring of the stent against the wall to provide maximal sealing at both ends; this delivery balloon was not used for full deployment of the stent. When we anticipated a large conduit tear or rupture that would require tight sealing to avoid blood extravasation, further dilation was postponed for 2 months to allow maximal fixation and thus sealing of the stent tissue to the wall. Further dilation was performed with high-pressure noncompliant balloons; angiograms and pressure recordings were done as indicated. If the coronary arteries were at risk for external compression, progressive dilation in small 2 mm steps was performed with intermittent coronarography. In the presence of significant recoil, additional bare stents were implanted

until no recoil or wringing motion was observed. The valved stent was subsequently implanted in the nonrestrictive, stiff stented tube.

Statistical Analysis

Data was captured using Excel spreadsheets. Results are presented as mean $\pm$ SD; the median and range are also given when the distribution is non-normal. Changes were statistically evaluated with student's t-test, and a P value < 0.05 was considered significant.

RESULTS

Baseline Characteristics

From November 2006 to February 2012, 81 valves were implanted percutaneously in the RVOT; 23 (28%) patients fulfilled the criteria for off-label PPVI (group 1: $n = 8$; group 2: $n = 2$; group 3: $n = 13$). Diagnoses and baseline characteristics are summarized in Table I. Tetralogy of Fallot or one of its variants was the most common intracardiac lesion (14/23, 61%). Four patients had conduits following Rastelli type repair of L-transposition of the great vessels with pulmonic stenosis and ventricular septal defect, 2 patients had undergone a Ross procedure for significant aortic valve regurgitation/stenosis, 1 patient had a homograft after truncus arteriosus repair, and 2 patients had PS. The mean age at PPVI was 16.9 ± 19.7 years (range 6.1–80.5 years) and mean weight 42.3 ± 20.4 kg (range 20–99 kg). The primary indication for valve implantation was PR in 9 patients (39%), RVOT obstruction in 11 (48%) and mixed disease in 3 (13%). Valve implantations were performed through the femoral vein in 21 patients, through the jugular vein in one patient (no femoral access possible) and via subxiphoid hybrid approach in one patient due to the unfavorable angle of the prestent in the RVOT. Two Sapien valves (one each in group 1 and group 2) and 21 Melody valves were implanted; the choice of the valve was based predominantly on RVOT size and reimbursement issues.

Group 1

Group 1 consisted of eight patients with tetralogy of Fallot after transannular or infundibular patch repair. None of these patients had RVOT calcifications on fluoroscopy. In a 15 month old patient, a Palmaz P128 (J&J, NJ) stent was implanted on a 14 mm diameter balloon for residual stenosis 13 months after surgical repair with an infundibular patch; 5 years later the stent was dilated to its maximal size of 18 mm, followed by implantation of a valved stent. The other seven patients presented at the age of 11.0 ± 4.4 years with unrestrictive pulmonary regurgitation in six and stenosis in one;

the mean minimal diameter of the RVOT diameter was 17.5 ± 2.0 mm (range 14–20). Prestenting was performed in all seven patients [six bare hybrid open cell (Andrastent; Andramed, Germany) and two covered stents (Covered CP Stent, NuMED, NY)] up to 20.0 ± 3.7 mm (range 14–24 mm) diameter. A valved stent was implanted subsequently in the patient with original stenosis, and in the other six patients 2.3 ± 0.6 months later; final valve diameter (minimal lumen) measured 21.5 ± 2.8 mm (range 16–26 mm).

Group 2

The two patients in group 2 were both elderly patients with PS and severe RVOT calcifications on fluoroscopy. Patient 9 (age 73.4 years) underwent a redo pulmonary balloon dilatation 31.2 years after a previous open valvotomy for severe native pulmonary stenosis. The procedure was complicated by rupture of the calcified annulus and urgent bailout stenting with a 34 mm CCP stent. Subsequent PPVI 4.8 months later was uneventful. Patient 10 (age 80.5 years) had a PPVI after a failed balloon dilatation; this is the only patient in this series without prestenting.

Group 3

Group 3 consisted of 13 patients with a conduit [8 homografts (European Homograft Bank, Brussels, Belgium); 5 Contegra conduits (Medtronic, MN); mean nominal conduit diameter 15.9 ± 3.2 mm (range 10–20 mm)]. RVOT calcifications were seen on fluoroscopy in seven patients. The narrowest diameter of the conduit was 14.7 ± 3.5 mm. Prestenting was performed in all patients: 12 covered stents (CCP Stent, NuMED, NY) and 4 bare metal stents (3 Andrastent, Andramed, Germany; 1 Intrastent, ev3) were implanted; 3 patients received 2 stents. In six patients, the valved stent was implanted subsequently at the initial procedure; in seven patients, we preferred to wait 2.3 ± 0.5 months to obtain more sealing by the covering before expanding the conduit. The mean final valve diameter was 20.0 ± 1.6 mm (range 18–22 mm). The mean true increase in RVOT size (difference between minimal angiographic baseline diameter and final valve diameter) was 5.3 ± 2.6 mm (range 2–11 mm; $P < 0.001$).

RVOT Gradient Reduction

In all patients with significant PS ($n = 14$), a decrease in peak Doppler gradient across the conduit was observed from 70.6 ± 15.0 mm Hg (range 55–110 mm Hg) before the procedure to 20.7 ± 9.3 mm Hg (range 5–30 mm Hg) on the day following valve implantation ($P < 0.001$). Patient 1 developed progressive

TABLE I. Patient Characteristics and Procedure Details

	Patient	Diagnosis	Previous intervention	Indication	Conduit size (mm)	Age prestent (years)	RVOT min mm	Type Prestent	Prestent to valve (months)	Age at valve (years)	Weight at valve (kg)	Valve size (mm)	Size increase (mm)	Echo gradient pre (mm Hg)	Echo gradient post (mm Hg)	Cath gradient pre (mm Hg)	Cath gradient post (mm Hg)	PR post 0–4/4
GROUP 1	1	TF DORV	Infundibular	PS		1.1	4	P128 + 34CP	69.2*	6.9	30	22	18	90	10	31	13	<1
	2	TF	Transannular	PR		12.1	17	39 Andra	1.6	12.2	36	22	5	27	20	14	8	<1
	3	TF	Transannular	PR		7.1	16	39 Andra	2.4	7.3	21	22	6	10	10	4	2	<1
	4	TF	Transannular	PS		12.0	14	34 CCP	0*	12.0	36	16	2	75	30	24	10	<1
	5	TF	Transannular	PR		5.9	18.5	39 Andra	2.3	6.1	23	22	3.5	28	20	3	5	0
	6	TF	Transannular	PR		7.2	18	39 Andra	1.8	7.3	20	20	2	30	15	12	5	0
	7	TF AVSD	Infundibular	PR		16.5	19	39 Andra	2.1	16.7	67	22	3	45	25	15	13	<1
	8	TF	Transannular	PR		16.3	20	43 Andra + 39CCP	3.4	16.6	99	26	6	10	10	12	0	<1
	Mean					9.8	16		2.3	11.2	42	21.5	5.6	32.1	18.6	12.0	6.1	
	SD					5.4	5		0.6	4.4	28	2.8	2.2	22.5	7.5	7.1	4.5	
GROUP 2	9	PS	Valvotomy	PS		73.0	Valve 24	34 CCP + 43 Andra	4.8	73.4	66	26	2	80	5	62	0	1
	10	PS supra PS	Balloon dilation	PS		-	valve 22	39CCP	-	80.5	84	22	0	70	10	47	20	<1
GROUP 3	11	AR	Ross Contegra	PS + PR	20	13.0	18	45 CCP + 43 Andra	0	13.0	40	22	4	55	19	21	9	<1
	12	TF PA VSD	Repair homograft	PR	13	15.1	13	45 CCP + 43 Andra	1.8	15.2	42	20	7	25	12	12	0	0
	13	TGA VSD PS	Rastelli Contegra	PS	14	10.6	14	39 CCP	0	10.6	43	18	4	65	26	27	9	0
	14	L-TGA DORV VSD PS	Rastelli homograft	PS	18	8.9	14	34 CCP	0	8.9	26	20	6	75	23	32	6	0
	15	TF PA VSD	Repair homograft	PR	16	6.1	15	39 CCP	3.2	6.4	27	20	5	40	10	20	15	<1
	16	AS	Ross, homograft	PS	10	8.6	10	45 CCP	2.7	8.8	26	18	8	58	25	41	6	<1
	17	TF PA VSD	Redo Contegra	PS+PR	20	13.8	20	45 + 39 CCP	0	13.8	57	22	2	60	30	17	13	0
	18	DORV TGA VSD PS	Rastelli homograft	PS	20	10.4	20	45 CCP + 43 Andra	1.9	10.6	42	22	2	110	13	32	8	<1
	19	TF	Repair Contegra	PS	14	10.4	14	Intrastent 26	0	10.4	36	18	4	65	37	28	10	0
	20	TGA VSD PS	Rastelli Contegra	PS	14	10.6	11	39 CCP	0	10.6	43	18	7	65	26	32	9	0
	21	TF	Repair homograft	PR	18	8.0	16	39 Andra	2.2	8.2	27	22	6	25	16	8	0	<1
	22	TF	Repair homograft	PS + PR	17	10.4	17	55 CCP	2.4	10.6	50	20	3	65	23	30	8	<1
	23	Truncus	Repair homograft	PS	13	11.8	9	34CCP	1.8	11.9	31	20	11	55	10	14	5	<1
	Mean				15.9	10.6	14.7		2.3	10.7	37.7	20.0	5.3	58.7	20.8	24.2	7.5	
	SD				3.2	2.4	3.5		0.5	2.4	9.9	1.6	2.6	21.8	8.3	9.6	4.3	

Abbreviations: Andra: Andrastent; AR: aortic valve regurgitation; AS: aortic valve stenosis; AVSD: atrio ventricular septal defect; CCP; covered Cheatham Platinum stent; PA: pulmonary valve atresia; PR: pulmonary valve regurgitation; PS: pulmonary valve stenosis; SD: standard deviation; TF: tetralogy of Fallot; TGA: transposition of great arteries; VSD: ventricular septal defect.*: outlier, not included for mean
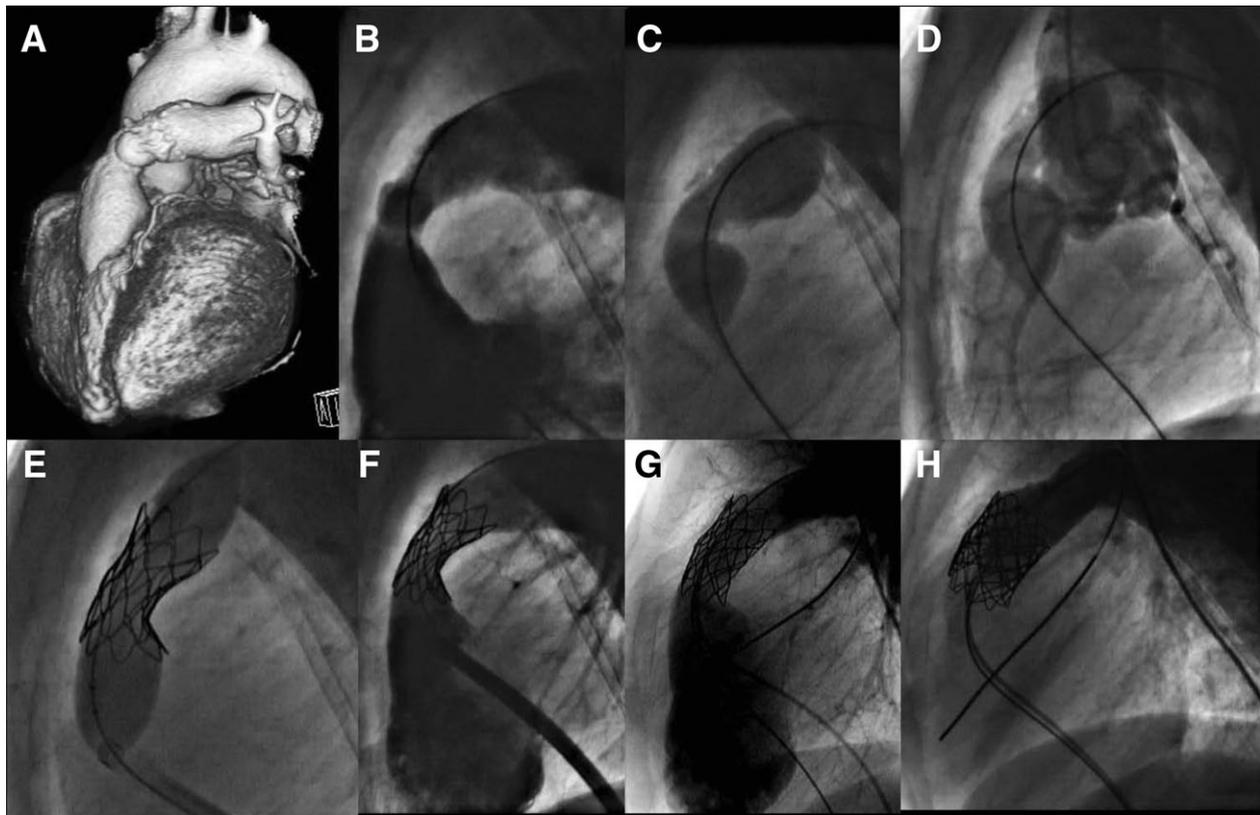
Fig. 2. Twelve-year-old patient after neonatal repair of truncus with 13 mm bicuspidized homograft. (a) 3D reconstruction demonstrating the small homograft; the LAD is not at risk for external compression; (b) RV angiogram demonstrates the small graft between the RV and pulmonary artery; (c) balloon interrogation with 20 mm balloon at low pressure to determine compliance of RV outflow and graft; (d) aortogram during balloon of RVOT: confirmation of safe distance of coronary arteries; (e) delivery of 20 mm covered CP stent by 18 mm BIB balloon, hand inflation; the stent is apposed to the wall; (f) RV angiogram shows the stent 15 > 11 < 18 mm; end of first procedure to allow maximal adhesion as significant fracture is anticipated; (g) 2 months later, the stent is first dilated with a 16 mm high-pressure balloon, then with an 18 mm balloon; no extravasation of contrast; (h) pulmonary angiogram after implantation of a Melody valve on a 20 mm Ensemble; dilation of stented graft up to 20 mm; no residual stenosis, no regurgitation.

stenosis due to a muscular band well below the valve after regression of RV dilation, necessitating surgical intervention 3.4 years after valve implantation. In patient 19, the PIG across the RVOT initially decreased from 65 to 37 mm Hg when dilated up to 18 mm, but gradually increased due to patient growth and a relatively small valve size. Further dilatation of the valve 2 years after the PPVI (peak-to-peak gradient 46 mm Hg) was aborted due to the risk of coronary compression.

Pulmonary Valve Competence

A near abolishment of PR was documented on echocardiography within 24 hr after valve implantation and remained stable during follow-up. The PR was graded as 0/4 in 8 patients, trivial in 14 patients, and mild in 1 patient due to a small paravalvular leak (patient 9; 26 mm Sapien valve in a bare stent).

Procedure related Problems and Complications

Final valve implantation was successful in all patients with no serious complications. Mean fluoroscopy duration was 16.3 ± 12 min (range 5–53.7 min). In patient 8, presenting of the large RVOT had to be performed via the right jugular vein due to an abnormal course of the inferior caval vein. Sapien valve implantation 2 months later via the jugular approach proved to be technically impossible due to the unfavorable position of the Andrastent in the angulated RVOT: when trying to advance a sheath through the stented RVOT, the proximal struts were crumpled. A 26 mm Sapien valve was implanted successfully 1 month later from a different angle via a hybrid subxyphoid approach. No vascular access site complications occurred. We observed no device-related adverse events (i.e., stent fractures, migration, or stent recompression) during follow up of 1.2 ± 1.2 years (range 0.1–4.5 years).

DISCUSSION

Transcatheter pulmonary valve replacement is a promising and evolving technique, but it is currently limited to patients with existing conduits between 16 and 26 mm in the RVOT, if adequate for patient size [2,9]. When these selection criteria are strictly applied, <20% of patients with congenital heart disease who develop postoperative RVOT dysfunction (PR and obstruction) are eligible for PPVI. In this study, we describe successful off-label PPVI according to product labeling and manufacturer guidelines. Relief of RVOT obstruction and valve competence were obtained in all patients, and the RVOT size increased significantly when indicated. The valve implantations were uneventful and all patients were hemodynamically stable throughout the procedure. In our opinion, adequate prestenting is essential for successful outcome.

PPVI in Aneurysmal RVOT

A valved stent can safely be implanted in a RVOT without conduit, even after an infundibular or transannular patch repair [10]. Key to successful RVOT reconstruction is adequate preparation of the landing zone for the valved stent. In patients with some residual stenosis, a stent can be implanted and sufficiently secured across the stenosis, allowing immediate implantation of the valved stent. In a large aneurysmal RVOT, stent migration may occur during or after valved stent implantation. We chose to deploy a bare stent with hybrid open cells. A bare stent will minimize the impact of blood flow throughout the cardiac cycle, and the open cells will maximize the grip of the stent on the wall at deployment (open cells hook like scales) and allow fast and efficient endothelial overgrowth. We typically allowed a period of about 2 months to obtain such endothelial fixation [11]. In this small series, the bare stent withstood later manipulations as typically occurs when delivering the valved stent. In 1 patient, we crumpled the proximal struts of the stent while trying to cross it with a sheath, illustrating that the stent was well fixed. While the open cell design is advantageous to anchor the stent in the RVOT, it is a disadvantage when positioning the valved stent as it might hook to the stent. Moreover, if the covering of the valved stent does not seal the retention band, a paravalvar leak may persist after valve deployment. When expected, both problems can be avoided by implanting a covered stent into the bare stent just prior to insertion of the valved stent.

After transannular patch repair of tetralogy of Fallot, severe RVOT failure with marked anatomic distortion and progressive aneurysmal dilation frequently develops. Typically such a large aneurysmal RVOT requires surgery with an adapted technique: reconstruction to reduce the size and shape of the outflow and implantation of a valve. Percutaneous devices designed for a large aneurysmal RVOT are being explored [12,13] but clinical reports are so far limited. Such devices will address the issue of inserting a new valve, but not the issue of adequate reconstruction and resizing of the outflow tract, which is probably important for long term RV function. Avoiding excessive dilation of the outflow tract can be achieved by fixing the progressively dilating outflow tract at a reasonable size; this can be done with a stent. This approach will not adversely affect the hemodynamics as PR is typically already maximal, but it will stabilize the outflow tract and prevent further dilation. Subsequently, the outflow tract stent can become the landing zone for safe and adequate PPVI with a currently available valved stent.

With the current 26 mm maximal diameter limit for PPVI valves, a mildly stretched RVOT with a retention zone of about 24 mm is now the upper limit; this RVOT diameter is usually reached by the age of 10–12 years. Prestenting should therefore ideally be performed prior to this age. PPVI can be performed once the stent is fixed by ingrowth or later when indicated. The optimal timing of the "RVOT preparation" has to be determined and the outcome should be evaluated in comparison with surgical pulmonary valve replacement and RVOT reconstruction.

Expansion of Surgical Conduits

Current official indications for PPVI are deployment in a conduit diameter >16 mm for the Melody valve and 22 mm for the Sapien valve; the conduit should not be dilated beyond nominal value. These restrictions disqualify many patients from PPVI. Current techniques allow for expanding many surgical conduits well beyond nominal values. Initially, interventionalists concentrated on the feasibility and safety of percutaneous valve delivery; this has now been proven. We now need to concentrate on adequate and optimal gradient relief, which frequently implies significant dilatation of the conduit. In such circumstances, use of a covered stent prior to PPVI is essential for safety: "conservative" expansion of shrunken conduits up to nominal value during PPVI may result in conduit fracture, extravascular leakage, and significant bleeding in 1–5% of cases, as the valved stent typically will not cover the ends of the conduit [14,15]. A much higher incidence of extravasation can be expected when expanding the conduit well beyond nominal size. Our series is small but in some patients we obtained significant conduit expansion. For example, expansion of the conduit diameter from 9

to 20 mm results in a 222% increase in circumference and a 493% increase in cross-sectional area, which could cause a conduit tear or fracture and major hemorrhage in the absence of a covered stent. In our opinion, it is important to cover the full conduit length, overlapping the proximal and distal anastomosis. This allows safe and adequate dilation at the initial implanting procedure, and subsequently if further dilation is required to accommodate for somatic growth or a new PPVI in time. The discussion is still open whether sealing by stent flaring and tissue ingrowth is required for safe overdilation of a shrunken and calcified conduit, both up to and beyond the nominal conduit size. A 2-step procedure appears safer when significant fracture or expansion of a conduit is anticipated.

Off-Label Use of Devices

Off-label device use in an informed consent case is a common and legal practice in most countries and is present in pediatric cardiology in up to 50% of interventions [16]. Issues that arise in off-label use are concerns about safety, ethics, reimbursement, and liability [17–21]. With off-label device use, authorization by the Ethics Committee is often requested, reimbursement may be refused, and if the patient develops unfavorable side effects or outcome—even when not related to the off-label indication—the treating physician may have difficulty legally. It is therefore desirable that labels are re-evaluated and updated. The basic responsibility of regulatory boards (CE, FDA) is to establish reasonable assurance of the safety and effectiveness of medical devices and to regulate their approval, marketing, and package labeling [4,22]. Device manufacturers design preliminary pivotal trials to maximize the possibility of demonstrating efficacy and safety to improve the likelihood of initial approval, thereby restricting the initial labeling. Later expansion of the "indications for use" for already approved devices is very slow if not absent, because the regulatory process is expensive and lengthy.

A small case series, as described in this manuscript, is not sufficient to change labeling of medical devices, but experience is accumulating worldwide. Not only does efficacy and safety of the device for the expanded indications need to be demonstrated, but moreover the patient's benefit, in comparison to the standard therapy, must be evaluated over the short, medium, and long term. Although growing experience with PPVI and the good initial and midterm results are promising, clinical studies comparing the long-term outcome with surgical pulmonary valve replacement are still lacking.

Proposal for Label Adaption

The "conditio sine qua non" for safe and efficient percutaneous valve implantation is the existence of an adequate landing zone. Valves are now being implanted in many locations, provided this basic condition is met [23–25]. If the label were rewritten with current knowledge, a good proposal would be: "PPVI can be performed in a RVOT if an adequate landing zone is available. A landing zone is adequate if it is sufficiently stiff to allow anchoring of the valved stent, and is large enough to be and remain a nonrestrictive connection between the ventricle and the pulmonary artery, without any interference to coronary flow. Ideally, the landing zone should be free of relative motion or wringing (to avoid metal fatigue predisposing for late compression or collapse), with the possibility for subsequent dilatation over its full length to accommodate for somatic growth or future PPVI." This definition will avoid excluding patients from PPVI based on outdated concepts.

Limitations of Study

The study is retrospective and suffers the biases of such investigations. The sample size is relatively small and the follow-up period is short. Mid- and long-term outcomes remain to be investigated.

CONCLUSION

PPVI is safe and feasible even in patients with "unfavorable anatomy" according to current device labeling. Creating an adequate "landing zone" by prestenting is crucial, and the technique of prestenting differs depending on anatomical features. Labels of medical devices need to be updated; this role should not be left to the companies or regulatory boards only, but experience and common sense from the field should have an appropriate input.

REFERENCES

1. Bonhoeffer P, Boudjemline Y, Saliba Z, Merckx J, Aggoun Y, Bonnet D, Acar P, Le Bidois J, Sidi D, Kachaner J. Percutaneous replacement of pulmonary valve in a right ventricle to pulmonary artery prosthetic conduit with valve dysfunction. Lancet 2000;21:1403–1405.
2. Khambadkone S, Nordmeyer J, Bonhoeffer P. Percutaneous implantation of the pulmonary and aortic valves: Indications and limitations. J Cardiovasc Med 2007;8:57–61.
3. Kenny D, Hijazi ZM, Kar S, Rhodes J, Mullen M, Makker R, Shirali G, Fogel M, Fahey J, Heitschmidt MG, Cain C. Percutaneous implantation of the Edwards SAPIEN transcatheter heart valve for conduit failure in the pulmonary position. J Am Coll Cardiol 2011;58:2248–2256.
4. Price MJ, Teirstein PS. The off-versus on-label use of medical devices in interventional cardiovascular medicine: Clarifying

the ambiguity between regulatory labeling and clinical decision-making, Part 1: PCI. Catheter Cardiovasc Interv 2008;72:500–504.

5. Lurz P, Coats L, Khambadkone S, Nordmeyer J, Boudjemline Y, Schievano S, Muthurangu V, Lee TY, Parenzan G, Derrick G, Cullen S, Walker F, Tsang V, Deanfield J, Taylor AM, Bonhoeffer P. Percutaneous pulmonary valve implantation: Impact of evolving technology and learning curve on clinical outcome. Circulation 2008;117:1964–1972.

6. Bonhoeffer P, Boudjemline Y, Qureshi SA, Le Bidois J, Iserin L, Acar P, Merckx J, Kachaner J, Sidi D. Percutaneous insertion of the pulmonary valve. J Am Coll Cardiol 2002;39:1664–1669.

7. Khambadkone S, Coats L, Taylor A, Boudjemline Y, Derrick G, Tsang V, Cooper J, Muthurangu V, Hegde SR, Razavi RS,Pellerin D, Deanfield J, Bonhoeffer P. Percutaneous pulmonary valve implantation in humans: Results in 59 consecutive patients. Circulation 2005;112:1189–1197.

8. Sridharan S, Coats L, Khambadkone S, Taylor AM, Bonhoeffer P. Images in cardiovascular medicine. Transcatheter right ventricular outflow tract intervention: The risk to the coronary circulation. Circulation 2006;113:e934–e935.

9. Schievano S, Coats L, Migliavacca F, Norman W, Frigiola A, Deanfield J, Bonhoeffer P, Taylor AM. Variations in right ventricular outflowtract morphology following repair of congenital heart disease: Implications for percutaneous valve implantation. J Cardiovasc Magn Reson 2007;9:687–695.

10. Momenah TS, El Oakley R, Al Najashi K, Khoshhal S, Al Qethamy H, Bonhoeffer P. Extended application of percutaneous pulmonary valve implantation. J Am Coll Cardiol 2009; 19;53:1859–1863.

11. Gewillig M, Mertens L, Stockx L. Percutaneous fenestration of the atrial septum with a stent: An experimental study. Cor Europaneum 1995;4:122–125.

12. Boudjemline Y, Agnoletti G, Bonnet D, Sidi D, Bonhoeffer P. Percutaneous pulmonary valve replacement in a large right ventricular outflow tract: An experimental study. J Am Coll Cardiol 2004;43:1082–1087.

13. Robb JD, Harris MA, Minakawa M, Rodriguez, Koomalsingh KJ, Shuto T, Shin DC, Dori Y, Glatz AC, Rome JJ, Gorman RC, Gorman JH III, Gillespie MJ. Melody valve implantation into the branch pulmonary arteries for treatment of pulmonary insufficiency in an ovine model of right ventricular outflow tract dysfunction following tetralogy of fallot repair. Circ Cardiovasc Interv 2011;4:80–87.

14. Kostolny M, Tsang V, Nordmeyer J, Van Doorn C, Frigiola A, Khambadkone S, de Leval MR, Bonhoeffer P. Rescue surgery following percutaneous pulmonary valve implantation. Eur J Cardiothorac Surg 2008;33:607–612.

15. McElhinney DB, Hellenbrand WE, Zahn EM, Jones TK, Cheatham JP, Lock JE, Vincent JA. Short- and medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US melody valve trial. Circulation 2010;122:507–516.

16. Sutherell JS, Hirch R, Beekman RH. Paediatric interventional cardiology in the United States is dependent on the off-label use of medical devices. Congenit Heart Dis 2010;5:2–7.

17. Smith JJ, Berlin L. Malpractive issues in radiology: Off-label use of interventional medical devices. Am J Radiol 1999;173:539–542.

18. Smith JJ. Regulatory and legal implications of modifying FDA-approved medical devices. J Vasc Interv Rad 2000;11:19–23.

19. Beekman RH, Duncan BW, Hagler DJ, Joned TK, Kugler JD, Moore JW, Jenkins KJ. Pathways to approval of pediatric cardiac devices in the United States: Challenges and solutions. Pediatrics 2009;124:155–162.

20. Hill P. Off license and off label prescribing in children: Litigation fears for physicians. Arch Dis Child 2005;90:i17–18.

21. Zvavanjanja RC, Odetoyinbo TO, Rowlands PC, Healey A, Abdelsalam H, Powell S, Evans JC, Hughes ML, Gould DA, McWilliams RG. Off label use of devices and drugs in interventional radiology. Clin Radiol 2012;67:239–243.

22. FDA. Device labeling guidance (G91-1). Available at: http://www.fda.gov/cdrh/g91-1.html;1991, Accessed February 2, 2012.

23. Gewillig M, Dubois C. Percutaneous re-revalvulation of the tricuspid valve. Catheter Cardiovasc Interv 2011;77:692–695.

24. Roberts PA, Boudjemline Y, Cheatham JP, Eicken A, Ewert P, McElhinney DB, Hill SL, Berger F, Khan D, Schranz D, Hess J, Ezekowitz MD, Celermajer D, Zahn E. Percutaneous tricuspid valve replacement in congenital and acquired heart disease. J Am Coll Cardiol 2011;58:117–122.

25. Kondo N, Shuto T, McGarvey JR, Koomalsingh KJ, Takebe M, Gorman RC, Gorman JH III, Gillespie MJ. Melody valve-in-ring procedure for mitral valve replacement: Feasibility in four annuloplasty types. Ann Thorac Surg 2012;93:783–788.