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Percutaneous pulmonary valve implantation: two-centre experience with more than 100 patients

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Aims Dysfunction of valved conduits in the right ventricular outflow tract (RVOT) limits durability and enforces repeated surgical interventions. We report on our combined two-centre experience with percutaneous pulmonary valve implantation (PPVI).

Methods and results One hundred and two patients with RVOT dysfunction [median weight: 63 kg (54.2–75.9 kg), median age: 21.5 years (16.2–30.1 years), diagnoses: TOF/PA 61, TAC 14, TGA 9, other 10, AoS post-Ross-OP 8] were scheduled for PPVI since December 2006. Percutaneous pulmonary valve implantation was performed in all patients. Pre-stenting of the RVOT was done in 97 patients (95%). The median peak systolic RVOT gradient decreased from 37 mmHg (29–46 mmHg) to 14 mmHg (9–17 mmHg, $P < 0.001$) and the ratio RV pressure/AoP decreased from 62% (53–76%) to 36% (30–42%, $P < 0.0001$). The median end-diastolic RV-volume index (MRI) decreased from 106 mL/m^2 (93–133 mL/m^2) to 90 mL/m^2 (71–108 mL/m^2, $P = 0.001$). Pulmonary regurgitation was significantly reduced in all patients. One patient died due to compression of the left coronary artery. The incidence of stent fractures was 5 of 102 (5%). During follow-up [median: 352 days (99–390 days)] one percutaneous valve had to be removed surgically 6 months after implantation due to bacterial endocarditis. In 8 of 102 patients, a repeated dilatation of the valve was done due to a significant residual systolic pressure gradient, which resulted in a valve-in-valve procedure in four.

Conclusion This study shows that PPVI is feasible and it improves the haemodynamics in a selected patient collective. Apart from one coronary compression, the rate of complications at short-term follow-up was low. Percutaneous pulmonary valve implantation can be performed by experienced interventionalists with similar results as originally published. The intervention is technically challenging and longer clinical follow-up is needed.

Keywords Right ventricular outflow tract dysfunction • Percutaneous pulmonary valve implantation

Introduction

Surgical procedures like correction of common arterial trunc involve placement of a conduit between the right ventricle and the pulmonary artery in young infants.[1] Due to patient growth and conduit degeneration, these conduits have to be exchanged frequently. Today surgical conduit revision can be performed with a very low perioperative mortality.[2,3] However, morbidity is significant in these repeated operations. One larger study showed that adult sized valved conduits (>18 mm) have a mean freedom from reoperation of 11.2 years.[4] To expand the lifetime of these biological conduits and to reduce the number of operations during a lifetime Bonhoeffer *et al.*[5] developed the concept of percutaneous pulmonary valve implantation (PPVI). Percutaneous pulmonary valve implantation has emerged as the preferred treatment for selected patients with conduit dysfunction in the

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pulmonary position at some centres. Percutaneous pulmonary valve implantation is feasible at a relatively low risk[6] and mid-term follow-up shows a sustained improvement of haemodynamics.[7] So far only limited experience with PPVI of other groups than Bonhoeffer's is available.[8]

The current study was undertaken to document safety and efficacy of PPVI at two large tertiary paediatric cardiological referral units and to answer the question whether the above-mentioned results can be reproduced by others.

Methods

Patient selection

All 102 consecutive patients who were scheduled for PPVI at the German Heart Centres Munich and Berlin between December 2006 and July 2010 were included in the study. The indication for PPVI is depicted in *Table 1*. Indication for treatment was a right ventricular outflow tract (RVOT) dysfunction resulting in significant pulmonary regurgitation with evidence of right ventricular dysfunction and/or an RVOT obstruction with right ventricular systolic pressures being a least 2/3 systemic. All patients received a clinical examination, a posterior–anterior chest X-ray, a standard 12-lead ECG, a 24 h Holter-ECG recording, a trans-thoracic echocardiography, and a cardiopulmonary exercise test. Peak oxygen consumption (VO_{2max}) at anaerobic threshold was measured by the V-slope method and cross checked with the ventilatory equivalent method. A cardiac MRI (cMRI) study was done and ventricular mass and volumes were acquired as previously described.[9]

Table 2 shows the schedule of examinations pre- and post-PPVI. If the conduit size exceeded 22 mm in diameter at the whole conduit length (cMRI) the patients were excluded.

Patients

Median patient age was 21.5 years (16.2–30.1 years), median weight was 63 kg (54.2–75.9 kg). There were 40 females and 62 males. A stenosis was the leading lesion in 36 patients, regurgitation in 18, and a combination of these two in the majority of patients (48). Sixty-one patients had undergone surgical correction of a tetralogy of Fallot/pulmonary atresia with VSD, 14 had a common arterial trunc, 9 a transposition of the great arteries after a Rastelli-operation/arterial switch OP, 8 patients with aortic stenosis after a Ross operation had early homograft dysfunction, and 10 patients had a variety of other cardiac lesions. The conduits used during previous surgery were: 79 homografts, 6 bovine jugular vein with valve (Contegra®, Medtronic, Inc., Minneapolis, MN, USA), 3 Hancock® conduits (Medtronic, Inc., Minneapolis, MN, USA), 1 matrix bioprosthesis, 6 non-valved tube grafts, 1 porcine valved conduit (Shelhigh® pulmonic valved conduit, Shelhigh, Inc., Union, NJ, USA), and 1 Carpentier-Edwards biological valve (Edwards Lifesciences, Irvine, CA, USA). Five patients had a 'native' RVOT without a conduit. On average the patients had three preceding cardiac operations (one to five operations; *Table 3*).

Table 1 Indication for percutaneous pulmonary valve implantation

Age >5 years, weight >20 kg
Conduit right ventricular outflow tract > (16) 18 mm ≤22 mm
Severe pulmonary regurgitation, progredient RV dilatation and reduced RV function
Symptomatic patients with declining exercise tolerance (<65% of normals)
Increased RV pressure (>/2/3 systemic pressure)
A combination of stenosis and regurgitation with RV dysfunction and dilatation
Supraventricular or ventricular rhythm disturbances

Percutaneous pulmonary valve implantation

The technique of PPVI has been described previously.[10] The intervention was carried out under general anaesthesia, or in deep sedation. After transcutaneous femoral vessel access was achieved (artery and vein) a complete haemodynamic study was done. This was followed by angiocardiography. A selective coronary angiogram was often combined with balloon inflation in the conduit as it was suggested by Sridharan *et al.*[11] This was done to exclude potential coronary arterial compression during valve implantation and dilatation with high-pressure balloons. Then, usually a stent was delivered into the conduit and if necessary redilated with high-pressure balloons to at least an internal diameter of 18 mm. The bovine valve integrated in a covered stent (Melody®, Medtronic, Inc., Minneapolis, MN, USA) was then delivered and redilated if necessary until the peak invasive systolic gradient was <20 mmHg. A complete haemodynamic study and angiograms were repeated to document the results. All interventions were carried out with surgical stand-by.

Follow-up

Before discharge (usually 2–3 days after PPVI), a clinical examination, a posterior–anterior and a lateral chest X-ray, a standard 12-lead ECG, a trans-thoracic echocardiography, and a cMRI study were repeated. Six to 12 months after the intervention, the cardiopulmonary exercise test and the MRI were repeated. From then on the patients were seen annually with chest X-rays in two planes and a complete out-patient cardiological work-up (*Table 2*).

Statistical analysis

All data are expressed as median values and the interquartile range (first and third quartiles). A Wilcoxon matched pairs signed-ranks test was used to assess statistical significance defined at P values < 0.05. For statistical analysis StatView 4.5 (Abacus concepts, Inc. 1992–95) was used.

Results

Immediate results of percutaneous pulmonary valve implantation

In 96 of 102 patients, pre-stenting of the RVOT was done. Usually, pre-stenting was performed with a 36- or 26 mm long EV3 Max® LD stent (ev3, Inc., Plymouth, MN, USA). In patients with severely narrowed or native RVOT-covered CP Stents® (NuMED, Inc., Hopkinton, NY, USA) were used for this purpose. Post-PPVI dilatation was performed in 75 of 102 (72%) of the patients. A high-pressure balloon (18, 20, or 22 mm in diameter) was used. The minimal conduit diameter was enlarged from a median value of 13 mm (11–15 mm) to 20 mm (19–22 mm) ($P < 0.0001$). In one patient the homograft diameter was decreased from 23 mm by pre-stenting with two covered 34 mm CP stents to prepare as a landing zone for a 22 mm delivery system. The systolic gradient

Table 2 Examinations of pre- and post-percutaneous pulmonary valve implantation

	Pre-PPVI	Discharge	6 months	Annually
Clinical assessment	x	x	x	x
Echocardiogram	x	x	x	x
2-plane thoracic X-ray[a]	x	x	x	x
Electrocardiogram	x	x	x	x
cMRI	x	x	x	x
Exercise test	x		x	x

x, this test was done.
[a]if stent fracture was suspected 2D fluoroscopy was done.

Table 3 Patient characteristics previous to percutaneous pulmonary valve implantation (102 patients)

Gender	Female, 40; male, 62	
Diagnosis	TOF/PA, 61; TAC, 14; TGA, 9; AoS, 8; other, 10	
Conduit RV-PA	Homograft, 79; Contegra, 6; non-valved, 6; Hancock, 3	
	Shelhigh, 1; matrix, 1; Carpentier-Edwards, 1; none, 5	
Pre-stenting	Yes, 97; no, 5	
Parameter	Median	First and third quartiles
Age at PPVI (years)	21.5	16.2–30.1
Weight (kg)	63.0	54.2–75.9
Pre-peak Doppler gradient (mmHg)	58	42–74
Pre mean Doppler gradient (mmHg)	36	26–44
Pre-peak systolic gradient (mmHg)	37	29–46
Conduit diameter at implant (mm)	21	19–23
Minimal conduit diameter (mm)	13	11–15
Pre-RVEDvol (mL/m^2)	106	93–133
Pre-RVEF (%)	51	41–58
Pre-pulmonary regurgitation MRI (%)	16	5–26
Pre-VO_{2max} (mLO_2/kg)	22	17–30

RV-PA, right ventricle to pulmonary artery; TOF, tetralogy of Fallot; PA, pulmonary atresia; TAC, common arterial trunc; TGA, transposition of the great arteries; AoS, aortic stenosis; RVEDvol, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; MRI, magnetic resonance imaging.

between the right ventricle and the pulmonary artery (*Figure 1*) was reduced from a median value of 37 mmHg (29–46 mmHg) to 14 mmHg (9–17 mmHg, $P < 0.0001$). The ratio between systolic right ventricular and aortic pressure (*Figure 2*) was decreased from a median value of 62% (53–76%) to 36% (30–42%, $P < 0.001$). In patients with nearly normal RV pressure, pulmonary regurgitation was the prevailing cardiac lesion. Pulmonary regurgitation assessed by MRI was reduced from a median value of 16% (5–26%) to 1% (0–2%, $P < 0.001$; *Figure 3*). Median fluoroscopy

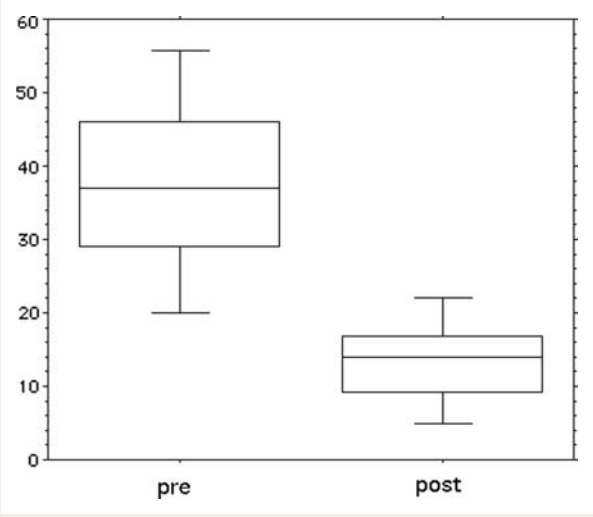

Figure 1 The median peak invasive gradient between the right ventricle and the pulmonary artery was reduced from 37 to 14 mmHg ($P < 0.001$).

time was 32.2 min (19.3–45 min). The right ventricular end-diastolic volume index assessed by MRI decreased from a median value of 106 mL/m^2 (93–133 mL/m^2) to a median value of 90 mL/m^2 (71–108 mL/m^2, $P < 0.001$) before hospital discharge. The patients were discharged home at median 2 days after the intervention.

Complications

One patient showed severe compression of the left coronary artery at the origin of the vessel. He had TGA after a Rastelli procedure and primarily the intervention was uneventful with documented unchanged perfusion of the left coronary artery (LCA) at the end of the procedure. Four hours after, PPVI cardiopulmonary resuscitation led to an emergency operation. An intraoperative aortogram showed complete occlusion of the LCA. Even though the Melody valve was replaced by a Contegra graft and the coronary artery was patent afterwards the patient could not be weaned from an LVAD and died 2 weeks later. Complete AV block occurred in one patient during PPVI. After 21 days sinus rhythm recurred until today without pacemaker implantation. Two

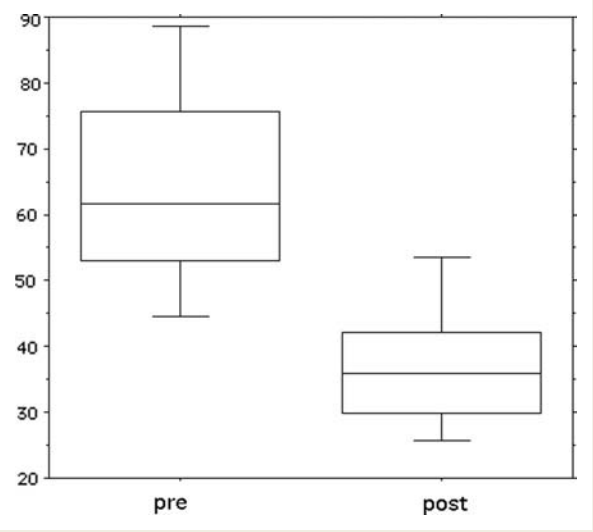

Figure 2 The pressure ratio between the right ventricle and the aorta decreased from 62 to 36% ($P < 0.0001$).

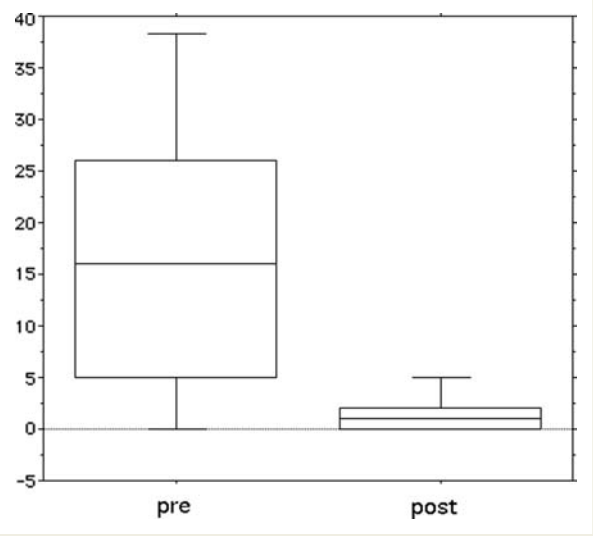

Figure 3 Pulmonary regurgitation assessed by magnetic resonance imaging was reduced from a median value of 16 to 1% ($P < 0.001$).

patients showed fracture of a single stent strut, which was present on chest X-ray before hospital discharge. All of these fractures were classified as a type-I fracture (stent fracture of one or more struts, no loss of stent integrity) using the classification suggested by Nordmeyer *et al.*[12] One patient developed endocarditis with *Staphylococcus aureus* 6 months after PPVI. The Melody valve was removed surgically and replaced by a homograft valve.

Repeated catheterization

So far, 9 of 102 (9%) patients had a repeated catheterization due to a peak systolic Doppler gradient >50 mmHg between the RV and the pulmonary artery. In eight of these patients, a repeated balloon dilatation was done. In three of these patients, the Melody stent showed longitudinal fractures during redilatation and a valve-in-valve procedure resulted in an adequate gradient relief. One additional valve-in-valve procedure was done. In the other four patients, a redilatation of the valve sufficiently improved the haemodynamic result. Finally, in one patient with a distal pulmonary artery stenosis PPVI resulted in partial occlusion (90%) of the origin of the right pulmonary artery. On re-catheterization, the right pulmonary artery (RPA) was dilated with an 18 mm balloon, which led to free flow to the RPA.

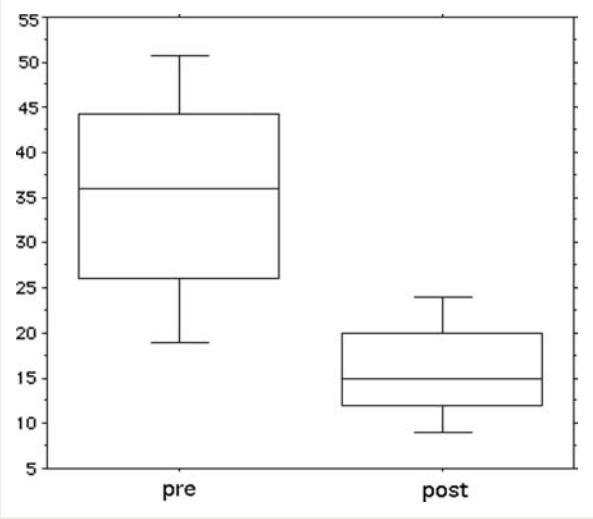

Figure 4 The mean Doppler gradient in the right ventricular outflow tract decreased from a median value of 36 mmHg pre PPVI, to a median value of 15 mmHg at the latest follow-up examination ($P < 0.0001$).

Follow-up

The median follow-up time is 357 days (99–388 days). The median mean Doppler gradient in the RVOT decreased from a median value of 36 mmHg (26–44 mmHg) pre-PPVI, to a median value of 15 mmHg (12–20 mmHg) at the latest follow-up examination ($P < 0.0001$; *Figure 4*). On exercise testing VO_{2max} remained unchanged with a median value of 22.4 mlO_2/kg/min pre- vs. 22.8 mlO_2/kg/min post PPVI.

Discussion

Immediate results after percutaneous pulmonary valve implantation

This study shows that PPVI can be performed in patients with conduit dysfunction in the RVOT by experienced paediatric interventionalists after adequate training. The haemodynamics of the treated patients improved and the rate of complications was low in our two-centre series. Following PPVI, the patients were discharged home at median 2 days post-PPVI. Hence, patients are discharged home earlier than patients after surgical valve replacement. The gradient reduction between the right ventricle and the pulmonary artery in our study is similar to the values

reported by Lurz et al.[7] in a recent publication. The same holds true for the abolishment of pulmonary regurgitation and the improvement of the ratio of systolic pressures in the right ventricle in correlation with the aortic pressures (RV:AoP).

At present we can only report a limited follow-up experience. So far, only 1 of 102 patients needed surgical RVOT revision because of the onset of endocarditis 6 months after PPVI. In the study by Lurz et al.[7] freedom from reoperation was 93, 86, 84 and 70% at 10, 30, 50 and 70 months, respectively. The rate of repeated catheterizations due to a peak systolic pressure gradient >50 mmHg was 9%. Balloon dilatation was successful in four patients and resulted in a valve-in-valve procedure in the remaining four patients.

Pre-stenting during PPVI

Nordmeyer et al.[12] reported an incidence of 21.1% (26 of 123) of stent fractures 0–843 days after PPVI. Type-I fractures ($n = 17$) were classified to be without haemodynamic relevance. Two of our patients presented type-I stent fractures at hospital discharge. These patients did not present with an increasing gradient in the RVOT and hence, the fractures are yet without any haemodynamic relevance. In the publication by Nordmeyer et al., nine fractures were classified to be significant type II: loss of integrity with restenosis on echocardiography ($n = 8$) and type III: separation of fragments or embolization ($n = 1$). It is expected that pre-stenting the conduit with a strong stent may reduce the incidence of type-II or -III stent fractures. If they occur, a valve-in-valve procedure has been suggested.[13] In our series pre-stenting was performed in 95% of all cases. The total incidence of stent fractures was only 5 of 102 (5%) and significantly lower than that reported by Nordmeyer et al.[13] Three patients developed type-II stent fractures during repeated balloon dilatation at a second catheterizatiton for significant residual RVOT obstruction. A successful valve-in-valve procedure was done in all three. High-pressure balloon dilatation of a Melody valve in a heavily calcified conduit may increase the risk for stent fracture. Preparing the landing zone of the valve with strong metal stents may help to avoid this complication. Homograft rupture during PPVI has occurred[14] but was not a clinical problem in this series. Preparing the RVOT by pre-stenting to at least a diameter of 18 mm without any residual stenosis facilitates the actual deployment of the transvenous valve and is in our eyes a key issue to achieve a good haemodynamic result. In patients with narrow stenotic RVOTs the implantation of a covered stent during pre-stenting may reduce the possible clinical impact of conduit rupture. Using this policy we experienced no RVOT perforation with the need of surgical intervention.

Coronary arterial compression

The only mortality in our series occurred due to coronary arterial compression. Patients at risk can be identified by a dedicated cMRI examination. If at risk, a selective coronary angiogram together with a dilatation of a high-pressure balloon to the maximal estimated diameter in the RVOT may help to prevent this fatal complication.[11] Although in our case we were fully aware of the vicinity of the left coronary artery and the RVOT stents, the fatal coronary occlusion occurred hours after the successful intervention. Thus, in any doubtful cases PPVI should not be performed.

Indication for treatment and patient selection for PPVI

Originally, only patients with dysfunction of a biological valved conduit were treated by PPVI. However, as has recently been shown, selected patients (five in our group) with a 'native' RVOT are amenable for PPVI.[15] As for surgery, a right ventricular systolic pressure >2/3 systemic pressure was an indication for treatment if the RVOT was primarily stenotic. Severe pulmonary regurgitation after an intervention in the RVOT can be tolerated well for years[16] but is not a benign cardiac lesion. Even though these patients feel well subjectively, exercise tolerance is reduced[17] and only 24% of patients are free of cardiac symptoms at an age of 64 years.[16] The correlation between QRS duration and RV dilation as a risk factor for sudden death long term after Fallot correction is known for years.[18,19] Today cMRI is the best diagnostic tool to assess ventricular volumes, mass, and function.[9,20] Serial MRI examinations are possible and may document improvement of RV dimensions and function after RVOT valve replacement.[21]

Yet the timing of when to intervene in the presence of severe pulmonary regurgitation is unclear. A RV volume index of >180 mL/m^2 was critical in adults after TOF repair[22] but younger children showed right ventricular remodelling at even larger RV volumes.[23] Prospective randomized trials on the timing for intervention in the presence of pulmonary regurgitation or a critical right ventricular volume 'point of no return' are not available. One recent multicentre study[24] found normalization of RV volume after pulmonary valve replacement when preoperative RV end-diastolic volume was <160 mL/m^2 or RV end-systolic volume was <82 mL/m^2. Another study stated that a policy of pulmonary valve replacement at a RV end-diastolic volume of <150 mL/m^2 lead to normalization of right ventricular volumes, improvement of biventricular function, and submaximal exercise capacity.[25] In contrast to these recommendations, Harrild et al.[26] stated that late pulmonary valve replacement for symptomatic pulmonary regurgitation/RV dilatation did not reduce the incidence of VT or death.

In our institution we use a combination of cMRI assessment (sometimes serial examinations), exercise testing, and clinical evaluation (Holter-ECG, echoardiography) to find the right time for pulmonary valve replacement. If PPVI proves to be effective on the long term, the threshold to implant the valve may be lowered since it results in a significant improvement of haemodynamics.

Study limitations

So far only short-term follow-up is available. It remains to be proved whether the improvements in haemodynamics by PPVI persist and the goal to reduce the number of cardio-thoracic operations during a lifetime of the treated patients can be achieved in a large patient collective.

Conclusion

This study shows that PPVI can be performed by an experienced structural heart disease interventionalist in patients with

dysfunction of the RVOT. The presented results are similar to those presented by Bonhoeffer *et al.*[5]. The rate of complications was low and the patients could be discharged home earlier than after a regular surgical pulmonary valve replacement. Medium- and long-term follow-up needs to be assessed to document sustained benefit for the patients.

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