Surgical therapy of infective endocarditis following interventional or surgical pulmonary valve replacement

Gregor Gierlinger [iD] [a,*], Eva Sames-Dolzer[a], Michaela Kreuzer[a], Roland Mair [iD] [a],

Andreas Zierer[b] and Rudolf Mair [iD] [a]

[a] Division of Pediatric and Congenital Heart Surgery, Kepler University Hospital, JKU, Linz, Austria
[b] Department for Thoracic and Cardiovascular Surgery, Kepler University Hospital, JKU, Linz, Austria

* Corresponding author. Department für Kinderherzchirurgie, Kepler Universitätsklinik, JKU, Med Campus III. Krankenhausstrasse 9, Linz 4020, Austria.
  Tel: +43-732-7806-78230; e-mail: gregor.gierlinger@kepleruniklinikum.at (G. Gierlinger).
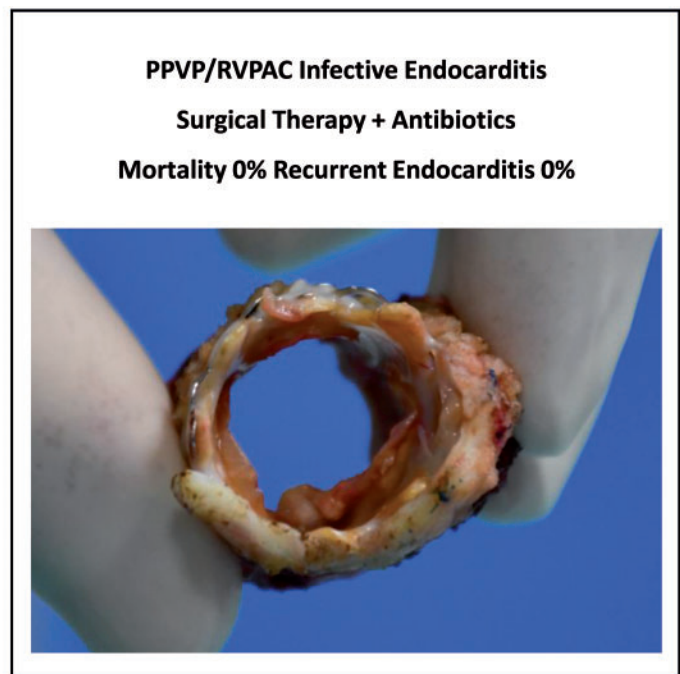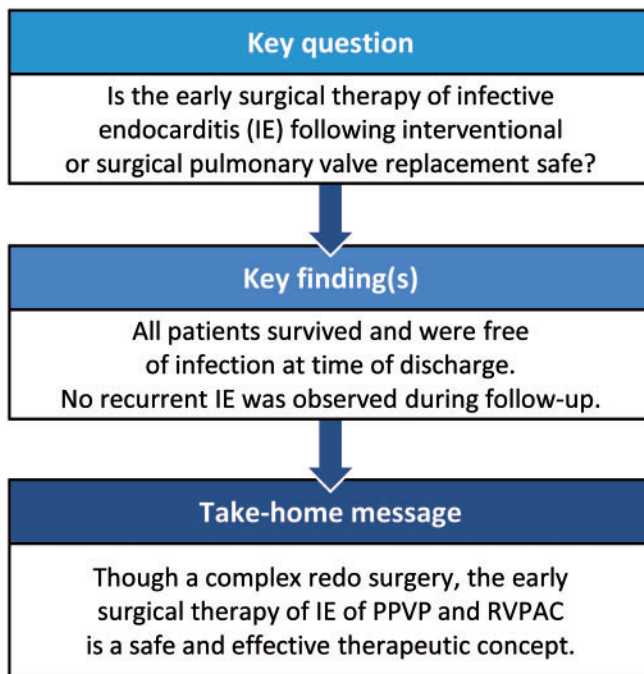
Abstract

OBJECTIVES: Percutaneous pulmonary valve prostheses and right ventricle-to-pulmonary artery conduits are at risk for infective endocarditis (IE). In children and adults with a congenital heart disease, a pulmonary valve implant is frequently necessary. Prosthetic valve endocarditis is a conservatively barely manageable, serious life-threatening condition. We investigated the results of surgical pulmonary valve replacements in patients with IE.

METHODS: A total of 20 patients with congenital heart disease with the definite diagnosis of IE between March 2013 and July 2020 were included in this single institutional, retrospective review. Infected conduits were 11 Melody, 5 Contegra, 3 homografts and 1 Matrix P Plus. All of the infected prosthetic material was removed from the right ventricular outflow tract up to the pulmonary bifurcation. Pulmonary homografts were implanted after pulmonary root resection as right ventricle-to-pulmonary artery conduits.

RESULTS: All patients survived and were discharged infection-free. The mean time from the conduit implant to the operation for IE was 4.9 years [95% confidence interval (CI), 3.0–6.9]. The median intensive care unit stay was 3.0 days (95% CI, 2.0–4.7), and the median hospital time was 25.0 days (95% CI, 19.2–42.0). Median follow-up time was 204.5 days (range 30 days to 5 years) without death or recurrent endocarditis.

CONCLUSIONS: The surgical treatment of IE of percutaneous pulmonary valve prostheses and right ventricle-to-pulmonary artery conduits is a safe and effective therapeutic concept. Early surgical referral of patients with suspicion of IE should be pursued to avoid sequelae such as right ventricular failure, septic emboli, intracardiac expansion and antibiotic resistance.

Keywords: Infective endocarditis • Prosthetic pulmonary valve • Congenital heart disease • Percutaneous pulmonary valve prosthesis • Right ventricle-to-pulmonary artery conduit

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ABBREVIATIONS

CAT	Common arterial trunk
CI	Confidence interval
IE	Infective endocarditis
PPVP	Percutaneous pulmonary valve prosthesis
RVPAC	Right ventricle-to-pulmonary artery conduit

INTRODUCTION

Percutaneous pulmonary valve prosthesis (PPVP) and right ventricle-to-pulmonary artery conduit (RVPAC) are at risk for infective endocarditis (IE) [1, 2]. In children and adults with a congenital heart disease like tetralogy of Fallot, double outlet right ventricle, common arterial trunk (CAT), pulmonary atresia with intact ventricular septum and aortic valve disease managed with a Ross or Ross–Konno procedure, a pulmonary valve implant is frequently necessary.

Septic vegetations and infected valve leaflets of the pulmonary valve prosthesis produce stenosis and insufficiency that compromise right ventricular function and potentially lead to severe tricuspid regurgitation. An alarming clinical course can show fewer, dyspnoea, venous congestion resulting in ascites and lower extremity oedema. Vegetations can embolize into the pulmonary arteries leading to right ventricular failure or local abscess formation.

Typical microbes found in blood cultures from prosthetic pulmonary valve endocarditis are *Viridans streptococci*, *Staphylococcus aureus* (methicillin resistant and sensitive), *Staphylococcus epidermidis*, the *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* species group, *Enterococcus faecalis* and *Candida* species [3–7].

The 2015 European Society of Cardiology guidelines for management of IE recommended antibiotic prophylaxis in high-risk procedures for patients with congenital heart disease who have prosthetic valves or cyanotic congenital heart disease or if prosthetic material was implanted in the last 6 months [8].

Although it is a general surgical principle to remove infected foreign bodies, the optimal treatment for prosthetic pulmonary valve IE is still debated and varies between medical treatment only and surgery plus medical treatment favouring the combined therapy in only 50–64.5% [6, 7, 9] of cases. Clear indications for or against those 2 strategies were not found in the literature.

Our goal was to investigate the results of surgical prosthetic valve replacement in patients with IE at our centre.

Table 1: Patient details

Variable	Patients (*n* = 20)		
Male sex, *n*	15	(75%)	
Mean height (cm)	152.7	[139.4–165.9]	95% CI
Mean weight (kg)	53.6	[41.1–66.1]	95% CI
Mean age (years)	15.9	[12.3–19.4]	95% CI
Children (<18 years), *n*	11	(55%)	
Diagnosis, *n*			
TOF/DORV	9	(45%)	
Aortic valve disease, status post Ross/Ross–Konno	5	(25%)	
Common arterial trunk	4	(20%)	
PA/IVS	1	(5%)	
Borderline LV, status post biventricular conversion after Norwood	1	(5%)	
Infected conduit, *n*			
Melody	11	(55%)	
Contegra	5	(25%)	
Homograft	3	(15%)	
Matrix P Plus	1	(5%)	
Median prior sternotomies	2	(range 1–4)	

CI: confidence interval; DORV: double outlet right ventricle; LV: left ventricle; PA/IVS: pulmonary atresia with intact ventricular septum; TOF: tetralogy of Fallot.

PATIENTS AND METHODS

This retrospective study was approved by the ethics committee of the Medical Faculty at Johannes Kepler University Linz on 14 October 2020 (EK Nr: 1208/2020); written patient informed consent was waived. A total of 20 patients (11 children and 9 adults) were admitted to our centre between March 2013 and July 2020 who had IE following interventional or surgical pulmonary valve replacement. Infected conduits were stented bovine jugular vein grafts (Melody valve; Medtronic, Minneapolis, MN, USA) in 11 (55%) patients, non-stented bovine jugular vein grafts (Contegra; Medtronic) in 5 (25%), homografts in 3 (15%) and a decellularized porcine aortic valve (Matrix P Plus; Auto Tissue Berlin GmbH, Berlin, Germany) in 1 (5%). All of them underwent surgical therapy plus antibiotic treatment. Patient details at the time of surgery are shown in Table 1.

Initial diagnosis of IE was made according to the modified Duke criteria [10] from clinical course, blood culture studies, transthoracic echocardiography and transoesophageal echocardiography. Transthoracic echocardiography was performed in every patient, transoesophageal echocardiography was

Table 2: Patient overview

Results	Patients (*n* = 20)		
Median bypass time (min)	156.5	[111.9–223.7]	95% CI
Mean cross-clamp time (min) (*n* = 12)	64.1	[42.8–85.4]	95% CI
Postoperative complications (bleeding)	5%	[0.1–24.9]	95% CI
Mean time between conduit implant and surgery for IE (years)	4.9	[3.0–6.9]	95% CI
Mean time, Melody (*n* = 11)	4.2	[2.4–5.9]	95% CI
Mean time, Contegra (*n* = 5)	4.1	[0.5–7.7]	95% CI
Median time, homograft (*n* = 3)	12.3	[Not calculable]	
Extubation on day of operation (*n* = 15)	75%	[50.9–91.3]	95% CI
Median ICU stay (days)	3.0	[2.0–4.7]	95% CI
Median hospital time (days)	25.0	[19.2–42.0]	95% CI
Median follow-up after surgery for prosthetic pulmonary valve IE (days)	204.5	[54.5–1031.7]	95% CI

CI: confidence interval; ICU: intensive care unit; IE: infective endocarditis.

undertaken when transthoracic echocardiography was not reliable enough to assess the pulmonary valve. This approach was necessary in 5 out of 20 patients, especially in the adult group. Additional positron emission tomography–computed tomography scans were performed in uncertain cases. Patients with IE were discussed in the heart team meeting, which included paediatric or adult cardiologists who specialized in echocardiography, paediatric and congenital cardiac surgeons and intensive care specialists. We obtained the opinion of infectious disease specialists. The indication for surgery was made if prosthetic pulmonary valve IE was suspected. In 2 patients with IE of the Melody valve, conservative, sole antibiotic therapy was initially started but failed; surgical therapy followed. In all our other patients, we used a primary surgical approach once the diagnosis of prosthetic pulmonary valve IE was made at our centre.

The procedure was performed via a median resternotomy on continuous cardiopulmonary bypass via central cannulation using mild hypothermia. Single or double venous cannulation was used. The aorta was cross-clamped in selected cases due to difficult anatomical conditions and additional procedures. All of the infected prosthetic material and the main pulmonary artery were removed from the right ventricular outflow tract until the pulmonary bifurcation. Additional procedures were necessary in 6 patients (1 in each patient): aortic root replacement with a homograft valve due to the spread of endocarditis and insufficiency of the aortic homograft conduit after CAT repair, replacement of the ventricular septal defect patch, tricuspid valve repair, patent foramen ovale closure, bilateral pulmonary artery stent excision plus pulmonary bifurcation reconstruction and atrial septal defect Amplatzer device removal plus atrial septal defect and residual ventricular septal defect closure (Table 2). In 1 case, an embolectomy of the left pulmonary artery was performed due to an obstructive septic vegetation. In most cases, pulmonary homografts were implanted as orthotopic RVPAC after resection of the pulmonary root. In cases with previous right ventricular outflow tract creation (e.g. CAT and pulmonary atresia with intact ventricular septum), the RVPAC was resected completely, and the homograft was implanted distally to the novel right ventricular outflow tract.

Specific antibiotic treatment was maintained for at least 6 weeks after the initial effective antibiotic therapy according to guideline recommendations [8]. Amoxicillin/clavulanic acid or cephalosporin antibiotics were used for highly susceptible infections. If a positive microbial culture could no longer be achieved, teicoplanin or gentamicin was given for broad antibiotic coverage. Amphotericin B combined with voriconazole was given to 1 patient with invasive aspergillosis. Antibiotics were switched from intravenous to oral administration in only 3 selected patients because we identified the specific microbe and because we administered an antibiotic intravenous course over several days postoperatively: dalbavancin (intravenously every 2 weeks) plus oral penicillin was used in 1 patient; oral penicillin alone was used in the other 2 patients.

Statistical analyses

All data sets of continuous variables (total collective) were checked for normal distribution (test of normality: Kolmogorov–Smirnov with Lilliefors significance correction, type I error = 10%). For normally distributed data sets, parametric two-sided 95% confidence intervals were calculated; otherwise, we calculated non-parametric two-sided 95% confidence intervals. For categorical variables, two-sided 95% confidence intervals according to the Clopper–Pearson method were calculated.

RESULTS

All patients survived and were discharged home infection-free. The median bypass time was 156.5 min [95% confidence interval (CI), 111.9–223.7] and aortic cross-clamp time was required in 12 patients [mean 64.1 min (95% CI, 42.8–85.4)] (Table 3). One patient needed early revision because of postoperative bleeding [5% (95% CI, 0.1–24.9)].

Patient ventilation charts showed that 15 [75% (95% CI, 50.9–91.3)] patients could be weaned off the ventilator on the day of the operation. Four [20% (95% CI, 5.7–43.7)] more patients were extubated on postoperative day 1, and 1 [5% (95% CI, 0.1–24.9)] patient had a prolonged ventilation course due to respiratory insufficiency and right ventricular dysfunction. All in all, the median stay in the intensive care unit was 3.0 days (95% CI, 2.0–4.7), and the median hospital stay was 25.0 days (95% CI, 19.2–42.0). A prolonged hospital stay was caused mainly by the need for extensive antibiotic treatment. One patient with preoperative severe chronic cardiac failure is still suffering from right heart failure but could be discharged home. This patient failed an initial prolonged antibiotic treatment in a foreign centre and underwent surgery in a highly critical status. One patient had a delayed sternum closure on postoperative day 1 due to temporary post-bypass suprasystemic right ventricle pressures and haemodynamic instability. No extracorporeal membrane oxygenation therapy was necessary. No neurological complications were observed.

The mean time from the conduit implant to surgery for IE was 4.9 years (95% CI, 3.0–6.9). The Melody [mean 4.2 years (95% CI, 2.4–5.9)] and the Contegra [mean 4.1 years (95% CI, 0.5–7.7)] prosthetic pulmonary valves tended to show a shorter time to IE than the homografts [median 12.3 years (95% CI, not calculable)], but due to the low patient numbers, a statistical comparison was not possible.

Table 3: Results

Number	Diagnosis	Age at conduit implant (years)	Conduit	Time to endocarditis (years)	Additional procedures	Surgical findings on the conduit	Microbial organism
1	Aortic stenosis	13.9	Contegra	4.2	None	NA	NA
2	CAT	3.6	Contegra	0.3	None	Massive destruction	Gram-positive cocci
3	TOF	20.6	Homograft	12.3	None	Massive destruction, extended vegetations	Streptococcus mitis
4	TOF	13.1	Melody	4.1	None	NA	Staphylococcus aureus
5	CAT	12.6	Homograft	16.7	VSD patch replacement	Massive destruction, purulence and extension to VSD patch	Streptococcus anginosus
6	DORV, PA	10.8	Contegra	7.8	None	Massive destruction	HACEK organism
7	TOF	8.4	Matrix P Plus	2.2	None	Massive destruction	Streptococcus species
8	Aortic insufficiency	15.1	Melody	7.2	Tricuspid valve repair	Infection confined to the valve leaflets only	NA
9	CAT	2.3	Contegra	5.9	Aortic root replacement	Inner and outside endocarditis	Streptococcus salivarius
10	TOF	6.3	Melody	3.1	None	Massive destruction of all valve leaflets	Viridans group streptococci
11	DORV, d-TGA, VSD, interrupted aortic arch	14.2	Homograft	0.9	None	Massive destruction, multiple thrombotic structures, fully occluding thrombus in LPA	Aspergillus species
12	TOF	6.2	Melody	2.5	PFO closure	Massive destruction, vegetation to RPA	Gram-positive cocci
13	TOF	12.1	Melody	5.9	None	Massive chronic infective destruction inside and outside, adhesion to thoracic wall	NA
14	DORV, TGA, PA	9.5	Melody	2.1	ASD Amplatzer device removal plus ASD and residual VSD closure	Massive destruction, infective overlay of ASD Amplatzer device	Staphylococcus aureus
15	Aortic stenosis	17.6	Melody	2.0	None	Infection confined to the valve leaflets only	HACEK organism
16	Aortic stenosis	14.5	Melody	0.5	None	Infection confined to the valve leaflets only	NA
17	Aortic stenosis/aortic insufficiency	10.3	Melody	9.4	None	Massive destruction	Gram-positive cocci
18	Borderline LV, status post biventricular conversion after Norwood	0.9	Contegra	2.6	Bilateral pulmonary artery stent excision plus pulmonary bifurcation reconstruction	Inner infection with extension to the pulmonary artery stents	Staphylococcus epidermidis
19	CAT	9.2	Melody	4.7	None	Infection confined to the valve leaflets only	NA
20	PA/IVS	17.9	Melody	4.2	None	Infection confined to the valve leaflets only	NA

ASD: atrial septal defect; CAT: common arterial trunk; DORV: double outlet right ventricle; HACEK: Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens and Kingella species; LPA: left pulmonary artery; LV: left ventricle; NA: not available; PA: pulmonary atresia; PA/IVS: pulmonary atresia with intact ventricular septum; PFO: patent foramen ovale; RPA: right pulmonary artery; TGA: transposition of the great arteries; TOF: tetralogy of Fallot; VSD: ventricular septal defect.
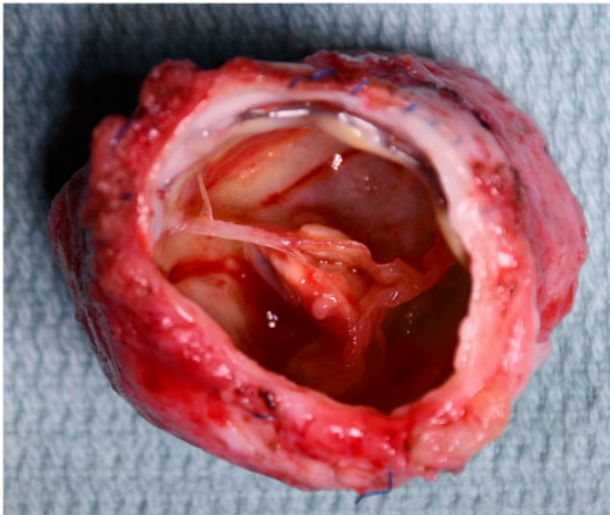
Figure 1: Infected valve.

Figure 2: Vegetation attached to the infected conduit.

The main symptom for the diagnosis of IE was fever in 9 (45%) patients. Transthoracic and/or transoesophageal echocardiographic studies showed vegetations in 9 (45%) patients,

thickening and irregularities of the valve leaflets in 8 (40%) patients and stenosis only in the remaining 3 (15%) patients. Considerable to severe right ventricular dysfunction was seen in 6 (30%) patients preoperatively, and massive pulmonary artery embolism was found in 2 (10%) patients.

Surgical findings were described in 18 patients (90%) including 5 (25%) patients in whom infection seemed to be confined only to the valve leaflets (Fig. 1). In an additional 8 (40%) cases the valve showed massive destruction and additional vegetations of the infected conduit (Fig. 2). In 4 patients (20%) the valve and surrounding structures showed infective destruction. One (5%) patient showed a massive in- and outside chronic infection of the conduit with no distinguishable adhesions to the thoracic wall and chronic mediastinitis (Fig. 3).

Microbial organisms could be obtained from 14 (=70%) patients and showed a majority of streptococcal species (*n* = 5), 2 types of bacteria from the *Haemophilus* species, *Aggregatibacter* species, *C. hominis*, *E. corrodens* and *Kingella* species group, 2 patients with *S. aureus* IE, 1 with *S. epidermidis* and 1 case of aspergillosis. The remaining 3 patients had gram-positive cocci that could not be distinguished any further. Preoperative blood cultures were taken from all patients; and positive cultures were obtained preoperatively from 10 (50%) patients.

Recent postoperative follow-up information (range 30 days–5 years) was obtained from 18 patients (90%) with prosthetic pulmonary valve IE. A total of 30.1 patient years [median 204.5 days (95% CI, 54.5–1031.7)] showed no deaths and no recurrent endocarditis during this observation period. The median follow-up times for our Melody [171.0 days (95% CI, 51.6–566.5)] and Contegra [51.0 days (95% CI, not calculable)] subgroups were shorter than those for patients with an infected homograft [1345.0 days (95% CI, not calculable)] valve.

DISCUSSION

Prosthetic valve endocarditis in general is a serious life-threatening condition with a mortality of 21% to 36%. The mortality observed during a 32-month follow-up period increased to 44.7% [11–14]. IE of prosthetic pulmonary valves in patients with congenital heart disease bears a high risk for the patients with serious complications such as bleeding issues, renal damage, septic shock and death [6, 7, 9]. Mortality rates in small case series of patients with congenital conditions are as high as 17.6% [7]. Tissue and any prosthetic material (e.g. pulmonary artery stents, synthetic patch material) adjacent to the infected prosthetic valve is at great risk to become infected as well.

Transcatheter prosthetic valve implants evolved into a new therapy concept in patients with acquired and congenital heart disease, but the risk for endocarditis with significant mortality rates is high [2]. Previous studies have shown the risk profile for different types of conduits such as the PPVP or the RVPAC [3–5, 9, 15, 16]. A PPVP such as the Melody valve is assumed to have the highest risk for endocarditis, whereas implanting these prostheses is feasible and does not require resternotomy or cardiopulmonary bypass in patients with complex congenital heart disease. Contegra valves are associated with the second most frequent rate of endocarditis when used for RVPAC. Nevertheless, they are chosen especially in paediatric patients because of easy availability in different size modalities. Homografts have the lowest rate of endocarditis, but the lack of availability and the need for open-heart surgery are relevant disadvantages for patients,

parents and the interdisciplinary cardiac team in selected patients.

Studies about different treatment recommendations for IE in patients with prosthetic pulmonary valves are rare. Therefore, the ideal therapeutic strategy is still under discussion and varies between conservative antibiotic treatment only and surgical removal of all infected material plus antibiotic treatment [6, 7, 9]. Multi-institutional comparative studies or meta-analyses are desirable to investigate treatment experiences from other centres and longer follow-up periods. Prosthetic valve IE in patients with congenital heart disease applies to a young patient cohort who will require more heart operations during their lives. Delaying replacement of the conduit can lead to repeated episodes of IE, chronic infection and mediastinitis with the risk of creating an even higher perioperative risk profile. Therefore, an early surgical approach may be advisable. Close follow-up of all patients after initial in-hospital therapy is important to assess the incidence of recurrent endocarditis, conduit function, right ventricular function and late deaths.

The results of this study have shown that surgical therapy of IE following interventional or surgical pulmonary valve replacement in a small (*n* = 20) patient case series is a safe and effective treatment concept. At our centre, all patients suspected of having IE underwent surgical therapy. In all cases, a pulmonary homograft was implanted as an orthotopic RVPAC, which currently is the conduit with the lowest rate of IE [5]. For that reason, an adult size homograft is stored in our homograft bank, for readily available use in adolescents and adults. Flexibility towards the optimal size may be necessary in smaller children with IE when deciding on a homograft as the desirable choice of prosthesis. Despite the fact that many of the operations were technically challenging, redo procedures with severely prolonged bypass times and the need for several additional procedures, the infected material could be removed and replaced successfully in all patients. Although not shown in our data, the suspicion is high that severe cases occur especially in those patients with a prolonged prehospital course or with extended antibiotic use before surgery. These facts should be focused on in further studies.

Bearing in mind that the risk for severe complications in prosthetic valve IE is high, we followed a thorough protocol when examining patients who were suspected of having IE. Especially in patients with congenital heart disease, prosthetic material is used extensively surgically and interventionally. Therefore, infectious spreading can become problematic. One of our patients with status post aortic root replacement in CAT needed an additional aortic root re-replacement at the time of prosthetic pulmonary valve IE because the infection spread from a neighbouring Contegra valve.

The increasing number of patients with pulmonary valve conduits will lead to more patients with pulmonary valve endocarditis. The Melody valve, which is a PPVP, has become a well-established therapy option for patients with congenital heart disease [17]. Because Melody valves are known to have a higher risk for IE compared to other conduit types, we should expect an increasing number of patients with IE in this cohort. At our centre, we introduced Melody valves in 2009, concurring with surgical RVPAC replacements using pulmonary homografts or Contegra valves, if no homografts were available. Although the implantation period for the Melody valve was shorter than that for other conduits and the incidence of implants is lowest in comparison to RVPAC at our centre, the quantity of this subgroup in our study is concerningly high. This result is also well

Figure 3: Massive in- and outside chronic infection of the conduit.

documented in several follow-up studies in which Melody valves have been implanted [18, 19]. From our point of view, increased risk factors could be, e.g. leaving pathological valve tissue in the right ventricular outflow tract, abnormal flow patterns that favour the accumulation of microbial bacteria, extensive synthetic material containing stents and foreign tissue in multiple layers. Participants in interdisciplinary consensus conferences for the choice of the initial prosthetic valve for these patients should be aware of these issues. Contraindications for percutaneous pulmonary valve implants to prevent endocarditis should be investigated in further studies. In our centre, we favour a surgical approach for pulmonary valve replacements over percutaneous pulmonary valves in the following circumstances: synthetic material in close relationship to the pulmonary valve/conduit (e.g. pulmonary artery stents, synthetic prostheses and septal occlusion devices); autologous patch material in close contact with the infected conduit; stenotic percutaneous pulmonary valves and multiple layer homografts, Contegra or Melody valves. Prophylactic antibiotic treatment and early referral to a specialized centre in cases with a suspicious clinical course are key to managing patients with prosthetic pulmonary valves. Life-threatening conditions can evolve after delayed therapy, with patient disease leading to barely irreversible right ventricular dysfunction and a prolonged infectious status with all its consequences.

Patients with IE require prolonged antibiotic treatment in order to suppress recurrent infections on the newly implanted prosthetic material. Especially in our paediatric patients, this treatment can lead to an exhausting, extended hospital stay. Central intravenous lines are necessary because of the short interval for applying antibiotics but can carry the risk of additional microbial infection. Professional outpatient treatment should be supported in the long run.

Limitations

The small number of patients and the inhomogeneous postoperative follow-up period for IE are limitations to this study. A

comparison between conservatively and surgically treated patients was not possible at our centre.

CONCLUSIONS

Though it is a complex redo operation, early surgical therapy of IE of PPVP and RVPAC is a safe and effective therapeutic concept. This approach should be kept in mind when conservative therapy is initiated. The goal of the surgical procedure should be the radical removal of all potentially infected prosthetic and autologous material as early as possible. All our patients were free from infection at the time of discharge, and no recurrent IE was observed during the follow-up period.

ACKNOWLEDGEMENTS

Conflict of interest: none declared.

Author contributions

Gregor Gierlinger: Conceptualization; Data curation; Methodology; Writing—original draft; Writing—review & editing. **Eva Sames-Dolzer:** Conceptualization; Formal analysis; Supervision; Validation; Visualization; Writing—review & editing. **Michaela Kreuzer:** Conceptualization; Supervision; Writing—review & editing. **Roland Mair:** Data curation; Writing—review & editing. **Andreas Zierer:** Supervision; Validation; Writing—review & editing. **Rudolf Mair:** Conceptualization; Methodology; Supervision; Validation; Visualization; Writing—review & editing.

Reviewer information

European Journal of Cardio-Thoracic Surgery thanks Frank A. Baciewicz Jr., Ko Bando and Sertac M. Cicek for their contribution to the peer review process of this article.

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