International Journal of Cardiology 323 (2021) 40–46

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Infective endocarditis in patients after percutaneous pulmonary valve implantation with the stent-mounted bovine jugular vein valve: Clinical experience and evaluation of the modified Duke criteria.

D. Bos [a], D. De Wolf [b], B. Cools [a], B. Eyskens [a], J. Hubrechts [a], D. Boshoff [a], J. Louw [c], S. Frerich [c], B. Ditkowski [a], F. Rega [d], B. Meyns [d], W. Budts [e], T. Sluysmans [f], M. Gewillig [a], R. Heying [a,*]

[a] Pediatric Cardiology, Department of Cardiovascular Developmental Biology, University Hospitals Leuven, Belgium,
[b] Pediatric Cardiology, University Hospital of Ghent, Belgium,
[c] Pediatric Cardiology, AZM, Maastricht, the Netherlands,
[d] Division of Clinical Cardiac Surgery, KU Leuven, Leuven, Belgium,
[e] Congenital and Structural Cardiology, University Hospitals Leuven, and Department of Cardiovascular Sciences, Catholic University Leuven, Belgium,
[f] Pediatric Cardiology, Cliniques Universitaires St. Luc, Brussels, Belgium.

ARTICLE INFO

Article history:
Received 3 January 2020
Received in revised form 21 July 2020
Accepted 17 August 2020
Available online 27 August 2020

Keywords:
Congenital heart disease
Infective endocarditis
Percutaneous valve replacement

ABSTRACT

Aims: Percutaneous pulmonary valve implantation (PPVI) has proven good hemodynamic results. As infective endocarditis (IE) remains a potential complication with limited available clinical data, we reviewed our patient records to improve future strategies of IE prevention, diagnosis and treatment.
Methods: Medical records of all patients diagnosed with Melody® valve IE according to the modified Duke criteria were retrospectively analyzed in three Belgian tertiary centers.
Results: 23 IE episodes in 22 out of 240 patients were identified (incidence 2.4% / patient year) with a clear male predominance (86%). Median age at IE was 17.9 years (range 8.2–45.9 years) and median time from PPVI to IE was 2.4 years (range 0.7–8 years). Streptococcal species caused 10 infections (43%), followed by *Staphylococcus aureus* ($n = 5$, 22%). In 13/23 IE episodes a possible entry-point was identified (57%). IE was classified as definite in 15 (65%) and as possible in 8 (35%) cases due to limitations of imaging. Echocardiography visualized vegetations in only 10 patients. PET-CT showed positive FDG signals in 5/7 patients (71%) and intracardiac echocardiography a vegetation in 1/1 patient (100%). Eleven cases (48%) had a hemodynamically relevant pulmonary stenosis at IE presentation. Nine early and 6 late percutaneous or surgical re-interventions were performed. No IE related deaths occurred.
Conclusions: IE after Melody® valve PPVI is associated with a relevant need of re-interventions. Communication to patients and physicians about risk factors is essential in prevention. The modified Duke criteria underperformed in diagnosing definite IE, but inclusion of new imaging modalities might improve diagnostic performance.

1. Introduction

Percutaneous pulmonary valve implantation (PPVI) using the Melody® valve (Medtronic Inc., Minneapolis, MN, US) has proven good technical feasibility and excellent hemodynamic results for right ventricular outflow tract (RVOT) valve replacement [1–3]. Infective endocarditis (IE) however is emerging as an important challenge after PPVI causing considerable morbidity and need for re-interventions [4,5]. Recent studies state that the risk of developing IE seems to be higher after Melody® valve PPVI compared to surgical homograft implantation [6,7]. Incidences of about 3.2–12.9% are described in mid- to long-term follow-up studies, versus 2% in surgical groups [3,4,8–10].

Streptococcus and *Staphylococcus* species are the most frequent causative agents, but many other microorganisms have been reported [4,11]. Changes in IE epidemiology are of major interest after the guidelines for IE prophylaxis have been restricted from 2007 onwards [12]. *S. aureus* infections are becoming more frequent due to an increase of medical procedures and subsequent hospitalization while *Streptococci* remain the most relevant underlying cause of community acquired IE [13,14].

Abbreviation list: CHD, congenital heart disease; BJV, bovine jugular vein; IE, infective endocarditis; PPVI, percutaneous pulmonary valve implantation; RVOT, right ventricular outflow tract; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

* Corresponding author at: Department of Pediatric Cardiology, UZ Leuven, Herestraat 49 3000 Leuven, Belgium.
E-mail address: ruth.heying@uzleuven.be (R. Heying).

https://doi.org/10.1016/j.ijcard.2020.08.058
0167-5273/

Despite advances in medical treatment, IE diagnosis remains challenging and is frequently delayed. PPVI IE often presents late and is subacute in onset rather than peri-procedural, and clinical symptoms are variable and non-specific [4,5,13]. Clinical IE presentations raise the question on specific predictors and risk factors for PPVI IE while data on the subject are still limited.

IE diagnosis is based on the modified Duke criteria, by which a definite diagnosis is made mainly on the presence of multiple positive blood cultures and positive imaging for IE. The Duke criteria are characterized by a sensitivity of 70–80%, but have proven to be less accurate in the detection of prosthetic valve IE [12].

Therefore, this study aims to investigate the clinical and epidemiological findings in all IE patients after Melody® valve implantation in three Belgian centers to improve future strategies of IE diagnosis, treatment and prevention in this patient group. In addition, we focused on a critical evaluation of the role of the modified Duke criteria in diagnosing IE after Melody® valve PPVI.

2. Methods

Patients.

A multi-center retrospective, observational study was performed by analyzing the Melody® valve registry from 1/1/2006–1/6/2017. Pediatric and adult patients who presented with IE after Melody® valve implantation in the RVOT in three Belgian tertiary referral centers, namely University Hospitals (UZ) Leuven, UZ Ghent and University Hospital Brussels Saint-Luc (UCL), were identified and clinical data were reviewed. Interventional Melody® valve implantation was performed according to the standard protocol provided by the company. Details are described in the supplementary data. The study complies with the Declaration of Helsinki. Informed consent was taken from all patients or parents and data analysis was approved by the local ethic committees.

Clinical IE data.

We gathered general demographic data, data on health history, underlying diagnosis and valve implantation. Data on clinical presentation and diagnosis of IE included predisposing factors, echocardiographic findings, biochemical data, underlying microorganisms, medical and surgical treatment, length of hospitalization, complications and outcome. IE was diagnosed according to the modified Duke criteria and all criteria were recorded and critically evaluated for their presence [12,15]. Diagnostic testing and antibiotic treatment was performed according to the ESC guidelines (detailed protocol in Supplementary Data) [12]. Transcatheter or surgical treatment required within 3 months after IE presentation were defined as early interventions and after more than 3 months as late interventions. A detailed definition is given in the supplementary data.

2.1. Statistical analysis

Continuous variables are reported as median ± range. Categorical variables are mentioned as frequencies and percentages of the specific group. Statistical analysis of group comparisons were performed by application of the Fischer's exact test, the Pearson's χ^2 test and the independent sample *t*-test. Annualized rates of IE were calculated using the total period of patient follow-up until diagnosis of IE or end point of the study period. Potential risk factors for IE with a calculated *p*-value of <0.1 were further analyzed by a multivariate Cox regression analyses. Hazard ratios (HRs) and incidence rates were demonstrated with the 95% confidence intervals (CIs). Statistical analysis was performed using GraphPad Prism (7.0d; GraphPad Software, San Diego California USA) and IBM SPSS Statistics 26 (IBM, New York, New York, USA).

3. Results

Patients.

Twenty-three cases of possible and definite IE after Melody® valve implantation were identified in 22 patients according to the modified Duke criteria. A total of 240 patients (158 male, 66%; and 82 female, 34%) who underwent Melody® valve implantation between 1/1/2006

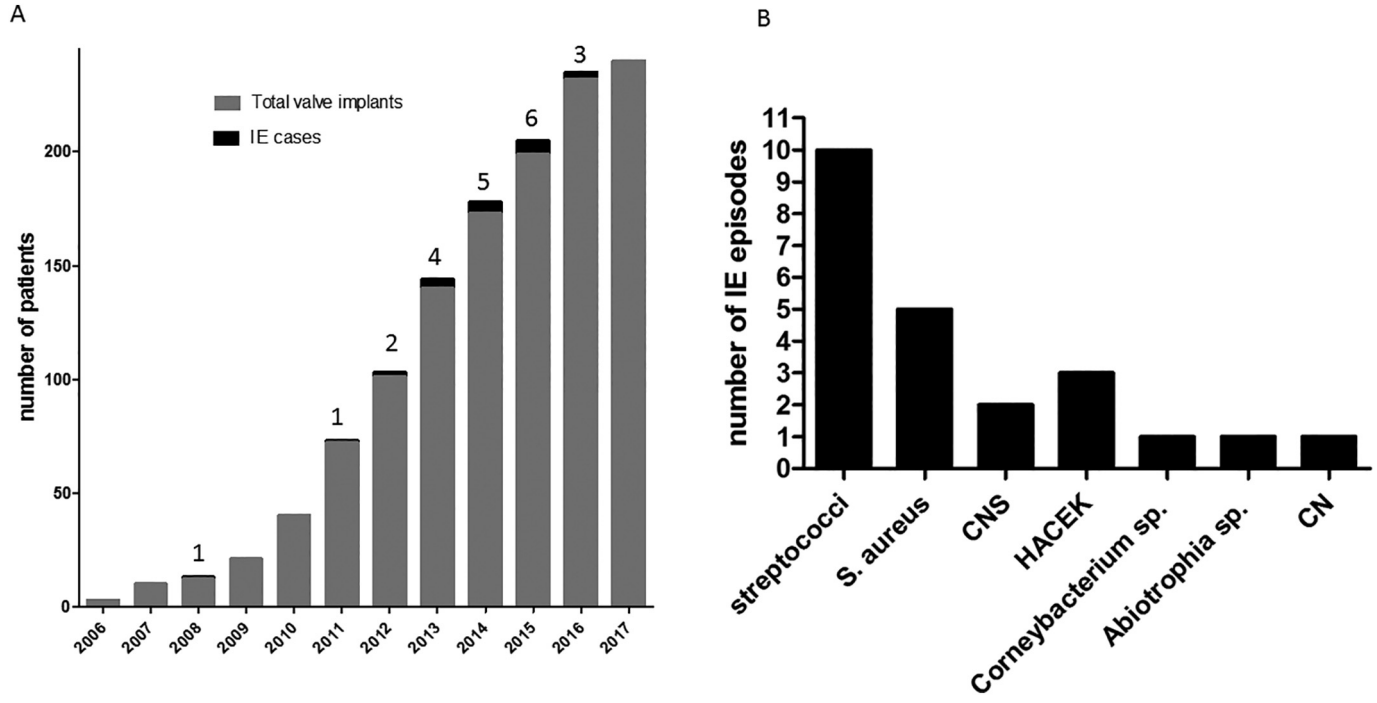

Fig. 1. Infective endocarditis. 1A shows the occurrence of Infective endocarditis over time. The cumulative number of patients receiving a Melody© valve in the three centers over time is presented (grey columns). In black, patients diagnosed with IE are indicated. 1B shows the proportion of the underlying microorganisms. CNS = coagulase negative staphylococci, sp. = species, CN = culture negative.

and 1/6/2017 were observed for 939.5 patient years in the study period. We report an overall IE incidence of 9.2% and an incidence of 2.4% / patient year: 16 out of 165 patients in UZ Leuven, 3 out of 27 in UZ Ghent and 3 out of 48 in UCL (Fig. 1A). The median age at IE occurrence was 17.9 years (range 8.2–45.9 years) and IE onset was reported at a median of 2.4 years (range 0.7–8.0 years) after valve implantation. There was a male predominance, as 19/22 IE patients were male (86%). The IE incidence in male patients was significantly higher compared to female patients (*P* value 0.03). Twelve percent (19 out of 158) of all male Melody® patients or 3.0% / patient year developed IE compared to 3.7% (3 out of 82) of all female patients with an implanted Melody® stent or 0.9% / patient year. The male gender has been identified as an independent risk factor for developing IE (Table 1, HR 3.60).

One patient had an epicardial pacemaker implanted. Three patients were taking aspirin at the time of infection for prevention of thromboembolic events. In 2 patients, aspirin was prescribed at discharge from UZ Ghent and in 1 patient aspirin intake was not related to Melody® valve implantation. All but one patient underwent regular follow-up in each center at 1, 3, 6 and 12 months after implantation and thereafter yearly. Further patient characteristics are summarized in Table 1.

Clinical presentation of IE.

Fever was the major presenting symptom in 17 patients. Three additional patients described sub-febrile symptoms. When fever was absent, patients complained of effort intolerance and/or general malaise. Four patients developed sepsis which turned into septic shock in 1 patient. The causative microorganism in these 4 patients were *S. aureus* ($n = 3$) and *H. parainfluenza* ($n = 1$). One patient presented with peripheral edema due to right heart failure. Data on IE presentation are shown in Table 2. Results on the time point of diagnosis and predisposing factors are found in the Supplementary Data.

Microbiology.

An underlying microorganism could be identified in the blood culture in all but 1 patient. Viridans group streptococci were the most frequent cause of IE ($n = 10$), followed by *S. aureus* ($n = 5$). Cultures remained negative after oral antibiotic treatment of episodic fever in 1 patient.

In 4/5 patients with a *S. aureus* infection and 1/2 patients with a CNS infection a possible cutaneous entry-point could be identified. A viridans group streptococcus infection was associated with a dental predisposing factor in 5/10 patients. Fig. 1B shows the causative microorganisms.

Diagnosis of IE according to the modified Duke criteria.

Fifteen cases of IE were classified as definite and 8 cases as possible IE according to the modified Duke criteria [15]. Table 3 shows the results for each of the detailed criteria. A minimum of 3 blood cultures were taken before the start of antibiotics and the majority of patients had 2–5 positive cultures (17 episodes). In 5 patients only 1 blood culture turned out positive and in one patient the cultures remained negative.

In 5 patients requiring an early valve explantation, additionally a histopathological ($n = 2$) or molecular microbiological investigation (pan-bacterial PCR, $n = 3$) was performed. The PCR on tissue explants verified the underlying bacteria already identified in the blood culture in all patients: *S. aureus* in 2 patients and *H. influenza* in 1 patient. The histopathological findings showed a fibrin rich, purulent inflammation, confirming IE diagnosis. In 3 of the 5 patients, histopathological ($n = 2$) or bacterial PCR examination ($n = 1$) of the explanted Melody® valve contributed to the diagnosis of definite IE.

Transthoracic echocardiographic (TTE) evaluation, including assessment of the gradient across the infected valve, was performed in all patients at the time of IE diagnosis and results are summarized in Supplementary Fig. 1. Vegetations on TTE were seen in 9 patients. Eleven patients received a transesophageal echocardiography (TEE) of which 7 presented with an initially negative TTE. Importantly, TEE could only visualize a vegetation in one patient, in which it had not been seen by TTE before. In 4 patients TEE verified the vegetation known from TTE and TEE remained negative in the 6 other patients. Eleven patients developed a moderate or severe pulmonary stenosis (PS PIG >40 mmHg or PS PIG >60 mmHg, respectively, Table 2, Supplementary Data and Supplementary Fig. 1 A and B). Seven of these 11 patients required an early transcatheter or surgical treatment.

Imaging by PET-CT was performed in 7 patients and revealed positive signs (increased FDG-captation) in 5 of them at the Melody® valve. In 3 of these 5 patients vegetations were seen on TTE or TEE at the Melody® valve. Intracardiac echography was performed in 1 patient and could clearly visualize the vegetation. None of the patients had concomitant involvement of the left heart valves or other locations besides the Melody® valve.

Treatment and outcome.

All patients received 6 weeks of antibiotic treatment according to the ESC guidelines [12]. Thirteen of 22 patients (59%) required an RVOT intervention early or late after the IE episode due to the development of a stenosis of the Melody® valve. Supplementary Picture 1 shows an explanted Melody® valve infected by *S. aureus*. Two patients required urgent RVOT stent placement 1 day after presentation. Four patients underwent homograft implantation having an early elective surgical procedure after 9, 16, 18 and 32 days. In 2 additional patients a delayed homograft implantation was performed after 48 and 63 days. One patient underwent a delayed percutaneous balloon valvuloplasty after 51 days.

A late intervention was performed in 6 patients. The 2 patients with an urgent RVOT stent placement received a Melody® and a Sapien® valve 3 and 10 months later. Three additional patients underwent RVOT valve replacement after more than 2 years (a Melody® valve, Sapien® valve and homograft in 1 patient each). Data are shown in Table 4. Detailed data on treatment and outcome comparing the IE cases treated medically and those who required an interventional treatment are summarized in the Supplementary Data and Supplementary Table 1.

No deaths related to IE were seen. During follow-up 1 patient died after a status epilepticus, unrelated to IE.

4. Discussion

IE remains a diagnostic and therapeutic challenge in patients after PPVI [5,8,13]. After reviewing records of patients presenting with Melody® valve IE in three Belgian tertiary referral centers, our data clearly show a relatively high incidence of IE (2.4% / patient year) after a median time period of 2.4 years with a distinct male predomination of 86%. Viridans group streptococci accounted for 10/23 infections, followed by *S. aureus* ($n = 5$). The course and outcome of the infection were mostly favorable and no deaths occurred related to IE. However, we saw a high rate of RVOT re-interventions. Early re-interventions were more frequent with IE caused by *S. aureus* or HACEK-group organisms and in the presence of pulmonary septic emboli.

Clinical presentation and outcome.

Several clinical observations support our documented high incidence of IE after PPVI showing incidences of 3.2 to 12.8% [3–5,8,16]. The same annual incidence of 2.4% / patient year for Melody® related IE was recently described [17]. Being male was associated with a higher risk to develop IE and identified as an independent risk factor. The IE incidence was significantly higher in male (3.0% / patient year) compared to female patients after Melody® valve implantation (0.9% / patient year). The gender difference can partly be explained by the higher incidence of CHD in men [17,18]. In our centers, 67–78% of all patients who had a Melody® valve implanted were male [2]. A male predominance is also known in adult patients with IE of a percutaneous implanted aortic valve which could be partially associated with a potential endothelial protection via estrogen in females [19]. In contrast to the findings of McElhinney et al., in our cohort a younger age (<12y) at PPVI was not associated with an increased risk of IE or a higher rate of IE associated valve explantations [17].

Table 1
Characteristics of all patients.

	IE patients ($n = 22$)	**Patients without IE ($n = 218$)**	**IE**	
	n or median (% or range)	n or median (% or range)	P-value	HR (95% CI)
Gender (male/female)	19/3	139/79	0.033	3.602 (1.063–12.204)
Age at PPVI (years)	14.7 (7–43.5)	17.2 (3.5–81.6)	0.077	0.959 (0.013–1.007)
Weight (kg)	50.8 (23–91)	55.0 (15–147)	ns (0.588)	
Final diameter Melody® (mm)	22 (16–22)	22 (18–24)	ns (0.303)	
Diagnosis			ns (0.101)	
Tetralogy of Fallot	10 (45%)	117 (54%)		
Truncus arteriosus	5 (23%)	16 (7%)		
Pulmonary stenosis / atresia	0	28 (13%)		
Post Rastelli procedure	4 (18%)	19 (9%)		
Post Ross procedure	3 (14%)	38 (17%)		
RVOT conduit type			ns (0.697)	
Native RVOT	4 (18%)	63 (29%)		
Homograft	16 73%)	137 (63%)		
Bovine heterograft (Contegra®)	2 (9%)	27 (12%)		
Bioprosthesis	0	9 (4%)		
Melody®	0	3 (1%)		
Indication for PPVI			ns (0.215)	
Stenosis	14 (64%)	97 (45%)		
Insufficiency	4 (18%)	70 (32%)		
Mixed	4 (18%)	51 (23%)		

IE = infective endocarditis, PPVI = Percutaneous pulmonary valve implantation, RVOT = right ventricle outflow tract, n = number of patients. CI = confidence interval. Hazard ratios (HR) are calculated from a multivariate analysis. IE patients were analyzed in comparison to non-IE patients.

All IE cases in this study were late and community-acquired with a minimum period of 8 months from implantation to IE development, and seem therefore not to be procedure related, as described by others [1,8,11,18].

IE of the Melody® valve caused by viridans group streptococci were most dominant in our series being responsible for 43% of cases versus 30% in other studies, in which staphylococci are the most prevalent species (47%) [5,8,17].

Our data further reveal that Melody® IE presents clinically severe in distinct cases with 4 patients having developed sepsis and 1 patient presenting with right-sided heart failure. In addition, clinical presentation with severe RVOT obstruction is frequent as seen in 7/23 cases (30%). These severe presentations are relevant in clinical practice, which is also supported by others reporting about 30% of patients presenting in emergency situations as sepsis, shock or severe right ventricular dysfunction and 34% of patients presenting with a RVOT gradient of >60 mmHg [4,8,18]. This has led to an attempt to categorize patients upon the clinical severity of IE presentation in order to enable a more accurate diagnosis and adequate treatment of IE [17].

RVOT re-intervention is frequently required after Melody® valve IE (13/22 patients, 59%) and our data are comparable to other reports which documented re-interventions in about 60% [1,3,5,17]. The indication and timing for an invasive treatment remain challenging. Criteria leading to the choice of re-intervention have not been clearly defined yet. The decision may depend on the severity of IE and on the experience of each center. Transcatheter treatment has proven to be effective and safe in 6/22 (27%) of our patients compared to 13–14% of IE patients in other reviews [3,18]. It mainly has a role in the treatment of critically

Table 2
Patient characteristics at IE presentation.

	n or median (% or range)
Age at IE (years)	17.9 (8.2–45.9)
Time from PPVI to IE episode (years)	2.4 (0.7–8.0)
Presenting symptoms	
Fever or subfebrility	20 (87%)
Effort intolerance or fatigue	10 (43%)
Sepsis	4 (17%)
Predisposing factors and possible entry-point	
Dental hygiene or procedure	9 (39%)
Cutaneous	8 (35%)
Previous episode of IE	2 (9%)
Positive blood culture	
Multiple	17 (74%)
Single	5 (22%)
None	1 (4%)
Maximal RVOT gradient at IE	
0–39 mmHg	12 (52%)
40–60 mmHg	4 (17%)
> 60 mmHg	7 (30%)
Increase in RVOT gradient at IE	
≤ 10 mmHg	11 (48%)
11–30 mmHg	4 (17%)
31–50 mmHg	4 (17%)
> 50 mmHg	4 (17%)

IE = infective endocarditis, PPVI = Percutaneous pulmonary valve implantation, RVOT = right ventricular outflow tract, n = number of patients, % of all 23 IE episodes.

Table 3
Duke criteria.

	n (%)
Definite IE	15 (65%)
Possible IE	8 (35%)
Pathological criteria	3 (13%)
Major clinical criteria	
Blood culture positive (≥ 2)	17 (74%)
Positive imaging:	13 (57%)
TTE and TEE	10 (43%)
PET-CT	5 (22%)
Intracardiac echocardiography	1 (4%)
Minor clinical criteria	
CHD	23 (100%)
Fever >38 °C	21 (91%)
Vascular phenomena:	
Pulmonary septic embolism	8 (35%)
Minor microbiologic criteria	5 (22%)
Immunological phenomena	0 (0%)

IE = infective endocarditis, TTE = transthoracic echocardiography, TEE = transesophageal echocardiography, PET-CT = 18 FDG-positron emission tomography, CHD = congenital heart disease, n = number of patients.

Table 4
Treatment and outcome.

	n (%)
Antibiotic treatment (6 weeks)	23
ICU admission	0
Early interventions	9 (39%)
Emergency surgery	0
Urgent transcatheter treatment	2 (8%)
Urgent surgery	0
Early elective surgery	4 (17%)
Delayed balloon valvuloplasty	1 (4%)
Delayed surgery	2 (8%)
Late interventions	6 (26%)
Late balloon valvuloplasty	1 (4%)
Second TPV	4 (17%)
Late surgery	1 (4%)
Total RVOT reinterventions after IE	13/22 (59%)
Death related to IE	0/22 (0%)

ICU = Intensive care unit, TPV = transcatheter pulmonary valve, RVOT = right ventricle outflow tract, IE = infective endocarditis, n = number of patients.

ill patients presenting with severe RVOT obstruction where it leads to an immediate decrease of the RVOT gradient and hemodynamical stabilization of the patient (2 patients in our study) [4,10,17]. In semi-urgent cases, decision making in our centers favored a surgical implantation of a homograft in patients with no contraindications for an operative treatment (7/22 patients), which is comparable to 43–48% Melody® valve explantations in other reports [3,18]. In further studies, some cases are reported where interventional treatment has been performed as the primary and definite invasive treatment with a good result [4,11,17]. Longtime follow-up studies need to evaluate the hemodynamic results and the risk of re-infection post re-intervention for IE. A focus on determinants for decision making concerning the need of invasive IE treatment and the choice on intervention or surgery would support best patients' outcome.

Our study however shows no deaths related to IE, whereas a mortality rate up to 10% has been described earlier [4,11]. Importantly, *S. aureus* IE accounts for 80–90% of the patients with fatal outcome and is associated with a high need for re-interventions [11].

Diagnosis and modified Duke criteria.

Questions have been raised whether the modified Duke criteria are sensitive enough to make a definite diagnosis of IE after PPVI as up to 38% of patients are classified as possible IE [3,17,18,20]. In our study as well, the number of definite diagnoses of IE was lower than expected, namely 15/23 cases. Negative imaging for IE is leading to a major limitation of the Duke criteria and accounted for the classification as possible IE in all 8 patients. In general, imaging often fails to demonstrate vegetations, being positive for IE in just over half of our cases. The presence of prosthetic material in the anterior positioned RVOT hampers the visualization of vegetations on the Melody® valve.

The sensitivity of TTE for detecting vegetations in prosthetic IE is variable with 36–69%, whereas TEE shows a higher sensitivity of 86–94% [21]. Our data support the diagnostic limitation of repeated TTE and TEE, as in less than 50% of the episodes a vegetation could be detected (9/23 for TTE and 5/11 episodes for TEE). Importantly, TEE appeared to have limited additional diagnostic value as only in 1 patient a vegetation was visible, that had not been seen by TTE before. This is supported by McElhinney et al., where the Melody® valve was well visualized in only 5/18 patients on TEE [17].

To overcome these problems, extended imaging modalities may be indicated to enable the diagnosis of definite IE. PET-CT, included as a possible imaging modality in the 2015 ESC modified diagnostic criteria, showed inflammation at the Melody® valve in 2 patients in whom no vegetations could be visualized by TTE, thereby allowing for the diagnosis of definite IE. PET-CT has only been of confirmed value in prosthetic valve IE, not in native IE [22,23]. Pizzi et al. demonstrated the diagnostic value of PET-CT in CHD patients with IE, especially by visualizing abscesses and pseudoaneurysms important for treatment decisions [21,24]. However, an intrinsic FDG uptake in non-biological material as Dacron® or Teflon® or in other surgical adhesives in close proximity to the infected biological material has to be considered and could limit the sensitivity of PET-CT [22,24].

Next to the added diagnostic value of PET-CT in prosthetic valve IE, recent experience supports the use of intracardiac echocardiography [25,26]. Requiring an invasive procedure, intracardiac echocardiography provides clear visualization of vegetations and potentially enables the diagnosis of definite IE [11,17].

Additionally, we observed a severe pulmonary stenosis in 7 patients at presentation. A mild residual obstruction is not uncommon after PPVI and therefore cannot be considered a specific indicator of IE [18]. However, a suddenly developed increased pressure gradient over the RVOT at the time of IE presentation is found as a valuable criterion to diagnose IE [3]. The diagnosis would change from possible to definite IE in 2 patients if a newly elevated gradient of >30 mmHg was considered a minor criterion. In patients presenting with sepsis, a hyperdynamic state as a cause of an increased gradient has to be taken into account [27]. In addition, a progressive valve failure could be masked by high cardiac output in sepsis [28]. In our 4 patients presenting with sepsis however, no signs of this pathophysiologic state have been observed.

Furthermore, our data reveal the importance of the number of positive blood cultures concerning assessment by the Duke classification. In our cohort, in 5/23 episodes only one positive blood culture could be found. Three of these patients could still be diagnosed with definite IE based on either pathological criteria after valve explantation or vegetations on TTE. Even though the Duke classification would not have changed for these patients, in cases where only 1 blood culture is positive next to negative imaging, no major criterion can be met and the diagnosis of possible IE has to be based on minor criteria alone.

In patients undergoing early valve explantation,additional histopathological findings for infection or a positive bacterial PCR on explanted valve tissue allow for a diagnosis of definite IE, being supportive in 3 of our cases.

The minor criteria of the modified Duke classification also seem to show shortcomings for diagnosing definite IE in patients with a Melody® valve. Differentiation by predisposing factors is limited as all patients present with underlying CHD. Thereby no other predisposing factors, such as a possible entry-point or a previous history of IE, are taken into consideration as minor criteria. As fever is also frequently present, it does not help in discriminating cases. Immunologic phenomena remain negative due to the right-sided nature of IE [18]. For the same reason, only pulmonary septic emboli were seen in the category of vascular phenomena. Visualization of pulmonary septic emboli on CT contributed to the diagnosis of definite IE in 2 patients with otherwise negative imaging.

Therefore, being attentive for >1 positive blood culture and the use of adequate additional imaging modalities increases the sensitivity of the actual modified Duke criteria. The addition of an increased gradient to the minor criteria seems an improvement of the Duke criteria. This algorithm is presented in Fig. 2.

Predisposing factors.

In recent reports, a higher incidence of IE was found in bovine jugular vein (BJV) valves compared to homografts and other valve types [6,20]. Potential risk factors and pathways evoking IE at the conduit site are not fully elucidated yet. These are discussed to be mainly associated to patient characteristics (male gender), immunological interactions (drug users), the valve endothelium (damaged or inflamed endothelium), the flow pattern (an increased gradient over the RVOT), tissue factors (fixation and preparation of the graft tissue) and thrombogenicity (discontinuation of aspirin administration). Currently, in-vitro studies showed that the BJV tissue itself is not more prone for bacterial adhesion than e.g. homograft tissue [29]. Interestingly, non-

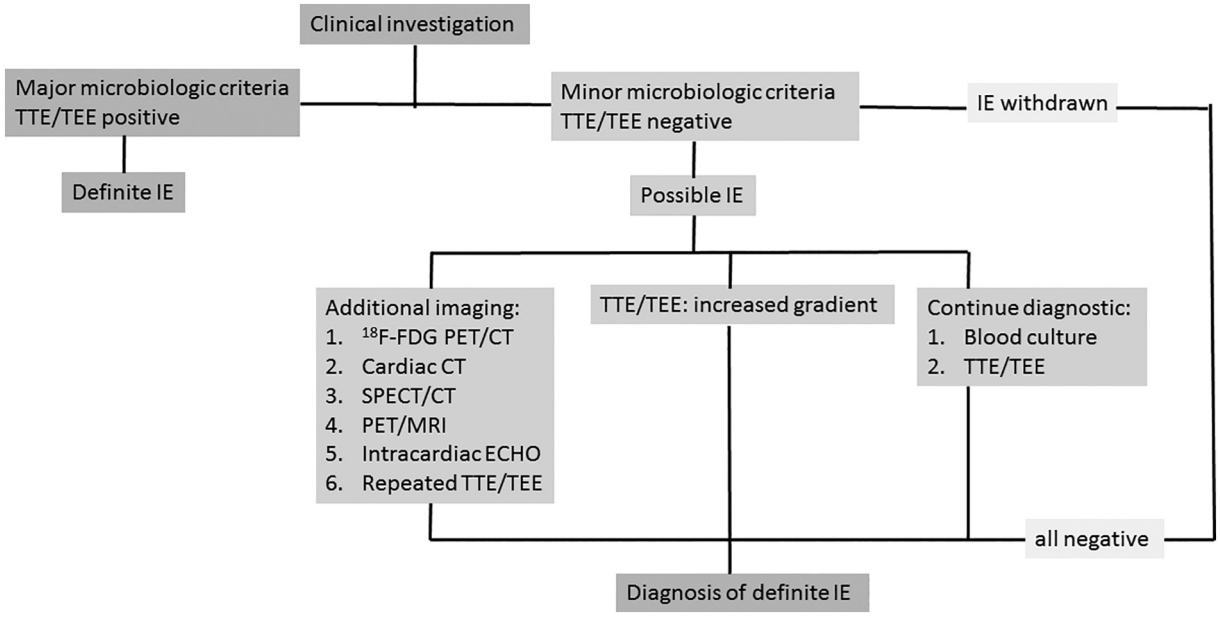

Fig. 2. Algorithm for suspected infective endocarditis after percutaneous pulmonary valve implantation. Suggested strategy in case of suspected infective endocarditis (IE) in cases where the Duke classification allows only a possible diagnosis. Taking >2 blood cultures before the start of antibiotic treatment is of importance and additional imaging could allow the visualization of vegetations when transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) fails. 18 FDG-positron emission tomography (PET/CT) and the combination with magnetic resonance imaging (MRI), intracardiac echocardiography (ECHO) or single photon emission computed tomography (SPECT/CT) might allow to make a definite IE diagnosis based on improved imaging. An increased Doppler gradient could count as a positive minor criterion.

infected RVOT conduits revealed fibrin deposition in the valve sinus, which could act as a preferred matrix for bacterial adhesion upon bacteremia [30]. Further research should elucidate further possible relevant pathogenic factors, as tissue origin and the phenotype of endothelial cells repopulating the graft tissue [7,13]. A residual gradient after PPVI causing turbulent flow patterns has been identified by Nordmeyer et al. as a risk factor for IE with an increased risk by every 5 mmHg [3]. McElhinney et al. and others stated that the post-procedural RVOT gradient after PPVI correlates with the risk of IE [5,17,31]. These important findings have led to the intention to implant the Melody® valve at the largest possible diameter, balancing this decision with the risk of coronary compression and conduit rupture. The discontinuation of aspirin has been discussed to be associated with IE, yet there is no proven evidence as few centers give preventive aspirin after PPVI [4,32]. Besides one, none of our patients received anti-platelet prophylaxis, since this strategy is currently only followed in one of our centers. An increased thrombogenicity plays a role, especially in *S. aureus* infections, where the bacterium interferes with platelet activation [33]. In this context, a benefit of anti-platelet agents as aspirin or ticagrelor in the prevention of *S. aureus* IE is discussed and might be a valuable future preventive strategy as antibiotic prophylaxis is timewise limited to medical procedures [12,34]. The recently reported anti-bactericidal effect of ticagrelor might open additional perspectives [34].

In more than half of our patients, a possible dental or cutaneous entry-point could be identified and especially striking, even an orthodontic treatment was found as a possible causal procedure. Therefore, our data support evidence that the patient's hygiene and prevention measures are an extremely important issue. Investigations on adolescents with CHD found the striking result that they have insufficient knowledge of risk factors for IE, its symptoms and the need for medical advice before starting antibiotics [35]. In general, a poor dental hygiene is a known risk factor for IE and plaque formation may lead to gingivitis risking to result in bacteremia. The incidence of bacteremia from tooth brushing and other daily activities on an annual basis is thought to exceed that of dental procedures by far. This strengthens the positive impact of a good daily oral hygiene which is therefore addressed in the actual recommendations of the European Society of Cardiology (ESC) and the American Heart Association (AHA) [12]. Atopic dermatitis is less well studied as a risk factor for IE, but various case reports describe an association, especially with *S. aureus* IE [13]. Therefore, we suggest that structured information should be provided to the general practitioners, dentists and patients about the increased risk for IE, preventable risk factors and how to respond when IE is suspected. A dental checkup before PPVI should be recommended and adding risk factors as transmucosal piercings should be avoided. A dental and general health care check-up could be secured, if provided by the cardiac centers. Every episode of fever should be investigated by a physician and blood cultures must be taken before starting antibiotics in this patient group.

LIMITATIONS.

This is a retrospective analysis including a limited number of patients. Due to the incidence of IE after PPVI, multi-national, prospective surveys would be beneficial in the future.

5. Conclusions

IE remains an important complication after Melody® valve PPVI in three Belgian tertiary referral centers with a relevant need of re-interventions, especially in *S. aureus* IE. The choice of percutaneous or surgical re-intervention and the respective outcome needs further evaluation. PET-CT, intracardiac echocardiography and assessing the development of a new pressure gradient could improve the diagnostic performance of the modified Duke criteria. Structured education of patients and physicians on hygiene measures and IE associated issues is essential for an improvement in IE prevention and diagnosis in this patient group. Further investigations to elucidate the potential benefit of anti-platelet drugs in IE prevention could contribute towards new pharmacological strategies, as the effect of antibiotic prophylaxis seems limited.

Acknowledgement

We thank Claire Van Oostende for her support in data collection.

Funding

This work was supported by the Research Fund KU Leuven (OT/14/097). RH was sponsored by the Clinical Research Fund of UZ Leuven and the Flemish Research Foundation (FWO).

Conflict of interest statement

Marc Gewillig is proctor for Numed, Medtronic and Edwards. All other authors and study collaborators have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.08.058.

References

[1] J.P. Cheatham, W.E. Hellenbrand, E.M. Zahn, T.K. Jones, D.P. Berman, J.A. Vincent, et al., Clinical and hemodynamic outcomes up to 7 years after transcatheter pulmonary valve replacement in the US melody valve investigational device exemption trial, Circulation. 131 (22) (2015) 1960–1970.
[2] B. Cools, S. Brown, W. Budts, R. Heying, E. Troost, D. Boshoff, et al., Up to 11 years of experience with the melody valved stent in the right ventricular outflow tract, EuroIntervention. 14 (9) (2018) e94–e988.
[3] J. Nordmeyer, P. Ewert, M. Gewillig, M. AlJufan, M. Carminati, O. Kretschmar, et al., Acute and midterm outcomes of the post-approval MELODY registry: a multicentre registry of transcatheter pulmonary valve implantation, Eur. Heart J. 40 (27) (2019) 2255–2264.
[4] S. Malekzadeh-Milani, A. Houeijeh, Z. Jalal, S. Hascoet, M. Bakloul, P. Aldebert, et al., French national survey on infective endocarditis and the melody valve in percutaneous pulmonary valve implantation, Archives of cardiovascular diseases. 111 (8–9) (2018) 497–506.
[5] D.B. McElhinney, L.N. Benson, A. Eicken, J. Kreutzer, R.F. Padera, E.M. Zahn, Infective endocarditis after transcatheter pulmonary valve replacement using the melody valve: combined results of 3 prospective north American and European studies, Circ Cardiovasc Interv. 6 (3) (2013) 292–300.
[6] I. Van Dijck, W. Budts, B. Cools, B. Eyskens, D.E. Boshoff, R. Heying, et al., Infective endocarditis of a transcatheter pulmonary valve in comparison with surgical implants, Heart. 101 (10) (2015) 788–793.
[7] M. Groning, N.B. Tahri, L. Sondergaard, M. Helvind, M.K. Ersboll, Andersen H. Orbaek, Infective endocarditis in right ventricular outflow tract conduits: a register-based comparison of homografts, Contegra grafts and melody transcatheter valves, Eur. J. Cardiothorac. Surg. 56 (1) (2019) 87–93.
[8] C. O'Donnell, R. Holloway, E. Tilton, J. Stirling, K. Finucane, N. Wilson, Infective endocarditis following melody valve implantation: comparison with a surgical cohort, Cardiol. Young 27 (2) (2017) 294–301.
[9] N.A. Haas, S. Bach, R. Vcasna, K.T. Laser, E. Sandica, U. Blanz, et al., The risk of bacterial endocarditis after percutaneous and surgical biological pulmonary valve implantation, Int. J. Cardiol. 268 (2018) 55–60.
[10] S. Hascoet, L. Mauri, C. Claude, E. Fournier, J. Lourtet, J.Y. Riou, et al., Infective endocarditis risk after percutaneous pulmonary valve implantation with the melody and Sapien valves, JACC Cardiovascular interventions. 10 (5) (2017) 510–517.
[11] M. Abdelghani, M. Nassif, N.A. Blom, M.S. Van Mourik, B. Straver, D.R. Koolbergen, et al., Infective endocarditis after melody valve implantation in the pulmonary position: a systematic review, J. Am. Heart Assoc. 7 (13) (2018), e008163, .
[12] G. Habib, P. Lancellotti, M.J. Antunes, M.G. Bongiorni, J.P. Casalta, F. Del Zotti, et al., 2015 ESC guidelines for the management of infective endocarditis: the task force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM), Eur. Heart J. 36 (44) (2015) 3075–3128.
[13] G. Dixon, G. Christov, Infective endocarditis in children: an update, Curr. Opin. Infect. Dis. 30 (3) (2017) 257–267.
[14] P. Moreillon, Y.A. Que, Infective endocarditis, Lancet. 363 (9403) (2004) 139–149.
[15] J.S. Li, D.J. Sexton, N. Mick, R. Nettles, V.G. Fowler Jr., T. Ryan, et al., Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis, Clin. Infect. Dis. 30 (4) (2000) 633–638.
[16] A. Chatterjee, N.S. Bajaj, W.S. McMahon, M.G. Cribbs, J.S. White, A. Mukherjee, et al., Transcatheter pulmonary valve implantation: a comprehensive systematic review and meta-analyses of observational studies, J. Am. Heart Assoc. 6 (8) (2017), e006432, .
[17] D.B. McElhinney, L. Sondergaard, A.K. Armstrong, L. Bergersen, R.F. Padera, D.T. Balzer, et al., Endocarditis after Transcatheter pulmonary valve replacement, J. Am. Coll. Cardiol. 72 (22) (2018) 2717–2728.
[18] D.B. McElhinney, Reflection and rationalization: making sense of the literature on endocarditis after Transcatheter pulmonary valve replacement, Circ Cardiovasc Interv. 10 (2) (2017), e004983, .
[19] I.J. Amat-Santos, H.B. Ribeiro, M. Urena, R. Allende, C. Houde, E. Bedard, et al., Prosthetic valve endocarditis after transcatheter valve replacement: a systematic review, JACC Cardiovascular interventions. 8 (2) (2015) 334–346.
[20] A. Sharma, A.T. Cote, M.C.K. Hosking, K.C. Harris, A systematic review of infective endocarditis in patients with bovine jugular vein valves compared with other valve types, JACC Cardiovascular interventions. 10 (14) (2017) 1449–1458.
[21] T.L. Holland, L.M. Baddour, A.S. Bayer, B. Hoen, J.M. Miro, V.G. Fowler Jr., Infective endocarditis, Nature reviews Disease primers. 2 (2016) 16059.
[22] L.E. Swart, A. Gomes, A.M. Scholtens, B. Sinha, W. Tanis, M. Lam, et al., Improving the diagnostic performance of (18)F-Fluorodeoxyglucose positron-emission tomography/computed tomography in prosthetic heart valve endocarditis, Circulation. 138 (14) (2018) 1412–1427.
[23] S.P. Salomaki, A. Saraste, J. Kemppainen, J.J. Bax, J. Knuuti, P. Nuutila, et al., 18F-FDG positron emission tomography/computed tomography in infective endocarditis, Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology. 24 (1) (2017) 195–206.
[24] M.N. Pizzi, L. Dos-Subirà, A. Roque, N. Fernández-Hidalgo, H. Cuéllar-Calabria, A. Pijuan Domènech, et al., (18)F-FDG-PET/CT angiography in the diagnosis of infective endocarditis and cardiac device infection in adult patients with congenital heart disease and prosthetic material, Int. J. Cardiol. 248 (2017) 396–402.
[25] D. Tanase, P. Ewert, A. Hager, S. Georgiev, J. Cleuziou, J. Hess, et al., Infective endocarditis after percutaneous pulmonary valve implantation - a long-term single Centre experience, Int. J. Cardiol. 265 (2018) 47–51.
[26] T.J. Cahill, L.M. Baddour, G. Habib, B. Hoen, E. Salaun, G.B. Pettersson, et al., Challenges in infective endocarditis, J. Am. Coll. Cardiol. 69 (3) (2017) 325–344.
[27] L. Cioccari, N. Luethi, U. Weber, A. Hilton, J. Takala, R. Bellomo, The native cardiac output in human sepsis: a systematic review, Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine. 18 (3) (2016) 148–156.
[28] W.R. Davidson Jr., A.C. Stefanescu Schmidt, Transcatheter pulmonic valve replacement: Progress and pitfalls, J. Am. Coll. Cardiol. 72 (22) (2018) 2729–2731.
[29] Veloso TR, Claes J, Van Kerckhoven S, Ditkowski B, Hurtado-Aguilar LG, Jockenhoevel S, et al. Bacterial adherence to graft tissues in static and flow conditions. J Thorac Cardiovasc Surg. 2018;155(1):325–32.e4.
[30] P. Jewgenow, H. Schneider, R. Bokenkamp, J. Horer, J. Cleuziou, R. Foth, et al., Subclinical thrombus formation in bioprosthetic pulmonary valve conduits, Int. J. Cardiol. 281 (2019) 113–118.
[31] J. Buber, L. Bergersen, J.E. Lock, K. Gauvreau, J.J. Esch, M.J. Landzberg, et al., Bloodstream infections occurring in patients with percutaneously implanted bioprosthetic pulmonary valve: a single-center experience, Circ Cardiovasc Interv. 6 (3) (2013) 301–310.
[32] S. Malekzadeh-Milani, M. Ladouceur, M. Patel, F.M. Boughenou, L. Iserin, D. Bonnet, et al., Incidence and predictors of melody(R) valve endocarditis: a prospective study, Archives of cardiovascular diseases. 108 (2) (2015) 97–106.
[33] L. Liesenborghs, P. Verhamme, T. Vanassche, Staphylococcus aureus, master manipulator of the human hemostatic system, J. Thromb. Haemost. 16 (3) (2018) 441–454.
[34] P. Lancellotti, L. Musumeci, N. Jacques, L. Servais, E. Goffin, B. Pirotte, et al., Antibacterial activity of Ticagrelor in conventional antiplatelet dosages against antibiotic-resistant gram-positive Bacteria, JAMA Cardiol. 4 (6) (2019) 596–599.
[35] K. Van Deyk, E. Pelgrims, E. Troost, E. Goossens, W. Budts, M. Gewillig, et al., Adolescents' understanding of their congenital heart disease on transfer to adult-focused care, Am. J. Cardiol. 106 (12) (2010) 1803–1807.