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CLINICAL RESEARCH

French national survey on infective endocarditis and the Melody™ valve in percutaneous pulmonary valve implantation

Expérience nationale française sur endocardite infectieuse et valvulation pulmonaire percutanée par Mélody™

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Abbreviations: CI, confidence interval; IE, infective endocarditis; PA, pulmonary artery; PPVI, percutaneous pulmonary valve implantation; RV, right ventricle; RVOT, right ventricular outflow tract.

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KEYWORDS
Infective endocarditis;
Transcatheter pulmonary valve;
Melody valve;
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Summary
Background. — Percutaneous pulmonary valve implantation (PPVI) is a routine treatment for dysfunctional right ventricular outflow tract. Infective endocarditis (IE) is a major concern.
Aim. — To report French experience with the Melody™ valve (Medtronic Inc., Minneapolis, MN, USA).
Methods. — All patients who underwent PPVI were recorded in a multicentre French national survey. Demographic and procedural data were collected from patients with IE. Bacterial identification, diagnostic tools and outcome were recorded.
Results. — Forty-five cases of IE were diagnosed in 43 patients. The cumulative IE incidence was 11.8% (95% confidence interval [CI] 8.5—15.9). The annualized IE incidence was 3.6% (95% CI 0—4.8). Freedom from IE was 96.3% and 85.8% at 12 months and 60 months, respectively. IE incidence did not change during the study period. The mean interval between PPVI and IE was 2.6 ± 2.1 years (range, 5 days to 7.3 years). Fifteen patients with IE required intravenous antibiotics only. Seven patients had early interventional cardiac catheterization to relieve severe right ventricular outflow tract obstruction. Twenty-four patients had surgical valve replacement (six urgently; nine semi-urgently; nine electively). *Staphylococcus aureus* IE required surgery in all but one patient. Three patients died before any treatment. Three additional patients died, giving a mortality rate of 14%. Global survival in the total cohort of patients who received a Melody valve was excellent (96.5% at 5 years). When comparing survival curves between the IE and non-IE groups, death and cardiovascular events were statistically significantly higher in the IE group (log-rank $P < 0.0001$).
Conclusion. — Melody valve IE is a severe complication following PPVI. The annualized IE incidence in this cohort was similar to rates reported in other studies. With rapid diagnosis and adequate treatment, outcome has improved, and unfavourable outcome is mainly associated with *S. aureus*.

MOTS CLÉS
Endocardite infectieuse ;
Valvulation pulmonaire percutanée ;
Valve Mélody ;
Cardiopathie congénitale

Résumé
Introduction. — La valvulation pulmonaire percutanée est un traitement de routine de la *dysfunction* de la voie d'éjection droite. L'endocardite infectieuse (EI) est une préoccupation majeure.
But. — Rapporter l'expérience française des endocardites infectieuses après implantation de valve Mélody (Medtronic Inc., Minneapolis, MN, États-Unis).
Méthodes. — Tous les patients ayant eu une valvulation pulmonaire avec une Mélody ont été inclus dans une série multicentrique française. Les données démographiques et de cathétérisme ont été récoltées pour les patients ayant eu une EI. L'identification bactérienne, les moyens diagnostics et le devenir des patients ont été analysés.

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Résultats. — Quarante-cinq épisodes d'EI ont été diagnostiqués chez 43 patients. L'incidence cumulée d'EI était de 11,8 % (intervalle de confiance 95 % [IC] 8,5—15,9). L'incidence annualisée d'EI était de 3,6 % (95 % IC 0—4,8). L'absence d'EI était respectivement de 96,3 % et 85,8 % à 12 et 60 mois. L'incidence d'EI n'a pas changé durant la période étudiée. La durée moyenne entre l'implantation et l'EI était de 2,6 ± 2,1 ans (5 jours à 7,3 ans). Quinze patients ont été traités par antibiothérapie intraveineuse uniquement. Sept patients ont eu un cathétérisme interventionnel pour lever l'obstruction sévère de la voie droite. Vingt-quatre patients ont eu un remplacement valvulaire chirurgical (six en urgence, neuf en semi-urgence et neuf de manière élective). Les EI à *S. aureus* ont nécessité de la chirurgie chez tous les patients sauf un. Trois patients sont décédés avant tout traitement. Trois autres patients sont décédés. La mortalité dans l'EI est de 14 %. La survie globale de la population implantée avec une Mélody était excellente (96,5 % à 5 ans). La mortalité et les évènements cardiovasculaires étaient statistiquement plus élevés dans le groupe de patients avec EI (log-rank $P < 0.0001$).
Conclusion. — L'EI est une complication sévère après valvulation percutanée. L'incidence annualisée dans cette cohorte est similaire à celle rapportée dans d'autres séries. Avec un diagnostic rapide et un traitement approprié, le pronostic s'améliore. Les issues défavorables sont essentiellement dues aux EI à *S. aureus*.

Background

Percutaneous pulmonary valve implantation (PPVI) (Melody™ valve; Medtronic Inc., Minneapolis, MN, USA) has become established as a valuable treatment for dysfunctional right ventricular outflow tract (RVOT) since its introduction in 2000 [1]. Excellent haemodynamics and sustained results have been demonstrated in several large patient cohorts [2,3]. In all published cohorts, there were reports of infective endocarditis (IE) [2—5]. Since the first report focusing specifically on severe IE [6—8], multiple papers from various institutions have described an annualized IE incidence of 2.5—4% [9—13]. We and others have compared surgery with PPVI using the Melody valve. The incidence of IE with the Melody valve appeared to be higher [13,14] than with homografts, but similar to that with Contegra™ surgical conduits (Medtronic). This topic is still a matter of debate, as most surgical papers are based on retrospective collection of data, focusing mostly on IE associated with surgery, while PPVI data are prospective; this might underestimate the real number of cases of IE with surgical implants.

Nevertheless, the total number of published cases of IE remains limited, and information about IE continues to be scarce. We conducted a national survey on PPVI using the Melody valve and IE, and report here the incidence, characteristics and outcome of this complication.

Methods

The French working group of Cardiac Catheterization in Congenital Heart Diseases Patients (Club francais des cardiologues des cardiopathies congénitales [C4F]), which includes all Melody valve implanters, conducted a clinical study on IE with the Melody valve. To ensure that all the Melody valves implanted were collected, we matched our numbers with the number of Melody valves implanted in France from the Medtronic database. Informed consent was obtained from each patient.

Two data sets were prepared. The first data set concerned all patients with a Melody valve implanted from January 2008 to January 2016. We collected demographic data (date of birth, sex), procedural data (date of the PPVI implantation procedure) and outcome (date of Melody valve explantation and reasons, date of IE, type of treatment and death). The second data set concerned all patients with Melody valve IE. The Duke criteria were used to define definitive IE. However, in patients with possible IE, a definite diagnosis of IE was left at the discretion of the investigators. Diagnostic criteria used for diagnosis were collected and analysed. We excluded patients with bloodstream infections that were not treated as IE.

In the group with IE, we recorded demographic data (date of birth, sex, type of congenital heart disease, type of conduit, reason for Melody valve implantation, history of infection, presence of stent in RVOT and co-morbidities); procedural data (date of implantation, haemodynamics pre- and postimplantation, associated procedures and complications); and data regarding IE (date of occurrence, mode of presentation [acute, subacute or chronic], type of bacteria, potential port of entry, echocardiographic findings and treatment). Finally, we collected data on diagnostic tools, treatment and outcome. In case of surgical explantation, date of surgery, type of surgery and timing (defined as urgent if within a week from diagnosis, semi-urgent if within a month from diagnosis and elective otherwise) and reason for surgery were reported. Data sets were extracted from ongoing prospective studies in participating centres.

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The severity of IE was defined based on presentation and outcome. IE was considered as severe when patients presented with shock, died or needed urgent relief of RVOT obstruction by surgery or intervention. Cardiovascular events were collected, and included Melody valve dysfunction of any cause (IE, stent fracture or stenosis), need for surgery (any cause), death (any cardiac cause) and need for interventional cardiac catheterization (any cause).

Statistical analysis

SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. Nominal variables are expressed as numbers and percentages and were compared by Fisher's exact test or the χ^2 test, as appropriate. Ordinal variables are presented as means ± standard deviations and were compared with the Wilcoxon rank-sum test. Continuous variables are expressed as means ± standard deviations and were compared with the independent-variables *t* test. A *P* value < 0.05 was considered statistically significant. Survival curves were constructed using the Kaplan–Meier method. Groups were compared using log-rank statistics. The risk markers of IE were studied by univariate Cox proportional hazards survival analyses. The cumulative incidence of IE was calculated by dividing the number of cases of IE by the number of patients at risk, expressed as a percentage. Annualized IE incidence was calculated for the global population and for the population of each centre. Practice was modified during the time period. We started to modify our practice, to communicate and to publish our data regarding IE during 2012. We started to educate patients and their caregivers (cardiologists and general practitioners) about the risk of IE, on the importance of aspirin and antibioprophylaxis, and on the aggressive treatment required in case of IE. IE rates were compared before and after 2013 when all centres adopted new guidelines.

Results

Incidence

Between January 2008 and May 2016, 365 patients in 10 centres received the Melody valve in the pulmonary position (Table 1). Mean follow-up was 3.3 ± 2.3 years. Forty-five cases of IE were reported in 43 patients; two patients had two distinct episodes of IE with two different bacteria. The cumulative IE incidence was 11.8% (95% confidence interval [CI] 8.5–15.9). The annualized IE incidence was 3.6% (95% CI 0–4.8). Freedom from IE in the total cohort was 96.3% and 85.8% at 12 months and 60 months, respectively (Fig. 1A). The numbers of implanted patients and patients with IE, and the incidence and annualized incidence of IE are summarized for the total population and per centre (Table 1). In Fig. 1B, IE rates were similar before and after 2013 (difference not significant). Age at implantation ($P = 0.39$), age at diagnosis of IE ($P = 0.12$) were not risk factors.

Demographics of patients with IE

The mean age at diagnosis was 26.3 ± 12.6 years. There were nine women and 34 men. Male sex was a risk

Table 1 Cumulative and annualized incidence of infective endocarditis by centre and overall.

	Centre										Global
	1	2	3	4	5	6	7	8	9	10	
Number of patients	167	41	34	32	32	23	15	10	7	4	365
Mean follow-up (years)	3.4	2.5	2.8	4.8	3.8	3.6	2.0	0.6	4.6	2.4	3.3
Patient-years	569	102	94	158	125	84	29	6	32	10	ND
Number of patients with IE	19	4	5	8	2	4	0	0	0	1	43
Cumulative incidence of IE[a]	11 (7–18)	9.8 (3.3–23.1)	15 (5–34)	25 (13–42.3)	6	17 (5–44)	0	0	0	25	11.8 (8.5–15.9)
Annulized incidence of IE[a]	3.3 (2.0–52)	3.9 (1.1–10)	5.3 (1.7–12.4)	5.2 (2.2–10.0)	1.6 (0.2–5.8)	4.8 (1.3–12.2)	0	0	0	10 (0.2–56)	3.55 (0–4.77)

IE: infective endocarditis; ND: not done.
[a] Data are expressed as % (95% confidence interval).

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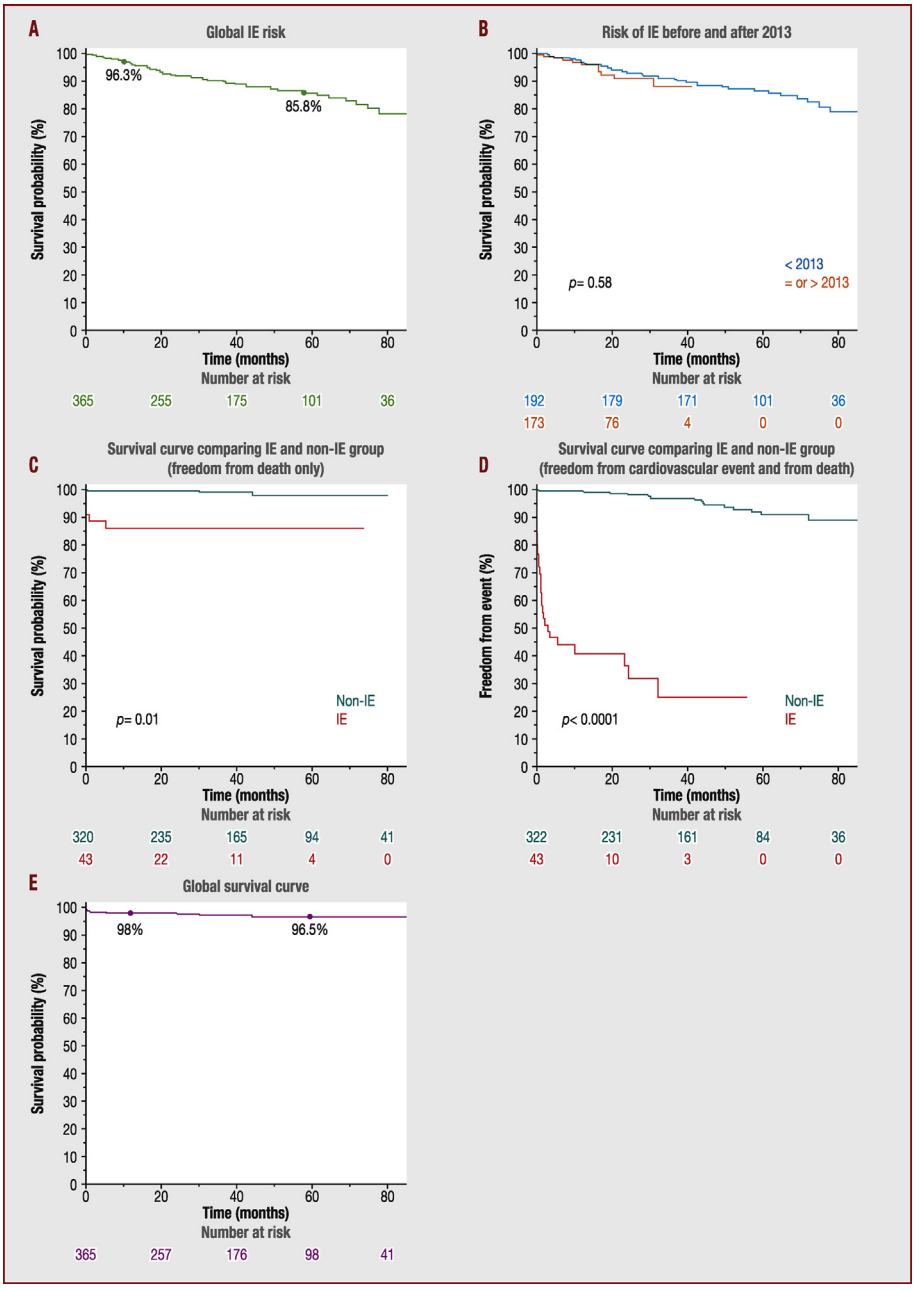

Figure 1. Survival curves. A. Global infective endocarditis (IE) risk. B. IE risk before and after 2013. C. Survival curve comparing IE and non-IE groups (freedom from death). D. Survival curve comparing IE and non-IE groups (freedom from cardiovascular event and death). E. Global survival curve.

factor for IE (unadjusted odds ratio 2.7, 95% CI 1.3—5.6; $P < 0.05$). Only two patients had a history of IE. Co-morbidities were noted in 19 patients, who had syndromes or extracardiac chronic diseases (Di George syndrome [$n = 7$], syndrome associated with limited intelligence quotient [$n = 5$], asplenia [$n = 1$], hepatitis C [$n = 1$], cirrhosis [$n = 1$], thrombocytopoenia [$n = 1$], beta thalassaemia [$n = 1$], smoking/alcoholic intoxication [$n = 1$] and intestinal polyposis [$n = 1$]). IE occurred in the Melody valve inserted within bioprosthetic and conduit valves in 28 patients (Contegra [$n = 5$]; Hancock™ (Medtronic) [$n = 11$]; Dacron conduit [$n = 2$]; Vascuteck® (Terumo, Tokyo, Japan) [$n = 3$]; miscellaneous bioprosthetic valves [$n = 7$]), in homografts in 11 patients and in native RVOT in the four remaining patients.

Procedural data at PPVI from patients with IE

The mean age at implantation was 23.0 ± 11.1 years. The mean duration of the procedure was 108 ± 59 minutes. Basal mean right ventricle-to-pulmonary artery (RV-to-PA) gradient was 43 ± 25 mmHg, and the mean RV/aortic pressure ratio was 0.78 ± 0.24. The final mean RV-to-PA gradient was

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14 ± 9.5 mmHg, and the mean RV/Ao pressure ratio was 0.43 ± 0.16. The reasons for Melody valve implantation were stenotic lesion with (n = 20) or without (n = 20) regurgitation in 40 patients, and regurgitant RVOT in the remaining three patients. Nineteen patients had a stent placed during a previous cardiac catheterization. Prestenting at PPVI procedure was performed in 34 patients with a bare-metal stent (n = 33) or a covered stent (n = 1). Nine patients had multiple stents placed in the RVOT to cover a long stenosis or to decrease recoil. There were 10 associated procedures: unilateral PA stenting (n = 6); bilateral PA stenting (n = 2); right PA reopening for procedural right PA occlusion (n = 1); and right coronary artery angioplasty for a pre-existing lesion (n = 1). The Melody valve was postdilated in 16 patients.

Timing and clinical presentation of IE

The mean interval between Melody valve implantation and IE was 2.6 ± 2.1 years (range, 5 days to 7.3 years). The mode of presentation was acute in 20 cases (44%), subacute in 19 cases (42%) and chronic in six cases (14%). Thirteen episodes (29%) had a hyperacute presentation, with septic, cardiogenic or mixed (cardiogenic and septic) shock. Thirty-three patients received antiplatelet therapy when they presented with IE. Aspirin discontinuation was statistically associated with severe IE (P = 0.031). The port of entry was identified in 27 cases (Table 2). On imaging, vegetations were found in 82% of cases of IE (31 on transthoracic or transoesophageal echocardiography; five on computed tomography scan; and one on intracardiac echocardiography). The mean RV-to-PA gradient increased from 34 ± 18 mmHg to 62 ± 29 mmHg. Six patients had significant pulmonary insufficiency. IE was diagnosed based on the modified Duke criteria in 37 cases (definitive IE). Five patients had possible IE according to the Duke criteria and a positive positron emission tomography scan. The remaining three patients were diagnosed using possible IE according to the Duke criteria (fever, positive blood culture and predisposing factors) and an increased gradient across the Melody valve.

Blood cultures were positive in 40/45 cases (89%). In negative blood cultures, the types of bacteria were identified on surgical explantation in one case (*Staphylococcus*) and on serology in one case (*Coxiella burnetti*). Bacteria were not identified in three cases, including two patients with previous antibiotherapy and one patient without bacterial identification. The types of bacteria are reported in Table 2. *S. aureus* was more often associated with acute onset and septic or cardiogenic shock than any other bacteria (P = 0.002).

Two patients had associated aortic valve vegetations. No systemic complication was reported. These patients had aortic valve replacement at the time of surgical pulmonary valve replacement. One patient with *S. aureus* IE presented with acute respiratory distress syndrome, renal failure and cutaneous necrosis; he ultimately survived at the cost of transient dialysis and limb amputation. One patient presented postembolic pulmonary hypertension.

Table 2 Portal of entry and type of bacterium in patients with infective endocarditis.

Portal of entry	Number of events reported
Cardiac catheterization	7
Diagnostic catheterization	2
Interventional catheterization (dilatation)	5
Electrophysiology	6
Electrophysiology evaluation	2
Ablation	2
Implantable cardioverter defibrillator implantation	1
Pacemaker	1
Dental source	8
Multiple teeth decay	4
Dental work	4
Medical condition	14
Hepatic biopsy with secondary sepsis	1
Gastrointestinal intervention	2
Urinary tract infection	1
Skin anomaly (psoriasis, piercing, acne, panaritium, furuncle, wound)	6
Abortion	1
Tonsillitis	1
Sinusitis	1
Open fracture with osteosynthesis infection	1
Episodes of IE with identified portal of entry[a]	27
Type of bacterium	**Number of patients**
Streptococcus	16
Staphylococcus	7
S. aureus	12
Abiotrophia defectiva	2
Klebsiella	2[b]
Propiniobacterium acnes	1
Corynebacterium	2[c]
Rothia dentocariosa	1
Coxiella burnetti	1
Acinetobacter	1[d]
Candida albicans	1[d]

[a] Some patients presented several potential portals of entry.
[b] In one patient, co-infection with *S. epidermidis*.
[c] In one patient, co-infection with *S. haemolyticus*.
[d] Co-infection with three germs in an immunocompromized (chemotherapy) patient (*S. aureus*).

Outcome

Outcome data are presented in Fig. 2. Fifteen patients with IE (15/45, 33%) required intravenous antibiotics only. Seven patients had early interventional cardiac catheterization to relieve a severe RVOT obstruction, in addition to antibiotics. In total, twenty-four patients had surgical valve replacement. Surgery was performed urgently in six patients, semi-urgently in nine patients and electively in nine patients. Three patients died before any surgery or catheterization could be performed; two because of severe

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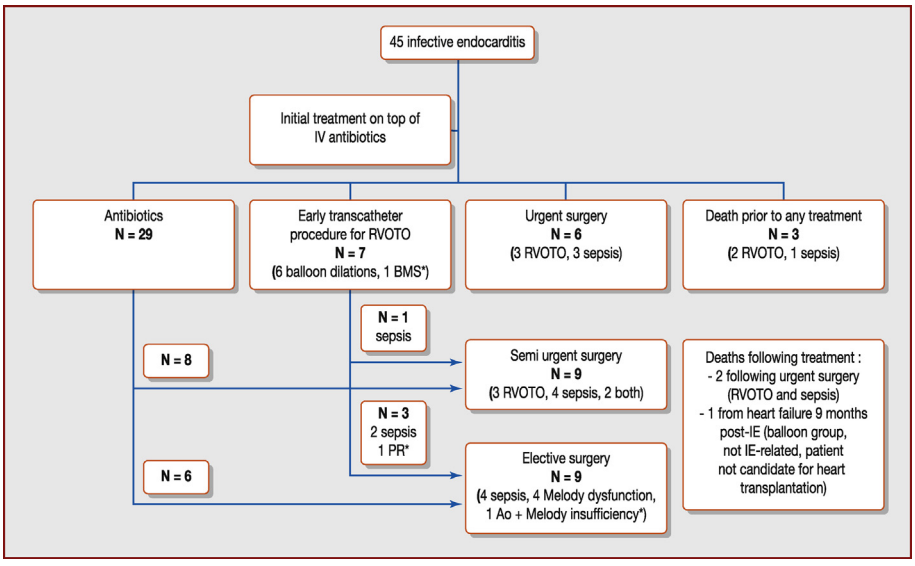

Figure 2. Flow chart showing type of treatment and outcome of Melody valve infective endocarditis (IE). Ao: aortic; BMS: bare-metal stent; IV: intravenous; PR: pulmonary regurgitation; RVOTO: right ventricular outflow tract obstruction.* Patient with associated aortic insufficiency, who underwent aortic valve replacement and pulmonary valve replacement of the stented Melody valve.

cardiogenic shock (RVOT obstruction, *Staphylococcus* infection, 2009 and 2010) and one because of septic shock (no RVOT obstruction, *Staphylococcus* infection, 2016). Three additional patients died, giving a mortality rate of 14%. The need for urgent surgery and acute onset were statistically associated with death ($P < 0.05$). *S. aureus* was associated with death and the need for urgent or semi-urgent surgery ($P = 0.002$). When comparing survival curves focusing on survival only, death was, as expected, statistically higher in the IE group ($P = 0.01$) (Fig. 1C). When comparing survival curves between the IE and non-IE groups, occurrence of death and cardiovascular events were statistically significantly higher in the IE group (log-rank $P < 0.0001$) (Fig. 1D). Nonetheless, the global survival of the total cohort of patients receiving a Melody valve was 96.5% at 60 months (Fig. 1E).

IE recurrence

Two patients had two distinct episodes of IE, with two different bacteria. The interval between the first and second episodes was 8.5 months in the first patient and 30 months in the second patient. One patient had recurrent IE with the same bacteria (*S. aureus*) after surgical replacement of the Melody valve by a Contegra conduit, 5 years after surgical explantation of the infected Melody valve.

Discussion

To our knowledge, this is the first series collecting all of the data regarding IE and the number of Melody valves implanted in a relatively large national cohort. We confirm the high incidence of IE, and provide descriptive data, including clinical and bacteriological features, as well as outcome. There are presently no data comparing surgical and transcatheter implants prospectively. Most series reporting surgical IE are retrospective studies from the surgical field, where non-surgical IE is not always reported. As a result, surgical implant IE is underestimated, making comparison with Melody valve cohorts biased.

Incidence

In this cohort, freedom from IE was 85.8% at 60 months. The annualized incidence of IE was 3.6% per year. This series reports results from 10 different centres, and local practice may vary somewhat. We observed that incidence varied greatly between centres (statistically insignificant). The reasons for this might be related to different practices in prevention and treatment, but also to indications and types of patients treated. Because of the small numbers of patients in some centres, and because data in the global population are lacking, further analysis is not possible. Medical experience and awareness of the burden of the disease vary greatly between congenital interventionalists in France, and this explains the extreme practice in some centres that no longer implant the Melody valve. Indeed, in some centres with small numbers of patients implanted, the occurrence of a few cases of IE (even as few as one case) will have a major impact on IE incidence. Based on their local experience, some centres have decided to stop their implantation programme.

Diagnostic tools

IE was diagnosed based on the modified Duke criteria (fever, predisposing factors and presence of vegetations) in most patients (37/45 cases). Vegetations were found using echo modalities in 31 patients, computed tomography scan in five patients and intracardiac echocardiography in one patient. The question of overdiagnosis of Melody valve IE could be raised in the remaining eight patients, where vegetations were not seen. We believe that this is not the case for several reasons.

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Vegetations not seen using conventional modalities does not mean absence of vegetations or no involvement of the valve. In such situations, other imaging modalities (positron emission tomography scan or intracardiac echocardiography) might be necessary to enhance the sensitivity of detection. Five patients out of eight with possible IE based on the Duke criteria had a positive positron emission tomography scan and were classified as having definitive IE. Three patients out of eight with possible IE based on the Duke criteria had an increased gradient across the Melody valve. We have hypothesized in earlier studies that a rapid increase in the gradient across the Melody valve is a sign of valvular involvement, besides new onset of pulmonary regurgitation, which is an item in the modified Duke criteria [10,15]. This feature has been tackled recently in a study on right-sided endocarditis, which stated that IE should be considered in patients presenting with new onset RVOT obstruction [16]. Based on that feature, IE was classified as definitive IE in those three patients. Because of financial considerations, the use of intracardiac echocardiography was very limited in that series, but, as advocated by various authors, it has a place beside other modalities in patients without definitive IE [17]. We think that a rapid increase in the gradient or new onset of gradient across the Melody valve should be considered as a major criterion for IE. We advise yearly follow-up and rapid echocardiographic assessment in case of any clinical change. A mild increase in the gradient should be taken into account in the global evaluation of the patient (is there presence of fatigue, malaise, etc.), but can also be explained by somatic growth of the patient in the paediatric population or mechanical alteration of the valve (i.e. stent fracture). Rapid or important increase in the gradient should prompt further investigation.

Bacteria

Causative microbial agents were found in the majority of episodes (Table 2). Bacteria were similar to those reported with other prosthetic devices. The type of bacterium should be taken into account when therapeutic strategies are decided upon. The presence of *S. aureus* required special attention. As described previously [15,18], *S. aureus* IE was associated with the most aggressive disease, with acute onset, death and often severe septic shock at presentation. As a result, surgery was necessary in most cases of *S. aureus* IE (11/12 patients required surgery). Only one patient presented without shock and was treated with antibiotics only.

Risk factors

Risk factors are multifactorial, and come from complex interactions between pre-, per- and postprocedural factors. Preprocedural factors include co-morbidities, male sex, dental status and degree of immunosuppression. Procedural factors include degree of residual obstruction, the valve itself and manipulation of the valve. Strict measures to reduce the residual gradient after implantation are important. Increased residual gradient has been shown to be a risk factor for IE by McElhinney et al. [11]. Postprocedural data include global healthcare after implantation.

Some questions about the valve and manipulation have been answered partially. It has been recognized in several studies that the Contegra conduit might be more prone to IE then other conduits [13,14]. Our group demonstrated recently that manipulation of the Melody valve was inducing damage to the valve leaflet, making it more fragile. This might explain, at least in part, why transcatheter valves in general are more prone to IE compared with surgical implants [19]. We also demonstrated higher in vitro bacterial adherence with the non-manipulated Melody valve, and after crimping and expansion of the Melody valve. This issue remains controversial for multiple reasons inherent to the study design. The study was in vitro. Bacteria used for the study were bacteria obtained for Melody valve IE that already showed a tropism for the Melody valve. Because of the complexity of the study and the low availability of valve tissue, we were unable to test adherence with other bacteria. For these reasons, one should be cautious about stopping using Melody valves. Another way to answer these questions would be to analyse midterm results of the SAPIEN™ valve (pericardic valve) (Edwards Lifesciences, Irvine, CA, USA) in the pulmonary position. From the SAPIEN Compassion trial, conducted in 69 patients, freedom from IE at 60 months was 87.1%, which is similar to the incidence in our population [20], confirming that the type of valve is not the only risk factor. In a recent study by Hascoet et al., the rate of IE was higher in the Melody valve group then in the SAPIEN valve group [21]. Because of some study limitations, we believe that the message from the authors should be softened: it was a retrospective single-centre series with a small number of patients, and the two cohorts (SAPIEN valves versus Melody valves) were not contemporary, with a shorter follow-up in the SAPIEN group. Potential risk factors have been corrected in the most recent patients. In addition, the included population differed between the two groups, making any comparison useless. Other studies have shown that patients with a small RVOT or stenotic or mixed lesions were more prone to IE. Patients who received the SAPIEN valve had a larger RVOT. Finally, the incidence of Melody valve IE was very high in their patients implanted with Melody valve (5.7% per person-years), much higher than in the other published series.

Good hygiene and health care is important, as for any patient with prosthetic valves. This is relevant for dental care, but also for skin conditions and any medical procedure performed on these patients. Interestingly, following reports of IE in patients who had undergone PPVI, in 2012 we modified our prevention to include education of patients and general practitioners, emphasizing antibioprophylaxis guidelines and perfect dental hygiene. Aspirin administration was modified in most of the centres after 2012. Indeed, in 9/10 centres, aspirin was administered for 6 months before 2012, and after the first reports of IE, administration was converted to lifelong treatment. We started to rule out tooth decay and ear/nose infection by routine dental and ear/nose examination before Melody valve implantation. Despite these practice modifications, we failed to demonstrate a reduction in IE incidence between the two periods. The reasons for this are unclear, but acceptance and comprehension of this advice by patients are questionable, as co-morbidities and syndromic patients were over-represented in the IE cohort, with 44% of the patients presenting co-morbidities. Some syndromes have immunological disorders that might explain a higher incidence of

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Table 3 Global health care with transcatheter pulmonary valve.

Preimplantation
Dental work-up
Ear, nose and throat work-up
Patient education on the risk of IE
Good dental hygiene
No tattoos, no piercing
Antibioprophylaxis according to ESC guidelines
Postimplantation
Good dental hygiene
Antibioprophylaxis according to ESC guidelines
Lifelong antiaggregation
Prompt clinical assessment in case of fever, malaise
Education of care providers
Educational patient card
Programme of therapeutic education

ESC: European Society of Cardiology.

IE; but patients with syndromes and a limited intelligence quotient may have poorer global and dental hygiene, and a poorer understanding of the need to maintain adequate hygiene. True therapeutic education, rather than simple advice in the outpatient clinic, might make a huge different in that population. The question of aspirin in the prevention of IE remains, because the incidence of IE did not change between the two eras of different treatment.

Education, prevention and prophylaxis are mandatory to reduce IE incidence. Table 3 summarizes our current guidelines pre- and postimplantation.

Recurrence and type of treatment

Recurrent IE was reported in two patients with different bacteria, leading to surgical replacement of the Melody valve. Recurrent IE was also reported 5 years after surgical removal of the Melody valve, on a surgical implant. This underlines that history of IE is a well-recognized risk factor for IE. Surgical and PPVI implantation, however, carry the same risk factors. As a result, there is, for us, no reason to prefer surgery in a patient with a history of IE. In patients with a dysfunctional Melody valve following IE, the questions of indication to redo PPVI and its timing are still under debate, as well as the need to change the type of valve in case of valvar replacement (Contegra conduit versus other prosthetic surgical valve, and Melody valve versus other transcatheter pulmonary valve). One should be cautious about reimplanting a valve too soon after IE, to avoid reinfecting the new valve. Because most recurrences of surgical IE have been described within the first year after initial diagnosis, our policy is to wait at least 1 year before implanting a new PPVI valve. If a patient experiences Melody valve obstruction during that time period, balloon dilatation with or without bare-metal stent implantation is proposed. If a patient has a regurgitant Melody valve resulting from destructive IE, there are usually no acute indications for valve implantation, and the patient can wait 1 year before redo PPVI.

Outcome

When comparing the two subgroups with and without IE statistically, survival curves were significantly different when we studied survival and cardiovascular events only, confirming the severity of this condition. Rate of death after IE was high in this cohort, but similar to the rate of death described in the congenital heart disease population (around 10%), and lower than in general prosthetic valve IE [16]. Thanks to the early reports of malignant IE, prompt diagnosis and aggressive treatment have resulted in a reduction in the death rate over the years in relation to acute RVOT obstruction. The two deaths in the recent experience were patients who presented with profound septic shock secondary to *S. aureus* IE, and not with cardiogenic shock resulting from severe RVOT obstruction. Another reassuring finding in this cohort was that about one-third of the cohort did not require surgery, and that IE could be treated by antibiotherapy (with balloon dilatation of the stenotic Melody valve in some cases). This number varied from one institution to another. Some institutions felt that all infected devices should be explanted, while others explanted only those with uncontrolled sepsis or local complications. Eight of 24 patients (four RVOT obstructions, four Melody valve dysfunctions) who underwent surgery could probably have been treated more conservatively with intravenous antibiotics and transcatheter treatment, including Melody valve dilatation, bare-metal stent insertion or redo Melody valve. Finally, one should be careful when focusing on one complication to keep the full picture of the technique in mind. The global survival curve (Fig. 1E) was excellent, despite occurrence of IE, as already demonstrated in various large cohorts, including this one.

Study limitations

We were unable to study risk factors in depth in the total cohort, because the data set for non-IE Melody valve patients did not include initial diagnosis, reason for Melody valve implantation, complete haemodynamic data, aspirin use, the presence of co-morbidities and medical invasive acts. As a result, comparisons were not possible. This is because the initial data set collected in 11 centres was mainly focused on IE clinical features, outcome and treatment. So far, no effect of initial diagnosis has been demonstrated.

Conclusions

This series demonstrates that IE is a real issue after Melody valve implantation. These cases of IE have similarities with other right-sided postsurgical IE in terms of pathogens, timing and outcomes; they have differences concerning incidence and early presentation. One should keep in mind the hyperacute presentation of IE in case of severe RVOT obstruction. IE can be acute and severe based on haemodynamic (RVOT obstruction) and septic (septic shock) status or because of infection with *S. aureus*. In case of severe IE, urgent treatment needs to be initiated to reduce mortality. Besides severe events, a large number of cases of IE were less invasive, and could be treated by antibiotherapy alone,

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postponing or eliminating the need for surgery. Questions remain about risk factors for IE, but therapeutic education is probably one key to reducing the incidence of IE in this patient population. Finally, one should be cautious about condemning this device, because the incidence of IE based on data presently available is similar to that with other available PPVI devices, and because global results are excellent, similar to the surgical cohort. Further studies are necessary to identify additional risk factors for PPVI valve IE, and to compare the results of surgical and transcatheter pulmonary valve replacement.

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Disclosure of interest

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The other authors declare that they have no competing interest.

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