REVIEW

Percutaneous pulmonary valve endocarditis: Incidence, prevention and management

Endocardite sur bioprothèses pulmonaires percutanées : incidence, prévention et prise en charge

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Summary  The epidemiology of infective endocarditis is changing rapidly due to the emergence of resistant microorganisms, the indiscriminate use of antibiotics, and an increase in the implantation of cardiovascular devices including percutaneous valves. Percutaneous pulmonary valve implantation has achieved standard of care for the management of certain patients with right ventricular outflow tract dysfunction. With its expanding use, several cases of early and delayed infective endocarditis with higher morbidity and mortality rates have been reported. This review summarizes the trends in percutaneous pulmonary valve infective endocarditis, postulates proposed mechanisms, and elaborates on the prevention and management of this unique and potentially fatal complication.

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Abbreviations: CHD, congenital heart disease; IE, infective endocarditis; PPV, percutaneous pulmonary valve; PPVI, percutaneous pulmonary valve implantation; RVOT, right ventricular outflow tract.

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MOTS CLÉS
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Introduction

Percutaneous pulmonary valve implantation (PPVI) (Melody® valve; Medtronic, Minneapolis, MN, USA) has become established as a valuable treatment option for patients with right ventricular outflow tract (RVOT) dysfunction since its clinical introduction in 2000 [1–4]. Excellent early, mid-term and even long-term success rates, with improvements in functional status, peak exercise capacity and ventricular function, have been reported since then [5–12]. Unfortunately, because of factors that are not clearly understood, several cases of early and delayed percutaneous pulmonary valve infective endocarditis (PPV IE) have been reported. IE is a burden in the congenital heart disease (CHD) population, particularly in patients with prosthetic valves in whom diagnosis is more difficult, prognosis is worse and the need for surgery is more frequent compared with CHD patients with native valves. Around half of the patients with CHD-associated IE develop severe episode-related complications and the mortality rate for surgery for IE is very high (40–50%) [13–15]. In this review article, we summarize the trends in PPV IE, postulate proposed mechanisms, and elaborate on the prevention and management of this unique and potentially fatal complication.

Clinical presentation and diagnosis

IE is a clinical diagnosis and requires a high index of suspicion, especially in the CHD population, as patients may present with non-specific symptoms. The Duke criteria for the diagnosis and management of IE were initially drafted in 1994; they were later modified in 2002 to include echocardiography criteria, and again in 2007 for optimal clinical use. The two major clinical criteria are abnormal blood cultures and evidence of endocardial involvement. The five minor clinical criteria are a predisposition to IE, a fever of > 38 °C, vascular phenomena, immunological phenomena or microbiological evidence of IE not meeting major criteria. Requirements for a clinical diagnosis of IE are: two major clinical criteria; one major and three minor clinical criteria; or five minor clinical criteria [16–18]. Although these criteria are still used universally for IE, the patient characteristics, timing and presentation of PPV IE are quite complex, and one may have to keep a high index of suspicion in such patients. It is important to note that the clinical presentation with atypical organisms, such as Coxiella burnetii endovascular infection, is usually insidious, lacks the typical features of bacterial endocarditis and often results in delayed diagnosis. Patients are often afebrile and vegetations are usually absent or small [19,20].

Definitive IE is diagnosed based on modified Duke criteria, although in patients with prosthetic or Melody valves, true valve involvement may be difficult to determine with a high degree of certainty, because of the acoustic shadowing artefacts from the prosthesis and the unusual anatomy of the RVOT. Transoesophageal echocardiography might be needed. However, the anterior position of the RVOT makes its visualization very difficult and the result is not always inconclusive. An increase in RVOT gradient from postprocedure echocardiogram to hospital admission is present in most patients with IE. The Duke criteria should be modified for this particular substrate (i.e. PPVI) because, in our opinion, any degree of increase of RVOT gradient (unexplained by a structural complication, such as stent fracture) demonstrates the valvular involvement and should be considered as a major criterion similar to new onset of pulmonary regurgitation, unless proved otherwise. Based on these features, blood stream infection with a rise in RVOT gradient may be reclassified as definitive endocarditis. The Duke criteria alone may very well explain the difference noted in the incidence of PPV IE between reported studies. Some other diagnostic tools may be helpful, such as intracardiac echocardiography, three-dimensional echocardiography or positron emission tomography. Positron emission tomography-computed tomography fusion imaging is a good diagnostic tool in case of difficulties in assessing hot spots and slow mouldering cardiac involvement.

Incidence

Several types of presentations and risk factors have been reported. The first series in 2008 by Lurz et al. [21] reported five cases of PPV IE out of 155 patients with an age range of 7–71 years. The possible risk factors reported included dental treatment (n = 1), septic wound after arm trauma (n = 1), reactivation of previously treated fungal infection
Melody valve endocarditis

(n = 1) and previous history of medically treated IE before PPVI (n = 2) [21]. Subsequently, there have been several anecdotal reports of PPV IE. Our group published a case series on four PPVI-related IE cases involving Streptococcus sanguis (n = 2), Streptococcus mitis and Staphylococcus epidermidis. Strikingly, three of these had a history of abrupt aspirin discontinuation. Two of the four patients died: one patient (with S. epidermidis) died on the day of presentation, with heart failure and ventricular fibrillation; and the other (with S. sanguis) died of multiorgan failure following emergency surgery [22]. Subsequently, Buber et al. [23] reported on 14 subjects who developed bloodstream infection, four of them with definite PPV IE. There were two deaths with methicillin-resistant Staphylococcus aureus bacteremia without valve involvement. All of these patients had recent onset of obstructive RVOT dysfunction before PPV IE. Male sex, previous IE, high number of stents and altered RVOT anatomy were identified as important risk factors. Only one of the four patients with documented valve involvement underwent surgical valve replacement. A more recent report combining the results of three manufacturer-sponsored prospective North American and European studies showed that 16 of 311 patients were diagnosed with definite or presumed IE, including six who met their criteria for PPV IE. One patient with valve-related IE died after bioprosthesis explantation and multiple complications. Another patient died with severe haemoptysis, 3 weeks after a second PPVI for progressive pulmonary stenosis. Only four patients required Melody valve replacement and two had a second PPVI. Two subjects presented with recurrent IE, 1.6 and 2.7 years after the initial diagnosis. One of the two patients had a second PPVI for stent fracture-related pulmonary stenosis after antibiotic treatment for the initial IE episode, and the other had vegetable at initial diagnosis but received non-surgical treatment [24]. Cheung et al. [25] reported six cases of PPV IE, and demonstrated the unique utility of intracardiac echocardiography for identifying small and subtle vegetations. The most recent report by Villafane et al. [26] described four paediatric patients with PPV IE: two had documented vegetations; three showed worsening pulmonary stenosis at the time of presentation; three underwent surgical valve replacement with no deaths.

It is interesting to note that there is no specific microbiology pattern of Melody valve involvement. Most organisms, from cutaneous commensals to pathogens commonly encountered in IE, have been reported. The annualized rate of first episode of valve-related IE is 0.88% per patient-year. None of the patients seen in our institution or reported in the literature showed any septic emboli to the pulmonary circulation. Table 1 shows the various studies and reports in the literature with Melody valve IE.

Vegetations

There are very few reports providing in-depth macroscopic and microscopic details of vegetations. We reported large, fleshy, sessile, loosely attached and easily retrievable vegetations on the Melody valve. The vegetations appeared glistening pink, filling the cusps and reducing the pulmonary orifice opening to a pinhole (Fig. 1). The underlying leaflets showed no signs of destruction or evidence of long-standing infection, and appeared normal (Fig. 2) [22]. A few other reports showed similar vegetations on macroscopic examination [27,28]. Histological examination showed voluminous fibrin strands with no microorganisms. Importantly, the bulk constituted amorphous material was mostly thrombus (Fig. 3) [22]. It is almost certain from the available literature that none of the cases reported so far represents accelerated degeneration of the bioprosthetic valve and none had tissue failure as the cause of IE.

Infective endocarditis in surgically repaired right ventricular outflow tract versus percutaneous valves

Two large surgical series of 165 and 193 Contegra conduits (Medtronic, Minneapolis, MN, USA) during 4.2–4.6 years of follow-up reported six cases of IE [29,30]. Seven cases of IE were reported by Lee et al. [31] out of 181 surgical implantations of bioprosthetic valves during a mean follow-up of 7.3 years. A risk comparison between PPVI and surgically implanted bioprosthetic valve was not performed, as that was not the primary objective of these three large surgical series and also due to discordance in the timing of

Figure 1. Explanted specimen of right ventricular outflow tract with Melody® valve, showing large fleshy vegetations on the melody valve, with significant narrowing of the pulmonary orifice.

Figure 2. The underlying leaflets of the Melody® valve are seen as glistening and transparent with no signs of destruction.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of publication</th>
<th>PPV IE cases/total cases</th>
<th>Patient age (years)</th>
<th>PPVI to IE interval (months)</th>
<th>Pathogen</th>
<th>Proposed major risk factors/trigger</th>
<th>Direct valve involvement</th>
<th>Mode of treatment</th>
<th>Outcomes of IE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lurz et al. [21]</td>
<td>2008</td>
<td>5/155</td>
<td>21 (7–71)</td>
<td>1.9–23.2</td>
<td>Staph aureus; Strept aurelius; Candida albicans</td>
<td>Unprotected dental treatment (n = 1); reactivation of previously-treated fungal infection (n = 1); septic wound after arm trauma (n = 1); prior IE (n = 2)</td>
<td>ND</td>
<td>Surgery (n = 3); medical (n = 2)</td>
<td>No deaths</td>
</tr>
<tr>
<td>Eicken et al. [47]</td>
<td>2011</td>
<td>1/102</td>
<td>21.5 (16–30)</td>
<td>6</td>
<td>Staph aureus</td>
<td>ND</td>
<td>1</td>
<td>Surgery</td>
<td>No deaths</td>
</tr>
<tr>
<td>Atamanyuk et al.</td>
<td>2011</td>
<td>1</td>
<td>15</td>
<td>65</td>
<td>Bartonella henselae</td>
<td>Paravalvular leak</td>
<td>1</td>
<td>Surgery</td>
<td>No deaths</td>
</tr>
<tr>
<td>Roberts et al.</td>
<td>2011</td>
<td>1/15</td>
<td>9</td>
<td>2</td>
<td>Strep sanguis (n = 2); Strep mitis; Staph epidermidis</td>
<td>Abrupt discontinuation of aspirin; inherent to bovine tissue; residual gradient</td>
<td>ND</td>
<td>Surgery (n = 3, including one with emergency RVOT stent)</td>
<td>Two deaths</td>
</tr>
<tr>
<td>Patel et al. [22]</td>
<td>2012</td>
<td>4</td>
<td>(11–26)</td>
<td>3–28</td>
<td>Strep sanguis (n = 2); Strep mitis; Staph epidermidis</td>
<td>Abrupt discontinuation of aspirin; inherent to bovine tissue; residual gradient</td>
<td>ND</td>
<td>Surgery (n = 3, including one with emergency RVOT stent)</td>
<td>Two deaths</td>
</tr>
<tr>
<td>Alsoufi et al.</td>
<td>2012</td>
<td>1</td>
<td>16</td>
<td>2.5</td>
<td>Aspergillus</td>
<td>Thrombus; stenosis</td>
<td>1</td>
<td>Surgery</td>
<td>No deaths</td>
</tr>
<tr>
<td>Bhat et al. [45]</td>
<td>2012</td>
<td>1</td>
<td>19</td>
<td>4</td>
<td>Staph aureus</td>
<td>ND</td>
<td>1</td>
<td>Surgery</td>
<td>No deaths</td>
</tr>
<tr>
<td>Gillespie et al.</td>
<td>2012</td>
<td>3 (confirmed in 2)/104</td>
<td>26 (3–63)</td>
<td>13, 18</td>
<td>ND</td>
<td>ND</td>
<td>2</td>
<td>Surgery</td>
<td>No deaths</td>
</tr>
<tr>
<td>Butera et al.</td>
<td>2013</td>
<td>2/63</td>
<td>24 (11–65)</td>
<td>2–3</td>
<td>Staph aureus</td>
<td>Disregarded IE prophylaxis</td>
<td>2</td>
<td>Surgery</td>
<td>No deaths</td>
</tr>
<tr>
<td>Buber et al. [23]</td>
<td>2013</td>
<td>14 BSI (4 PPV IE)/147</td>
<td>19 (3–59)</td>
<td>1–56</td>
<td>Strep (50%); Staph (43%); Haemophilus (7%)</td>
<td>High risk of systemic bacterial infections with male sex; previous endocarditis events; high number of stents at the RVOT; altered RVOT anatomy</td>
<td>4</td>
<td>Surgery (n = 2)</td>
<td>No deaths in confirmed IE</td>
</tr>
</tbody>
</table>
Table 1 (Continued)

<table>
<thead>
<tr>
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<th>Patient age (years)</th>
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<th>Mode of treatment</th>
<th>Outcomes of IE</th>
</tr>
</thead>
<tbody>
<tr>
<td>McElhinney et al.</td>
<td>2013</td>
<td>16 (6 PPV IE)/311</td>
<td>21 (11—41)</td>
<td>1.7—56</td>
<td>Strep; Staph; Moraxella catarrhalis</td>
<td>Prior IE; invasive procedure; bleeding oral ulcer; IVDU; high pre- and postimplantation gradients</td>
<td>4</td>
<td>Surgery (n = 4)</td>
<td>Two deaths</td>
</tr>
<tr>
<td>Cheung et al.</td>
<td>2013</td>
<td>6/43</td>
<td>25 (6—67)</td>
<td></td>
<td>Strep (n = 2); Staph aureus (n = 2); Staph epidermidis; Staph gordonii</td>
<td>ND</td>
<td>2</td>
<td>Surgery (n = 2)</td>
<td>One death</td>
</tr>
<tr>
<td>Villafane et al.</td>
<td>2014</td>
<td>4/143</td>
<td>11—20</td>
<td>1.7—16</td>
<td>Strep viridans; Strep sanguis; Staph aureus; Corynebacterium</td>
<td>Tattoo</td>
<td>3</td>
<td>Surgery (n = 3)</td>
<td>No deaths</td>
</tr>
</tbody>
</table>

BSI: blood stream infection; IVDU: intravenous drug user; ND: no data/description; PPVI: percutaneous pulmonary valve implantation; PPV IE: percutaneous pulmonary valve infective endocarditis; RVOT: right ventricular outflow tract; Staph: Staphylococcus; Strep: Streptococcus.

* Melody® valve in tricuspid position.
Figure 3. Microscopic examination of the vegetations, showing predominant amorphous material composed of thrombus.

head-to-head comparisons. There are several reports documenting an increased incidence of IE with bovine conduits [32–38]. Analysis of registry data showed a higher incidence of IE in the Melody valve group compared with in the surgical group in our own institution.

Between January 2000 and June 2013, 485 right ventricle-to-pulmonary artery conduit implantations (surgical group) and 93 percutaneous Melody valves implantations (PPVI group) were carried out in our institution. The rates of IE were 5.98 ± 2.11% (surgical group) and 8.6 ± 5.7% (PPVI group) (P = 0.34). The incidences of IE in the various RVOT conduits were different: 2.6% in homografts, 9.1% in Contegra conduits and 3.7% in bioprostheses (excluding Contegra). The incidence of IE was higher in the patients with Contegra conduits compared with in patients with homografts (P = 0.0245) or homografts and other bioprostheses (P = 0.0042). During the study period when both techniques were available (2009–2013), the person-time incidence rates of IE were 1.2 and 3.9 cases per 100 person-years in the surgical and PPVI groups, respectively (P = 0.03). Clinical presentations and microbiological diagnoses of IE were similar in the surgical and PPVI patients. History of IE is a major risk factor for the development of future IE in both groups. It is important to note that despite a higher incidence of Melody valve IE, probabilities of survival and event-free survival were similar to those in the surgical group.

Proposed hypothesis for percutaneous pulmonary valve infective endocarditis and possible pathogenesis

The development of PPV IE is probably multifactorial, although intrinsic characteristics of the bovine jugular vein appear to play a role in IE, as we found a similar rate of IE in surgical (Contegra) and transcatheter (Melody) implants.

As transient bacteraemia is noted every day during brushing, straining etc., and as there are no data on the relationship between IE and the dose of bacteria injected during physiological/pathological invasion, we are compelled to think of factors other than traditional invasive procedures as risk factors for IE. This may support bovine tissue immunological characteristics, which may cause an idiosyncratic reaction after implantation, favouring the formation of non-bacterial thrombotic endocarditis as the first step towards PPV IE. Incomplete opening of the RVOT conduit during PPVI, with resultant residual gradient, may be an important inciting factor, disrupting laminar flow and causing eccentric turbulence, endocardial injury and thrombus formation. The striking similarity between the behaviour of the Contegra and Melody valves supports this hypothesis. Thrombus formation has been seen to occur with Contegra conduits used in various surgical situations [29–31]. We also noted that three of four patients in our series had abruptly discontinued aspirin, which favours the thrombotic hypothesis. The voluminous thrombus and fibrin strands with amorphous material noted in all the vegetations suggest that thrombotic obstruction is an important and possibly an initial step in the pathogenesis. The severity of the clinical presentation is clearly related to the acute and severe obstruction of the RVOT [22]. Although commensals have been reported to be the causative organisms, the delay between PPVI and IE makes the possibility of hospital acquisition of infection during implantation very unlikely. It is possible that there is enhanced tropism of microbes to the bovine jugular vein, although in vitro studies may be required to establish this hypothesis. Fig. 4 shows a schematic representation of the proposed hypothesis for PPV IE.

The role of platelet clumping as the initial pathogenetic mechanism for non-bacterial thrombotic endocarditis has been described. The severity of endocarditis, with acute or chronic use of antiplatelets reducing the need for acute valve replacement and overall mortality, has been described extensively in vitro and in vivo studies [39]. However, to the best of our knowledge, there are no data showing that antiplatelet therapy prevents endocarditis.

In patients with synthetic conduits as the RVOT substrate and landing zone for the Melody valve, a striking absence of or incomplete endothelialization was noted (Fig. 2). This raises important questions about the need for more robust anticoagulation, with either traditional oral anticoagulants/newer oral anticoagulants or dual antiplatelet therapy [39].

Although there are no reports of IE so far with the Edwards SAPIENTTM valve in the pulmonary position, we are aware of multiple unreported cases (two in the initial series of 64 patients; oral presentation at the Paediatric and Adult Interventional Cardiac Symposium, 2014). Moreover, reports of endocarditis in transcatheter aortic valve implantation, which constitutes the same pericardial substrate, are up to 3.4% at one year, with a person-time incidence rate of 2.99% per patient year, which is very similar to what is reported with the Melody valve [40].

There is evidence to suggest that any instrumentation on the percutaneous valve during preparation, implantation and even postdilatation balloon injury may cause tissue injury and might favour thrombus formation and the seeding of microorganisms [41,42]. Such in vitro studies have only been done with pericardial valves. No data are presently available for the Melody valve.

It is possible that putative xenogeneic antigens may elicit some degree of immune response in the Melody valve.
However, little is known about the nature and identity of bovine proteins eliciting destructive or non-destructive immune responses. A variety of functional and structural protein types, including both cellular and extracellular proteins, may be implicated [43,44].

**Prevention**

As only a few cases have been reported in the literature, it is hard to identify predictors and definitive risk factors for PPV IE. History of endocarditis, male sex, multiple stents, dental treatment, previous fungal infection, tattoo, septic wound and abrupt discontinuation of aspirin, among others, have been reported as possible risk factors [21–28,45–49]. Worsening RVOT obstruction is a dominant finding in most patients. Buber et al. proposed life-long pre-procedural antibiotics for PPV patients with either a history of previous IE or a complex RVOT anatomy [23]. We feel that the core IE committee should convene to reframe the guidelines for PPV IE. It is hard to predict whether modification of the existing structure of Melody valve to decellularize it for targeted removal of xenoantigens would help to reduce the incidence of thrombus formation and IE.

**Patient management**

In view of the limited number of patients, it is hard to identify those who might benefit from a standardized approach. An individual approach for each patient may be required, due to the wide variations in presentation. It is important to determine if the PPV is anatomically involved or is a bystander, as the management algorithms would then change. Urgent intervention to relieve acute obstruction secondary to direct valve involvement is likely to reduce mortality and should always be considered, along with aggressive IE management. McElhinney et al. [24] proposed that Melody valve replacement is not required during the acute treatment of Melody valve IE, when there is no involvement of the valve system. In all cases, early surgery should be considered for valve...
dysfunction or absence of clinical improvement despite aggressive medical treatment. Use of alternative imaging modalities, such as transoesophageal echocardiography, intracardiac echocardiography, three-dimensional echocardiography and positron emission tomography-computed tomography, should be used freely for suspected IE. Fig. 5 shows a schematic representation of the algorithm we propose for the management of PPV IE.

**Prognosis**

The published reports and studies show an overall mortality rate of 13% in association with PPV IE. Over half of the patients reported underwent bioprosthesis explantation [24]. In our cohort, PPV IE significantly affected survival.

**Conclusions**

The rising incidence of PPV IE, its unpredictable clinical course and the associated poor outcomes raise serious safety concerns. The overall epidemiology of IE has shown a dynamic trend due to increased antibiotic use, the emergence of resistant microorganisms and the increased use of cardiovascular devices, including percutaneous valves. The 2007 American College of Cardiology/American Heart Association prevention and treatment guidelines are more comprehensive, making management easier for the treating physician. However, if the atypical and unnatural history of PPV IE is not anticipated, it could lead to a stormy and potentially fatal outcome. The data published so far on PPV IE are gathered from case series and a limited number
of patients from registries. We need more data from multicentre studies or global registries to identify the true incidence and annual risk of PPV IE in such patients. Tissue diagnosis along with immunohistochemical staining may help us to understand the underlying pathophysiology. There seems to be a striking similarity between the Contegra and Melody valves with respect to its common origin, in vivo characteristics for thrombus formation and risk of IE. Any degree of rise in RVOT gradient during follow-up, along with other subtle signs, as described—even in an asymptomatic patient—should not be ignored. Further data are required to identify definitively who would benefit from antibiotic therapy alone, without surgery or with another PPV, in the setting of PPV IE. It is important to identify if the valve is directly involved or if it is a bystander to near or remote IE. Urgent intervention to relieve acute obstruction is likely to reduce mortality and should always be considered along with aggressive IE management. Strict life-long aspirin treatment and IE prophylaxis must be followed in all cases during transcatheter insertion of the Melody valve and thereafter, even for low-risk invasive procedures. An extensive preprocedure infectious disease evaluation must be done in all patients, in search of possible port of entry for microorganisms, similar to the preoperative evaluation before surgical valve replacement. Multicentre studies are needed to pool larger numbers of patients and identify strong predictors of IE in this population. Additional input from studies on other transcatheter heart valves may answer the question about the percutaneous approach being a possible risk factor, along with other prosthetic material-based substrates as potential risk factors. Most importantly, there is an immediate need to address the prevention and treatment guidelines for percutaneous valve IE.

Disclosure of interest

Y. Boudjemline acts as a proctor for Medtronic. Other authors: none.

References


