Endocarditis in Patients with a Permanent Pacemaker: A 1-Year Epidemiological Survey on Infective Endocarditis due to Valvular and/or Pacemaker Infection


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To describe characteristics of infective endocarditis (IE) in pacemaker (PM) recipients, including the annual incidence and exact localization of IE on PM leads, cardiac valves, or both, we prospectively analyzed 45 PM recipients from a group of 559 patients with definite IE who responded to a population-based survey conducted in France in 1999. Thirty-three patients had definite PM-lead IE (group I), and 12 had valvular IE without evidence of PM involvement (group II). The valvular structure was involved in almost two-thirds of IE cases among PM recipients. Of the 28 patients (62%) with valvular IE, 10 group I patients had tricuspid involvement, and 6 group I patients had left heart–valve involvement. The most frequent causative organisms in groups I and II were staphylococci (82%) and streptococci (50%), respectively. The incidence of age- and sex-standardized IE was 550 cases/million PM recipients per year. The incidence of IE with PM involvement is between that of valvular IE in the general population and prosthetic valve IE.

In pacemaker (PM) recipients with intracardiac devices, infective endocarditis (IE) can theoretically be located on PM leads, on PM leads and ≥1 cardiac valve, or on cardiac valves only (without evidence of PM-lead involvement). Although there is increased interest concerning PM-lead IE, cardiac valve IE in PM recipients (regardless of whether PM leads are infected) is rarely analyzed in the literature and is sometimes even excluded to focus attention specifically on the characteristics of IE with PM involvement (PM-IE) [1–3]. However, because the exact localization of infection (i.e., intracardiac device and/or cardiac valves) may affect the clinical characteristics and therapeutic management of IE, it is of vital importance to analyze specifically the different demographic and clinical data for patients with PM-IE. Furthermore, although increasing amounts of data are available on the pathophysiology and clinical characteristics of PM-IE, data on its incidence remain imprecise, with reported values ranging widely, from 0.13% to 20% [4–12]. For these reasons, when we initiated the 1-year prospective survey of patients with IE in France in 1999 (i.e., the princeps study), we planned an ancillary study devoted to describing IE in PM recipients on the basis of the association between IE and PM leads, cardiac valves, or both and the incidence of IE among PM recipients [13].

PATIENTS AND METHODS

Patient enrollment. We analyzed all cases of definite IE that occurred in PM recipients who completed the prospective population-based survey on IE conducted...
in 1999 in 6 French regions (population, 16 million) [13]. The
survey had been launched on 1 December 1998 to initiate the
process and was stopped on 31 March 2000 to avoid missing
responses submitted after the end of the survey period. All cases
of definite IE in PM recipients that were recorded during the
16-month study period were included in the descriptive analy-
sis, which explains why we describe 559 patients in the present
article (rather than 390 patients, as described in the princeps
study [13]).

In addition to data obtained for description of IE, the fol-
lowing information on PMs was also prospectively obtained:
date and number of PM implantations, complications associ-
ated with PM implantation, and dates and methods of PM
removal [13]. All case report forms describing IE in PM re-
cipients were checked for accuracy and validated for diagnosis
by 2 expert investigators who used the Duke criteria [14]. PM-
lead infection was considered to be definite if transesophageal
echocardiography (TEE) or transthoracic echocardiography
(TTE) revealed a vegetation attached to at least 1 lead or if
results of macroscopic analysis and/or culture of removed leads
demonstrated the presence of microorganisms.

Patients were separated into 2 groups on the basis of the
localization of IE on PM leads and cardiac valves. Group I was
comprised of patients with definite PM-IE irrespective of any
concomitant valvular involvement. Group II was comprised of
patients with valvular IE but no evidence of PM-IE.

**Calculation of incidence and statistical analysis.** To cal-
culate the annual incidence of IE among PM recipients in
France, only patients who were first hospitalized between 1
January and 31 December 1999 and who permanently resided
in at least 1 of the 6 French regions (i.e., the princeps sub-
population) were included in the analysis. Incidence rates for
the princeps subpopulation were calculated for group I, to es-
timate the incidence of PM-IE, and for groups I and II, to
estimate the incidence of IE among PM recipients.

Incidence rates were expressed as the number of cases of IE
per million French population and as the number of cases of
IE per million PM recipients. Population data were based on
the total French population reported in the 1999 national cen-
sus [15]. The total number of living PM recipients in 1999
(230,000) was estimated using data from the French national
PM registry. It was assumed that PM recipients were equally
distributed throughout the country.

Quantitative variables are expressed as mean values ± SD
(95% CI) and were compared using Student’s unpaired t test.
Qualitative variables are expressed as percentages and were
compared using the Pearson χ² test or the Fisher exact test,
when appropriate.

**RESULTS**

Of 559 patients with definite IE, 45 were PM recipients (33
males and 12 females; age, 68.7 ± 12.2 years), including 33
patients with PM-IE (group I; 22 males and 11 females; age,
68.8 ± 13.7 years) and 12 patients with valvular IE without PM
involvement (group II; 10 males and 2 females; age, 69.1 ±
9.3 years) (figure 1). Table 1 summarizes the main character-
istics of these 45 patients. A history of complicated PM im-
plantation and multiple PM procedures was more frequent in
group I than in group II (24.2% vs. 8.3% [not significant] for
complicated PM implantations and 63.6% vs. 16.7% [P =
.008] for multiple PM procedures, respectively).

**Clinical findings and microorganisms isolated.** Fever was
present at admission to the hospital in all but 1 patient. Eleven
patients in group I had a pulmonary embolism. The distribu-
tion of causative microorganisms, which were identified in
44 of 45 patients, is displayed in table 2. Culture of the PM

![Diagram](cid:2004:39:1)
leads was positive for microorganisms in 21 (75%) of the 28 group I patients whose PM was removed (table 1). Among the 5 patients with negative blood culture results, culture of PM leads was positive for microorganisms in 4. The remaining patient, in whom no microorganism could be identified, had received antibiotics before blood was obtained for culture. Overall, staphylococci were the most frequent causative agents of IE, infecting 27 patients (81.8%) in group I and 5 patients (41.7%) in group II (table 2); a second microorganism was recovered from 4 of these 27 group I patients.

**Localization of IE and echocardiographic data.** Overall, valvular IE was noted in 28 patients (62.2%) (figure 1). All group I patients had a vegetation on PM leads, and 16 (48.5%) had an associated valvular IE: 10 patients had tricuspid involvement, which was diagnosed at the time of surgery for 2 patients and on the basis of echocardiographic data for 9 patients, and 6 patients had left heart–valve involvement (2 patients had mitral valve involvement, 3 had aortic involvement, and 1 had mitral and aortic involvement), which was diagnosed at the time of surgery for 2 patients and on the basis of echocardiographic data for 4 patients.

No group II patients had evidence of PM-IE on a TEE. Vegetations were localized on the mitral valve in 4 patients, on the aortic valve in 3, and on both valves in 2. Moreover, 2 patients each had a vegetation and an abscess (1 on the aortic valve and 1 on the mitral valve). The twelfth group II patient, who had a mitral valvular bioprosthesis, had no echocardiographic evidence of IE but repeatedly had blood cultures positive for *Enterococcus* species, fever, and peripheral embolism. In this patient, PM leads were removed using a transthoracic approach, and there was no histological or bacteriological evidence of IE on PM leads.

**Patients with preexisting valvular disease.** A known preexisting valvular disease was reported for 18 patients (40%) (tables 1 and 3). Eleven patients (24.4%) had a prosthetic valve (7 had a mechanical prosthesis and 4 had a bioprosthesis), and 7 (15.6%) had disease involvement on a native valve.

Of the 11 PM recipients with a prosthetic valve, 3 belonged to group I (9.1% of 33 group I patients), and 8 belonged to group II (66.7% of 12 group II patients). In these 11 patients with 2 intracardiac devices (PMs and prosthetic valves), the infectious process was located on the native cardiac valves, the prosthetic valves, and/or the PM leads (table 3). Staphylococci were the causative microorganisms in only 2 (18.2%) of these 11 patients, whereas they were the causative microorganisms in 29 (85.3%) of the 34 patients without a prosthetic valve. Among the 7 patients who had preexisting disease involvement on a native valve, 6 had PM-IE in addition to valvular IE, which was located on the abnormal native valve in 3 patients. The remaining patient had valvular IE located on a preexisting native valve without other localized IE. Staphylococci were responsible for all 6 cases in which causative microorganism could be identified.

**Outcome.** Complete removal of PM was performed for 30 patients (67%), 28 of whom were in group I and 2 of whom were in group II. This was done by thoracotomy for 23 patients (22 of whom were in group I) and percutaneously for 7 (6 of whom were in group I) (table 1). Seven patients underwent concomitant valvular surgery for the following reasons: 1 underwent tricuspid valve surgery because the valve was pierced by PM leads, 5 were treated for native valve IE, and 1 was treated for prosthetic valve IE. Of 5 patients (11%) who died =3 months after follow-up began, 3 (9%) were in group I (2 of whom did not undergo PM removal) and 2 (15%) were in group II (table 1). There was no relapse of infection in the 2 groups during a median follow-up period of 8 months.

**Incidences of PM-IE and IE in PM recipients.** The prin-
Endocarditis in Pacemaker Recipients • CID 2004:39 (1 July) • 71

ceps subpopulation consisted of 24 group I patients with definite PM-IE and 10 group II patients with valvular IE without evidence of PM involvement. The annual incidence of PM-IE was 1.83 cases/million inhabitants >15 years of age and 390 cases/million PM recipients. The annual incidence of IE, independent of localization, among PM recipients was 2.59 cases/million inhabitants >15 years of age and 550 cases/million PM recipients.

DISCUSSION

Our study clearly shows that, in the population of PM recipients who experienced IE, 3 infection scenarios with almost equal distribution were encountered: an infection exclusively localized on PM leads; the combination of a PM-lead infection and a valvular infection, the former being localized on right or left heart valves; and an isolated valvular infection that was apparently independent of PM leads. IE patterns between patients with and patients without PM involvement vary according to the causative microorganism, the number of previous PM procedures, and the existence of an associated valvulopathy. Furthermore, to our knowledge, this study permits the first-ever estimation of the incidence of IE among PM recipients.

Some of our findings in group I patients (those with PM-

IE) depict classical features of PM-lead infection, such as mean age >65 years, male predominance, high prevalence of staphylococci-based infection and pulmonary embolism, high frequency of positive results of lead cultures (75%), and high prevalence of diabetes mellitus [1–3, 16–18]. In contrast, our results differ from those of other studies, because this study has revealed a much higher rate of concomitant valve infection. This difference was partly due to the higher proportion of left-sided IE (18.2% of cases) in our study, compared with that (<10%) in the literature, and partly due to the higher rate of associated tricuspid IE. In fact, the 30% rate of tricuspid IE was similar to those reported by Arber et al. [1] (32%) and Cacoub et al. [2] (24%) but higher than those reported in other studies [3, 18, 19]. On one hand, this might reflect the high proportion of patients with preexisting native left-valve disease. On the other hand, this might reflect the more representative nature of our population of patients, given the absence of referral bias, which is present in most studies [1–3, 16, 18]. Furthermore, by asking for a detailed echocardiographic report on IE localization, our data report form permitted a more precise description of the localization of infection on PMs and/or valves. Moreover, the surprisingly high rate of thoracotomies performed to remove PM leads may be associated with the diversity of the centers, not all of which referred patients to a medical center specializing in percutaneous PM explantation.

Because normal TEE findings do not rule out with certainty the involvement of PM-lead IE in the infection process, we might wonder whether group II patients (i.e., those with valvular IE without evidence of PM-lead infection) may have had a PM-lead infection associated with the diagnosed native left-valve IE that was not detectable by TEE. However, there are arguments in favor of the legitimacy of the criteria used to define group II. First, there is no reason why PM recipients would not present with valvular IE (independent of PM involvement), as in the general population. Second, we identified distinctive characteristics in group I and group II patients: a higher prevalence of diabetes mellitus in group I; a significantly higher number of PM procedures in group I, which accords with the significantly higher rate of staphylococcal IE; and a significantly higher frequency of a history of native valve disease or receipt of a prosthetic valve in group II. These differences therefore suggest that the distinction between the 2 groups is real and of clinical relevance. Only systematic removal and bacteriological culture of all PM leads from all patients—which is not feasible—could have provided an answer to this issue. The absence of relapse among the surviving patients in group II argues against the involvement of PM.

The situation is even more complex for patients with multiple intracardiac devices. In our small population of PM recipients with a prosthetic valve, infection was most often localized on the prosthetic valve. This observation is consistent

Table 2. Distribution of causative microorganisms in 45 patients with a permanent endocardial pacemaker (PM) and definite infective endocarditis (IE) with (group I) or without (group II) PM involvement.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
</tr>
<tr>
<td></td>
<td>(n = 33)</td>
</tr>
<tr>
<td>Individual isolates</td>
<td>28 (84.8)</td>
</tr>
<tr>
<td>Staphylococccaeae</td>
<td>23 (69.7)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>8 (24.2)</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>15 (45.5)</td>
</tr>
<tr>
<td>Streptococccaeae</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Oral streptococci</td>
<td>0</td>
</tr>
<tr>
<td>Group D streptococci</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Streptococcus anginosus</td>
<td>0</td>
</tr>
<tr>
<td>Other&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Concomitant isolates</td>
<td>4 (12.1)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>No isolates</td>
<td>1 (3.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are 27 (81.8) when concomitantly isolated staphylococci are included in the analysis.

<sup>b</sup> Propionibacterium acnes was recovered from 1 patient in group I, and Actinobacillus actinomycetemcomitans was recovered from 1 patient in group II.

<sup>c</sup> The following combinations of microorganisms were recovered from 1 patient each: Staphylococcus epidermidis and Streptococcus mitis (both of which were recovered from a PM culture), S. epidermidis (recovered from a PM culture) and Streptococcus salivarius (recovered from blood cultures), S. epidermidis and enterococci (both of which were recovered from blood cultures and PM culture), and Staphylococcus capitis and Pseudomonas putida (both of which were recovered from blood cultures).
with the finding that the incidence of IE was higher among patients with a prosthetic valve than among those with a PM, which we will discuss below. Another interest of our study was the estimation of the incidence of PM-IE, which was unknown before this study. The incidence can be determined prospectively by following a cohort of patients with newly implanted devices or by using a transsectional population-based study, which we did in this survey. However, although the former option might be more accurate, it also consumes more time and resources. In a prospective cohort study, a high number of PM recipients should be followed-up for a long period, because of the low rate of IE among such patients and the possible delayed onset of IE after PM implantation. For instance, in a recent report of 467 patients who had PMs removed because of mechanical or infectious complications during a 3-year follow-up period, only 13 patients had PM-IE [20]. In fact, in our study, one-third of the patients developed PM-IE >3 years after the last PM procedure. Furthermore, the disadvantage of a follow-up period of sufficient duration for such a study is the increased risk of dropout over time.

Another advantage of a cross-sectional study in a large geographic area is the low influence of referral bias [13]. Therefore, we believe that our case population is fairly representative of the current profile of PM recipients with IE. There are, however, limitations in the way we determined the PM-IE incidence. The number of PM recipients living in the study area, which was comprised of 16 million inhabitants, could only be estimated on the basis of the number of PM recipients in the whole country. Another limitation to our study is the relatively short follow-up period of 15 months. Even if complementary information were obtained from the practitioners on an individual basis to identify additional arguments in favor of a diagnosis

Table 3. Characteristics of 18 of 45 patients with a pacemaker (PM) and definite infective endocarditis (IE) who presented with preexisting native valvulopathy or a prosthetic valve (PV).

<table>
<thead>
<tr>
<th>Characteristic, patient</th>
<th>Localization/type of valvulopathy</th>
<th>Location of IE</th>
<th>Interval between IE and implantation, months</th>
<th>Microorganism(s) isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting native valvulopathy (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>AV/S</td>
<td>PM</td>
<td>...</td>
<td>1.3</td>
</tr>
<tr>
<td>26</td>
<td>MV/I</td>
<td>PM</td>
<td>...</td>
<td>19</td>
</tr>
<tr>
<td>27</td>
<td>MV/I</td>
<td>PM</td>
<td>...</td>
<td>40</td>
</tr>
<tr>
<td>17</td>
<td>AV bicuspidy</td>
<td>AV, PM</td>
<td>...</td>
<td>18</td>
</tr>
<tr>
<td>22</td>
<td>AV/S</td>
<td>AV, PM</td>
<td>...</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>TV/I</td>
<td>TV, PM</td>
<td>...</td>
<td>87</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>AV/I</td>
<td>AV</td>
<td>...</td>
<td>27</td>
</tr>
<tr>
<td>Presence of PV (n = 11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>AV/MPV</td>
<td>PM</td>
<td>73</td>
<td>Unknown</td>
</tr>
<tr>
<td>19</td>
<td>MV/MPV</td>
<td>TV, PM</td>
<td>54</td>
<td>Unknown</td>
</tr>
<tr>
<td>18</td>
<td>AV/MPV</td>
<td>AV, PM</td>
<td>74</td>
<td>3</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>AV/BP</td>
<td>MV</td>
<td>18</td>
<td>81</td>
</tr>
<tr>
<td>43</td>
<td>AV/BP</td>
<td>MV</td>
<td>3.5</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>AV/MPV</td>
<td>AV</td>
<td>65</td>
<td>28</td>
</tr>
<tr>
<td>40</td>
<td>AV/MPV</td>
<td>AV</td>
<td>141</td>
<td>84</td>
</tr>
<tr>
<td>41</td>
<td>AV/MPV</td>
<td>AV</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>16</td>
<td>AV/BP</td>
<td>AV, MV</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>38</td>
<td>AV/MPV, MV/MPV</td>
<td>AV, MV</td>
<td>0.3</td>
<td>72</td>
</tr>
<tr>
<td>11</td>
<td>MV/BP</td>
<td>TV</td>
<td>149</td>
<td>15</td>
</tr>
</tbody>
</table>

NOTE. Patients in group I had IE with PM involvement, and patients in groups II had IE without PM involvement. AV, aortic valve; MV, mitral valve; TV, tricuspid valve; S, valvular stenosis; I, valvular insufficiency; MPV, mechanical PV; BP, bioprosthesis.

a Data are for the first or the final (for those with multiple PMs placed) implantation.

b Underwent valvular surgery.
of PM-lead infections, an extended follow-up period could have eventually revealed further PM involvement in group II patients, because the development of infection on PM leads is sometimes a slow process. For these reasons, we also determined the incidence of IE among group I and group II patients belonging to the princeps subpopulation, which could be considered to be a larger estimation of the incidence of definite PM-IE among PM recipients.

The incidence of ~400 cases of IE/million PM recipients per year is intermediate between the incidence of IE in the general population, which ranges from 15 to 60 cases/million population per year [21–24], and the incidence of IE among patients with prosthetic valves, which ranges from 3080 to 6300 cases/million PM recipients per year in 2 studies [25, 26]. The lower incidence of IE among PM recipients that was estimated in our study accords with the difference in the suspected mechanisms of IE on these 2 types of intravascular foreign body devices: up to 90% of cases of PM-IE may be associated with seeding of the device at the time of implantation, even in the cases where PM-IE is revealed several months or even years after implantation [3, 27]. In contrast, patients with a prosthetic valve have a cumulative risk of IE that increases over time, which may be due either to the inoculation of a microorganism at the time of prosthetic valve insertion or to the late seeding of microorganisms, such as streptococci, in the course of a bacteremic episode originating from a distant source [28–30]. Another explanation for the higher incidence of IE among patients with prosthetic valve IE could be the length of the procedure for implantation of the device, which has been linked positively to the rate of infection and is far longer for prosthetic valve implantation than for the PM implantation [31].

In those situations without evidence of PM infection, the diagnostic attitude may differ according to whether there is evidence of valvular infection. Ruling out PM infection may only be done after repeated TEE and elimination of indirect arguments for a diagnosis of PM infection (using pulmonary exploration with CT scanning and/or scintigraphy). In the absence of valvular vegetation, performance of specific scintigraphy to detect PM wire infection may be considered. The therapeutic attitude is even more complex and delicate, because PM removal is associated with a risk of morbidity and mortality. Without any direct or indirect arguments for a diagnosis of PM-IE (including TEE findings, no local sign of infection at the pocket of the PM, and no history of initial or subsequent complications after PM-related procedures), a “wait and see” policy could be the preferred choice. However, even in this situation, if valve surgery is needed because of the nature of the infectious process, removing the PM during the valvular surgery (keeping in mind the reason for initial PM implantation) could be considered, according to cardiologic requirements.

Thus, critical analysis of clinical characteristics, patient history, and TEE findings is of great importance for determining the precise localization of IE in PM recipients. Specifically, we found that, in more than one-half of PM recipients, IE involved the valvular structure in patients with and patients without PM-lead infection. In this situation, clinicians must be aware that an intracardiac focus of infection persists even after total removal of PM leads. The timing of intracardiac device reimplantation is a topic of ongoing controversy [32]. We suggest that PMs should not be reimplanted inside the cardiac cavities until the confirmed or suspected valvar focus of infection has been adequately treated so that the probability of reinfection of the new device is minimized.

ASSOCIATION POUR L’ETUDE ET LA PRÉVENTION DE L’ENDOCARDITE INFECTIEUSE


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