Risk factors for infection of implantable cardiac devices: data from a registry of 2496 patients

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Received 4 April 2012; accepted after revision 31 July 2012; online publish-ahead-of-print 24 October 2012

Aims
The increased use of implantable cardiac devices has been accompanied by an increase in infection. However, risk factors for infection of implanted devices are poorly documented. We aimed to identify risk factors in patients with long-term follow-up after implantation of cardiac devices.

Methods and results
Patients with first implantation of a cardiac device in our centre between October 1996 and July 2007 were entered in a registry. Each confirmed infection of the implanted device was matched to two controls for age, sex, and implantation year. We recorded cardiovascular risk factors (hypertension, diabetes), previous history of heart disease, renal failure, antiplatelet or anticoagulant therapy, as well as pre- and post-procedural characteristics (antibiotic prophylaxis, hyperthermia, number of leads, associated interventions, and early complications). During the study period, 2496 patients underwent implantation of a cardiac device; 35 infections were diagnosed (1.2%). Among these, 75% occurred during the first year after implantation. Early non-infectious complication requiring surgical intervention was observed only in patients with infection (9 of 35, \( P = 0.001 \)). Factors independently associated with infection were diabetes [odds ratio (OR) 3.5, 95% confidence interval (CI) [1.03, 12.97]], underlying heart disease (OR 3.12, 95% CI [1.13; 8.69]), and use of >1 lead (OR 4.07, 95% CI [1.23, 13.47]). These latter two risk factors were also independently associated with occurrence of infection within 1 year of implantation.

Conclusion
Our data show that the presence of diabetes and underlying heart disease are independent risk factors for infection after cardiac device implantation. As regards procedural characteristics, the use of several leads and early re-intervention are associated with a higher infection rate.

Keywords
Implantable cardiac device • Infection • Risk factors • Case control

Introduction
Since the advent of cardiac stimulators in the 1950s, their use has grown incessantly to reach a total of more than 3 million functioning pacemakers worldwide today.¹ Their increasing popularity can be explained by population ageing, simpler procedures, technical advances, multisite stimulation, and the availability of new types of devices such as implantable cardioverter defibrillators (ICDs). Between 1990 and 1999, the rate of implantation of cardiac devices increased by 42%, with a parallel increase of 124% in the number of reported infections for these devices.² The rate of infectious complications is reported to be on an average of 1–2% in recent studies, ranging from 0.13 to 19.9% for series with intra-abdominal implantation.³–⁶ Infection of an implantable cardiac device is a serious complication with a mortality rate of up to 26% in some reports.⁷ The cost engendered by these infections is difficult to quantify, but has been estimated at 25 000 US dollars for pacemakers, even exceeding 57 000 US dollars for ICDs.⁸,⁹

Diabetes and the use of intracavity temporary leads are factors that are generally associated with a higher rate of infection.³,¹⁰ Other risk factors remain debated, and few studies to date have

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investigated pre-operative, peri-procedural, and post-operative characteristics.3,11,12

We performed a case–control study to identify risk factors for early or late infection of implantable devices and leads based on a registry of patients followed in our centre.

Methods

Population

Case–control study with two controls matched to each case. Cases were defined as patients with confirmed device-related infection after first implantation or pulse generator or lead replacement performed between 1 October 1996 and 31 July 2007. Infection was defined as presence of at least one of the following criteria requiring explantation of the device: (i) positive culture from the explanted material; (ii) local signs of inflammation (abscess, fistula, and discharge), with or without general signs of infection (fever, elevated C-reactive protein, hyperleucocytosis) or positive haemoculture; (iii) presence of lead or valvular vegetations on echocardiography; (iv) repeated septic pulmonary embolism, suggestive of device-related infection requiring explantation of the device.

Identification of the germ responsible for infection was not required to confirm diagnosis of infection. Exclusion criteria were: first implantation performed in another centre; upgrading to an ICD or triple-chamber pacemaker; and multisite pacing.

Controls were selected from among the database of patients who underwent implantation of a cardiac device in our centre, after the exclusion of patients with infection, and procedures involving upgrade to or implantation of ICD or triple-chamber pacemakers. Two controls were matched to each case for sex, age (±5 years), and year of implantation. Controls also had to be followed up in our centre for duration at least equivalent to that of the cases.

Data collection

Exhaustive review of the medical files of all patients included in the registry was performed by two certified cardiologists (B.H. and R.S.). The data recorded were defined in advance and comprised:

- Pre-operative and prior history: Arterial hypertension, diabetes, presence of hypertrophic cardiomyopathy (thickness >13 mm), valvular heart disease (significant regurgitation or stenosis), hypokinesis (ejection fraction <50%), renal insufficiency (glomerular filtration rate <60 ml/min/1.73 m² according to the Modification of Diet in Renal Disease formula), prolonged treatment with antiplatelet agents (aspirin, clopidogrel, or ticlopidine) or anticoagulants, fever within the 48 h prior to implantation.

- Procedural characteristics: Use of antibiotic prophylaxis, use of other intracavity material within the same procedure (temporary cardiac pacing wire in place before procedure, radiofrequency, or other electrophysiological recording during the same procedure); single- or dual-lead pacing; venous approach used for pacing (cephalic or subclavian); occurrence of non-infectious complications requiring surgical reinvention within the first month after implantation (haematoma, displaced lead, and threatened exteriorisation of the pacing system).

Statistical analysis

Data are presented as mean ± SD, number and percentage, or odds ratio (OR) with a 95% confidence interval. A Mantel–Haenszel test was used for univariate analysis to investigate risk factors of infection. Multivariate analysis was performed using a conditional logistic regression model including all factors that were significantly associated with infection by univariate analysis. A subgroup analysis of infections occurring within the first year following implantation was planned. All analyses were performed using SPSS v19 (SPSS Inc., Chicago, IL, USA) and R version 2.9.0 (R Foundation, Vienna, Austria). All tests were two-sided and a P value of <0.05 was considered statistically significant.

Results

Between 1 October 1996 and 31 July 2007, 2496 patients underwent de novo implantation, of whom 372 patients had lead or pulse generator replacement, making a total of 2868 procedures. Device-related infection occurred in 35 cases. The majority of infections (32 of 35) occurred in patients who underwent de novo implantation, with only three infections occurring after scheduled replacement of the cardiac device, corresponding to an infection rate of 1.2% per procedure, or 1.4% per patient. Average age of the cases was 73.6 ± 13.5 years and 60% were males. Average time from implantation to infection was 325 ± 510 days (median 86). Seventy-five per cent of infections occurred within the first year after implantation (range 7 days–7 years).

Infection was diagnosed based on the presence of local signs in 87%, fever in 49%, and inflammation in 65%. The germ responsible for infection was identified by haemoculture or cultures from the material in 63% of cases, of which 55% were Staphylococcus aureus. A germ was found on haemoculture in 42% of cases (of which 65% were S. aureus). Diagnosis was confirmed by transthoracic or transoesophageal echocardiography in eight patients. The cardiac device and leads were explanted percutaneously in all cases but one, which required surgical explantation. A germ was identified by positive bioculture on the explanted material in 40% of cases.

The patient characteristics are shown in Table 1. Diabetes (P = 0.002) and presence of underlying heart disease (P = 0.047) were significantly associated with occurrence of device-related infection. The risk was also increased when more than one lead was implanted (P = 0.016) and when another invasive procedure was performed at the same time as implantation (P = 0.05). Early non-infectious complications requiring re-intervention were observed only among cases with infection (34%), and were highly significantly related to the presence of infection. Fever at the time of implantation, the presence of long-term antithrombotic therapy, or antibiotic prophylaxis were not associated with risk of infection. No patient or control presented with end-stage renal failure or haemodialysis.

Multivariate analysis did not take into account early non-infectious complications since no such events were observed in controls. By multivariate conditional logistic regression analysis, diabetes, underlying heart disease, and use of more than one lead were shown to be associated with infection (Table 2).

Subgroup analysis of early infectious complications occurring during the first year after implantation identified underlying heart disease (P = 0.037), and use of more than one lead (P = 0.027) as significant risk factors for infection in this population. By univariate analysis in this subgroup, occurrence of early complication requiring re-intervention (P < 0.001) was related to occurrence of infection, with nine such complications among the cases, vs. zero
The number of late infections (occurring beyond 1 year) was low (n = 10) and did not allow analysis of potential risk factors.

Discussion

In our study, we observed an infection rate of 1.4% per patient, and 1.2% per procedure, which is in line with previous reports from the literature. In the PEOPLE study, Klug et al. observed an infection rate of 0.68%, over a short follow-up period of only 1 year, and with more selective inclusion criteria than those applied in our study, since they included only local infection with major signs of infection (e.g. abscess, purulent discharge). In a recent Danish registry, Johansen et al. noted an incidence rate of 1.82/1000 pacemaker-years among 56,657 pacemaker implantations. Other retrospective studies have reported infection rates ranging from 0.9 to 4.6%, also with local signs of infection predominating. In our study, haemoculture or bacteriological analysis of the explanted material made it possible to identify the germ responsible for infection in only 62% of cases, and this can be explained by the relatively strong weight of local signs of infection in the definition of infection. This is in line with previously published registry data reporting identification of pathogens in 64% of cases, of which 72% were identified by haemoculture. Nonetheless, it has previously been shown that local signs alone can be associated with identification of a germ on the device, as reported by Klug et al., who identified a germ in 72% of explanted leads among 105 cases of infection with exclusively local symptoms of infection. In our study population, the devices were removed under appropriate antibiotic therapy. In the early years of the registry, only explanted leads were systematically sent for bacteriological analysis, which may have limited the proportion of cases in which pathogens responsible for infection could be identified.

In terms of patient-related factors, we identified diabetes and previous heart disease (hypertrophic, hypokinetic, or valvular) as being significantly associated with an increased risk of infection. Diabetes is often considered as a cause of minor immunodepression and thus can be responsible for an increased risk of infection, particularly in the context of surgery. However, there are conflicting reports in the literature, with diabetes identified as a risk factor for infection in one retrospective study, but not in the PEOPLE registry. The finding that underlying heart disease increases the risk of infection after implantation of a cardiac device is novel. In previous studies, variables recording the existence of previous heart conditions were generally not collected, although Sohail et al. reported that previous cardiac surgery or heart failure were not significant predictors of infectious risk. However, it should be noted that the definition used in our study was different, being based on echocardiographic data and not on clinical history. Underlying heart
The factor associated with the greatest increase in infectious risk in our study was the occurrence of early non-infectious complication (haematoma, pacemaker dysfunction, displacement of the intracavity leads), requiring re-intervention. Indeed, early complication was associated with a significant increase in risk, since one-third of the infections we report occurred after early re-intervention had been necessary. Klug et al. reported similar results in the PEOPLE study, and repeated procedures were also shown to increase risk of infection in the Danish registry.11 as well as in a recent study of risk factors for device infection.21 These findings should incite physicians to exercise caution in deciding on the need for re-intervention in the case of haematoma, or increased threshold of an atrial lead, and the risk–benefit ratio should be systematically evaluated. Indeed, voluminous haematoma could constitute a risk factor for infection, even in the absence of re-intervention.

The same caution should be applied to the number of leads implanted. This point has long been debated in the literature, since the increased risk of infection was first reported with the advent of dual-chamber pacemakers. Opponents of this technique purport that it is more expensive, more complex, and incurs a secondary risk of infection. These hypotheses were not confirmed by the retrospective study of Aggarwal et al., but the rate of infection observed in the study was particularly low, and the follow-up quite short. In our study, the use of more than one lead was shown to be an independent predictor of device-related infection, with a relative risk of 4.5. This variable was only found to be associated with infection by univariate analysis in the Danish registry.

Performing other electrophysiological procedures during the same procedure as implantation, or the presence of a temporary pacing wire before implantation were only found to be associated with infection by univariate analysis. Indeed, each procedure considered individually did not incur a significantly increased risk. The presence of a temporary pacing wire was significantly associated with infection in the PEOPLE study. Indeed, it is often the marker of emergency implantation, which can also be a source of infection. In our study, the relation between presence of a temporary pacing wire and infection did not attain statistical significance (P = 0.06), but we are limited by the low number of cases.

Surprisingly, some parameters were not shown to be associated with risk of infection in our study. The absence of antibiotic prophylaxis before implantation, for example, was not a predictor of increased infectious risk, even though the benefit of antibiotic prophylaxis in this context has previously been demonstrated in a meta-analysis by Da Costa et al. The use of antibiotic prophylaxis was at the cardiologist’s discretion until 1999, with selective prescription for patients at highest risk (patients with diabetes, undergoing device replacement or with a temporary pacing wire). From 1999 onwards, antibiotic prophylaxis became mandatory in all patients undergoing device implantation in our centre, in accordance with national guidelines from the French National authority for health (Haute Autorité de Santé, HAS). Naturally, this could introduce bias into our results, but this bias is limited by the fact that cases and controls were matched on year of implantation.

### Table 3 Multivariate conditional logistic regression analysis of early complications (occurring within <1 year of implantation)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 25)</th>
<th>Controls (n = 50)</th>
<th>P</th>
<th>OR [95% CI]a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70 ± 14</td>
<td>73 ± 10</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Male sex</td>
<td>19 (76%)</td>
<td>38 (76%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Time from implantation to infection (days)a</td>
<td>49 [7.36]</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>101 ± 44</td>
<td>109 ± 67</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>73 ± 29</td>
<td>67 ± 23</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (56%)</td>
<td>26 (52%)</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (32%)</td>
<td>5 (10%)</td>
<td>NS</td>
<td>2.9 [0.7, 12.6]</td>
</tr>
<tr>
<td>Heart disease</td>
<td>16 (64%)</td>
<td>20 (40%)</td>
<td>0.037</td>
<td>3.8 [1.1, 14.5]</td>
</tr>
<tr>
<td>Early complication</td>
<td>9 (36%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td>Two leads</td>
<td>17 (68%)</td>
<td>20 (40%)</td>
<td>0.027</td>
<td>5.5 [1.3, 23.4]</td>
</tr>
<tr>
<td>Fever</td>
<td>3 (12%)</td>
<td>3 (6%)</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Simultaneous other procedure</td>
<td>9 (36%)</td>
<td>11 (22%)</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Antibiotic prophylaxis</td>
<td>6 (25%)</td>
<td>13 (27%)</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>Anticoagulant or antiplatelet</td>
<td>18 (72%)</td>
<td>31 (62%)</td>
<td>NS</td>
<td>–</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; GFR, glomerular filtration rate; NS, non-significant.
a[median]
However, it does preclude any conclusions regarding the impact of antibiotic therapy on the incidence of infection in our study. Renal failure was previously shown to be associated with an increased risk of infection and complications, but we did not replicate these findings, likely due to the low number of patients with severe or end-stage renal failure or under dialysis.

Our data did not identify the presence of efficacious anticoagulant or antiplatelet therapy before implantation as a risk factor for infection, even though it could be considered responsible for increased early non-infectious complications, notably owing to the longer procedural time. In our study, occurrence of early non-infectious complications was a major risk factor for infections. In this context, assessment of the level of anticoagulation or antiplatelet activity at the time of implantation could yield more important information than simply noting whether there existed previous treatment with antimicrobials. However, our retrospective data did not allow us to analyse these points.

We did not find that fever in the days prior to implantation was associated with risk of device-related infection, in contrast to the observations of the PEOPLE study. However, this can probably be explained by a potential selection bias in our study, since, among the files we evaluated, no device implantation was performed in febrile patients with uncontrolled infection.

Several limitations of this study have already been raised, including the small sample size and retrospective analysis of data from among the variables that are systematically recorded for all patients undergoing device implantation in our centre. The case–control design of the study precluded evaluation of whether age and sex were risk factors, but the choice of matching on these factors was necessary in order to take into account the possible effect of underlying heart disease, which is known to be related to both age and sex. Similarly, matching on the year of implantation was necessary to minimize any possible bias related to changes in indications or technological advances over the study period. Lastly, the risk of missing data is also inherent to retrospective studies, although there were few missing data in our study. In conclusion, our results identify as independent risk factors for device-related infection both patient-related factors, i.e. diabetes and existence of underlying heart disease defined by echocardiographic criteria, and procedure-related factors, namely need for re-intervention and use of more than one lead. It is essential that these factors be taken into account in the prevention of infection, and we advocate the implementation of appropriate preventive measures during implantation of cardiac devices and management of early complications.

Acknowledgements

The authors would like to thank Fiona Eacrat for translation and editorial assistance.

Conflict of interest: none declared.

References


