Prevalence and risk factors related to infections of cardiac resynchronization therapy devices†

Cécile Romeyer-Bouchard1, Antoine Da Costa1,4*, Virginie Dauphinot2, Marc Messier3, Laurence Bisch1, Bernard Samuel1, Patrick Lafond1, Philippe Ricci1, and Karl Isaaz1

1Division of Cardiology, University Jean Monnet of Saint-Etienne, Saint-Etienne 42000, France; 2Neurology Unit D, Memory Research Centre University Medical Hospital P.Wertheimer, Lyon, France; 3Medtronic’s Bakken Research Centre, Maastricht, The Netherlands; and 4Service de Cardiologie, Hôpital Nord, Centre Hospitalier Universitaire de Saint-Etienne, Saint-Etienne Cedex 2 42055, France

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Aims

Device-related infections (DRI) are not well understood in patients implanted with a cardiac resynchronization therapy (CRT) device. The aims of this study were: (i) to evaluate the prevalence of CRT DRI; (ii) to establish the factors predictive of CRT DRI.

Methods and results

Between January 2001 and May 2007, CRT implantation was performed in 303 patients (247 men, 82%). The mean follow-up was 31 ± 19 months. Population characteristics were a mean age of 70 ± 10 years old; 56 female; aetiology includes (202 dilated and 101 ischaemic cardiomyopathy); NYHA class 3.2 ± 0.3; LVEF (26 ± 6%), and a QRS width of 171 ± 31 ms. Thirteen patients developed a DRI: endocarditis in four, pocket erosion in three, pocket abscess in five, and septicaemia in one. The prevalence of DRI was 4.3%. By univariate analysis, predictive factors of DRI were: procedure time (skin to skin: median of 85 vs. 57.5 min; P = 0.03), re-intervention (54 vs. 6.5%; P < 0.0001), haematoma (31 vs. 8.6%; P = 0.01), lead dislodgement (23 vs. 6.2%; P = 0.03), dialysis (23.1 vs. 1.72%; P = 0.003), and procedure type [CRT-ICD (8.6%) vs. CRT PM (1.6%) or system up-grade (1.5%); P = 0.03]. Significant correlations were found between re-intervention and lead dislodgement (r = 0.8; P < 0.001), haematoma (r = 0.2; P < 0.001). Four independent predictive factors of DRI were identified as procedure time (P = 0.002), dialysis (P = 0.0001); re-intervention (P = 0.006), and procedure type (CRT-ICD vs. other procedures; P = 0.01).

Conclusion

This study found that the prevalence of CRT DRI is close to 4.3% at 2.6 years (1.7% per year incidence). Four independent predictive factors of infections were identified including re-intervention, procedure time, dialysis, and primo CRT-ICD implantation. These parameters should be part of the risk–benefit evaluation in patients selected for CRT implantation.

Keywords

Infection • Cardiac resynchronization • Risk factors

Introduction

Despite improved surgical techniques, device-related infections (DRI) remain a serious, potentially life-threatening complication of permanent pacemaker (PM) and implantable cardioverter-defibrillators procedures (ICD).1–5 Rates varying between 0.5 and 5.1% have been reported in retrospective and prospective studies with current estimated risk close to 1%.6–10 Bacteraemia and/or endocarditis, which carry a high morbidity and mortality, have been reported in up to 0.5% of patients.1–5,11,12 Most investigators agree that infections occurring within 1 year of implantation are probably due to contamination at the time of surgery, whereas those occurring after 1 year are due to device handling such as generator change or blood borne infections.1,6,13 Virulent organisms such as Staphylococcus aureus cause infections early after PM or ICD implantation, whereas coagulase-negative staphylococci such as Staphylococcus epidermidis are responsible for delayed infections.13–16 Alternatively, skin erosion may be
a manifestation of local infection but much more frequently pocket infection is manifested as local pain, redness, swelling, etc. In a prospective study, we and others proved the role of local bacteriological flora on PM-related infection and skin erosion. The increasing number of indications for PM and ICD has logically led to more device implantation. Despite the use of a systematic antibiotic prophylaxis, a 124% increase in the rate of DRI was observed in one study population. Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in patients with LV systolic dysfunction and prolonged QRS duration. The CRT implantation, however, is frequently associated with several complications. Cardiac resynchronization therapy infection rate and factors predicting these DRI are not well understood in this clinical setting with literature reporting from 1.3 to 7%. The aim of this prospective study was to evaluate the prevalence of CRT DRI with a long-term follow-up and to analyse the factors predictive of CRT-related infections.

Methods

Selection of patients

Between January 2001 and May 2007, 316 consecutive patients underwent CRT implantation in our centre. Inclusion criteria required all the following conditions: (i) NYHA functional class III and IV heart failure; (ii) QRS width ≥ 150 ms with a left bundle branch block pattern or QRS ≥ 200 ms for paced patients (measured on three or more surface ECG lead; (iii) chronic LV systolic dysfunction defined by a left ventricular ejection fraction (LVEF) ≤ 35% and left ventricular end-diastolic diameter (≥ 60 mm) from echocardiography; (iv) optimal medical treatment for heart failure including angiotensin-converting enzyme inhibitors or AT1 receptor antagonists, diuretics, beta-receptor blockers, and spironolactone. The exclusion criteria were: (i) hypertrophic or restrictive cardiomyopathy; (ii) suspected acute myocarditis; (iii) correctable valvulopathy; (iv) acute coronary syndrome; (v) recent coronary revascularization (previous 3 months) or planned revascularization; (vi) treatment-resistant hypertension; (vii) severe obstructive lung disease; (viii) reduced life expectancy not associated with cardiovascular disease.

Study design

Between 5 and 30 days before implantation, all of the patients underwent a clinical examination, 12-lead electrocardiography, transthoracic echocardiography and Doppler evaluation. Intra-ventricular dys-synchronization or delay was defined as an overlap between the end of lateral-wall contraction and LV-filling onset. Intra-ventricular dys-synchronization was measured from the difference between LV lateral-wall contraction (delay between QRS onset and end of left lateral-wall contraction on tissue-Doppler imaging) and the delay between QRS onset and next E-wave onset. Inter-ventricular dys-synchronization or delay was defined as: left — right pre-ejection intervals = inter-ventricular (ms); this dys-synchrony requires a difference above ≥ 50 ms.

Implant procedure

The method of implantation was published elsewhere. Patients were systematically shaved and had an antiseptic shower with povidone iodine 10% aqueous solution on the night before the operation. Antisepsis was performed immediately before surgery; the skin was painted with two solutions, successively: aqueous povidone iodine 10% solution followed by a povidone iodine 7.5% solution. Implantations were performed by the same operators (A.D.C. and C.R.B.) under local anaesthesia and conscious sedation. Patients all received the same antibiotic prophylaxis. Venous administration was performed half an hour before incision using one single dose of Cefazolin (1.5 g). No local antibiotic pocket wash was used. Aspirin regimen was not modified prior to surgery. Clindamycin therapy was systematically withdrawn 6 days before the implantation and treatment with vitamin K antagonists and heparin was discontinued at least 3 days and 6 h, respectively, before the implantation procedure. All patients had an international normalized ratio (INR) ≤ 1.5 on the day of surgery. Patients with an indication for post-operative intravascular anticoagulation received intravenous heparin starting 6 h after device implantation. Post-operative intravenous heparin was infused at 1000 UI/h without a bolus dose or at a previously identified infusion rate that maintained the partial thromboplastin time between 1.5 and 2.0 times the control value. The partial thromboplastin time was measured 6 h after the initiation of heparin therapy and after dosage adjustments. These were made according to a standardized nomogram. When applicable vitamin K antagonist therapy was re-instituted at least 4 days after surgery. Heparin infusion was discontinued when the INR reached 2.0 or 2.5 when indicated. Patients were examined daily until hospital discharge. A pocket haematoma was defined by two investigators as a palpable mass that protruded 2 cm anterior to the pulse generator and lead (s). Patients were instructed to contact one of the investigators, if a haematoma developed after hospital discharge. All devices were implanted subcutaneously. Both procedure (skin to skin) and fluoroscopy time were systematically measured by a registered nurse (B.S., P.L., P.R.).

Endpoints

The primary objective of the study was to evaluate the prevalence of CRT DRI in the long-term follow-up. Device-related infection was defined as previously described by our group and others. Clinical evidence of DRI included local signs of inflammation at the generator pocket (e.g. erythema, warmth, fluctuance, wound dehiscence, tenderness, purulent drainage, or frank erosion by generator or lead puncturing the skin). Device-related endocarditis was clinically confirmed when valvular or lead vegetations were detected by echocardiography or if the modified Duke criteria for infective endocarditis were met. Device-related infection was microbiologically confirmed on the basis of positive culture results using samples obtained from the generator pocket, lead(s), or blood (in the presence of local inflammatory signs at generator pocket or absence of another source of bacteremia and resolution of bloodstream infection after device explantation). Device-related infections were defined as early or late when occurring within 30 days or after 30 days, respectively, and delayed when occurring after 364 days.

The secondary endpoint was to determine the predictive factors of DRI. Factors included age, gender, weight, diabetes mellitus, malignancy, kidney disease (as elevated creatinine), dialysis (related to renal disease), aetiology of the cardiomyopathy, NYHA class, LVEF, presence of atrial fibrillation, systolic arterial pulmonary pressure level, procedure duration (skin to skin; min), X-ray exposure time (min); long-term corticosteroid therapy or anticoagulant agents (presence of vitamin K antagonists), post-operative haematoma, re-intervention, lead dislodgement, and the procedure type (CRT-ICD vs. CRT PM vs. device up-grading procedure).

Temporary electrodes were not used and accordingly not analysed.

Re-intervention

Surgical re-intervention was defined as a surgical procedure required to manage a non-infectious complication of the device implant. It was further stratified as occurring early (< 30 days) or late (> 30 days).
A pocket haematoma was evacuated only if a tense swelling caused poor capillary perfusion of the affected skin or severe pain or if the haematoma enlarged progressively. Surgical re-intervention was systematically done in case of lead dislodgement.

**Follow-up**

Prospective data include: (i) patients’ demographic and clinical characteristics; (ii) pre-operative risk factors such as anticoagulants or antiplatelet regimen, cutaneous lesions, presence or signs/symptoms of infection; (iii) CRT characteristics (PM or defibrillator implantation, primo-implants, replacement or system upgrade of pulse generators, or leads; (iv) type of device implanted, number of leads; (v) duration of the procedure (skin to skin) and total X-ray exposure; (vi) occurrence of early (<30 days) or late complications (>30 days) requiring re-intervention or not. Infectious complications were defined prospectively in the study protocol.

Follow-up of patients was performed by two cardiologists (A.D.C. and C.R.B.) and by three registry nurses (B.S., P.L., P.R.). Electrocardiograms and devices control were performed the day after the procedure (day 1) and day 5, just before discharge. The patient scars and sutures were observed in the outpatient clinic on day 10, then followed at 3, 6, and every 6 months hence, with both a physical examination and device interrogation. Each occurrence requiring a surgical re-intervention reset the follow-up periods to 3 months follow-up.

**Statistical analysis**

All risk factors used in the analysis were assessed at the time of the device implantation. Comparisons between patients with or without a DRI were performed on continuous variables using unpaired Student t-test or Mann–Whitney test as appropriate. Data were reported as mean ± standard deviation if the underlying distribution was normal. Median and interquartile range were reported for data with skewed distribution. Categorical variables were compared using χ² test or Fisher’s exact test as appropriate. Patient data were censored at the time of the last contact, withdrawal from the study or time of death. The prognostic power of each covariate was analysed by a Cox regression model and covariates that were found significant in crude models were included in the multivariate analysis. Hazard ratios are reported with their 95% confidence interval. Interactions between the covariates were tested for significance in the model. Moreover, the relationships between continuous covariate were assessed with non-parametric (Spearman test) rank correlation coefficients. A probability value of p < 0.05 was accepted as statistically significant. All analyses were performed using StatView® 5.0 (StatView IV, Abacus Concept, Berkeley, CA, USA). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

**Baseline population characteristics**

Baseline clinical data are presented in Table 1. From January 2001 to May 2007, there were 316 consecutive patients planned for CRT implantation whom were prospectively included. The CRT implantation was obtained in 303 patients, a 95.9% success. Thirteen implantations failed (4.1%), unsuccessful LV lead implants in eight patients, coronary sinus catheterization failure in four patients, and hemo-pneumothorax with hemo-pericardium in one patient with a prior PM implanted (whom recovered without sequelae after peri-cardiocentesis). In the 303 successful patients, 198 patients were in sinus rhythm, 105 were in atrial fibrillation, and 64 had a previous device. The medical treatment was as follows: 194 patients were under angiotensin-converting enzyme inhibitors (64%), 80 patients under AT2 receptor antagonists (26.5%), 303 patients under diuretics (100%), 202 patients under beta-receptor blocker (67%), 80 patients under digoxis (26.5%), and 177 patients under aldosterone antagonists (58%).

**Implantation**

Procedure parameters were as follows: LV threshold (1.2 ± 0.9 V); LV wave amplitude (15 ± 8 mV); LV impedance (790 ± 220 Ω); procedure time (skin to skin) (67 ± 29 min); and fluoroscopy time (18 ± 14 min). The direct LV lead was successfully positioned as follows: lateral vein in 209 patients (69%), posterolateral vein in 79 patients (26%), posterior in seven patients (2.4%), and anterolateral in eight patients (2.6%). The devices implanted were CRT PM in 123 patients (40.6%), CRT-ICDs in 116 patients (38.3%), and an up-grading to CRT in 64 patients (21.1%) (36 PM and 28 ICD).

**Follow-up and complications**

The mean follow-up for the entire population was 31 ± 19 months (range from 1 to 81 months). The mortality rate was 14.9% (n = 45) over this follow-up, 40 patients died due to cardiac death (89%) (sudden death in seven patients and heart failure in 33 patients) and the remaining causes of death were due to cancer (n = 5).
Table 2  Characteristics of patients with a device-related infection

<table>
<thead>
<tr>
<th>Gender; age</th>
<th>Time to DRI (days)</th>
<th>Device implanted</th>
<th>Microorganism responsible</th>
<th>Event description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male; 66 years</td>
<td>7</td>
<td>CRT-D</td>
<td>Gram-negative bacillus</td>
<td>Septicaemia</td>
</tr>
<tr>
<td>Male; 82 years</td>
<td>22</td>
<td>CRT-D</td>
<td>S. aureus</td>
<td>Pocket abscess</td>
</tr>
<tr>
<td>Male; 67 years</td>
<td>30</td>
<td>CRT-D</td>
<td>S. aureus</td>
<td>Pocket abscess</td>
</tr>
<tr>
<td>Male; 75 years</td>
<td>30</td>
<td>CRT-D</td>
<td>S. aureus</td>
<td>Pocket abscess</td>
</tr>
<tr>
<td>Male; 43 years</td>
<td>30</td>
<td>CRT-PM</td>
<td>—</td>
<td>Erosion</td>
</tr>
<tr>
<td>Male; 53 years</td>
<td>30</td>
<td>CRT-D</td>
<td>—</td>
<td>Erosion</td>
</tr>
<tr>
<td>Male; 71 years</td>
<td>30</td>
<td>CRT-D</td>
<td>—</td>
<td>Erosion</td>
</tr>
<tr>
<td>Male; 70 years</td>
<td>60</td>
<td>CRT-PM</td>
<td>S. aureus</td>
<td>Pocket abscess</td>
</tr>
<tr>
<td>Male; 71 years</td>
<td>82</td>
<td>CRT-D</td>
<td>S. aureus</td>
<td>Endocarditis</td>
</tr>
<tr>
<td>Male; 52 years</td>
<td>90</td>
<td>CRT-D</td>
<td>Staphylococcus coagulase-negative</td>
<td>Pocket abscess</td>
</tr>
<tr>
<td>Male; 72 years</td>
<td>93</td>
<td>CRT-D</td>
<td>S. aureus</td>
<td>Endocarditis</td>
</tr>
<tr>
<td>Male; 61 years</td>
<td>240</td>
<td>CRT-D</td>
<td>Staphylococcus coagulase-negative</td>
<td>Endocarditis</td>
</tr>
<tr>
<td>Male; 76 years</td>
<td>330</td>
<td>CRT-D</td>
<td>S. aureus</td>
<td>Endocarditis</td>
</tr>
</tbody>
</table>

DRI, device-related infection; CRT-D, cardiac resynchronization therapy with defibrillation function; CRT-PM, cardiac resynchronization therapy pacemaker without defibrillation function.

Non-infectious complications

Haematoma and lead dislodgement occurred in 62 patients (20.4%) with four pericarditis reaction requiring anti-inflammatory agents (1.3%), three high LV thresholds above 5 V without the need of repositioning (0.9%), two pericardial effusion without tamponade but needing a peri-cardiocietesis at day 10 and day 60 in two patients under anticoagulant agents (0.6%), one phrenic nerve stimulation without possibility of CRT re-programming (0.3%), one pneumothorax (0.3%), and one ipsilateral proximal venous thrombosis (0.3%).

Leak dislodgement occurred in 21 patients (6.9%) including 16 left ventricular (nine early and seven late), three early atrial, and two early right ventricular leads. A large haematoma was present in 29 patients (9.5%). A re-intervention was required in 26 patients (8.6%), 21 patients (6.9%) with lead dislodgement, and five (1.66%) patients due to the size of the haematoma.

Infectious complications

Thirteen patients (seven early and six late) developed a DRI within a mean delay of 92 ± 4 days (range from 7 to 330 days, median 30 days) accompanied by endocarditis in four (1.3%), pocket erosion in three (1%), pocket abscess in five (1.8%), and septicaemia in one (0.3%) (Table 2). The prevalence of DRI was 4.3% (1.7% per year incidence). The microorganism responsible was isolated from blood cultures, from the device pocket, or from the lead when blood cultures were negative. The microorganisms involved were methicillin-susceptible S. aureus in seven patients, Staphylococcus coagulase-negative in two patients, and gram-negative bacillus in one patient. Cultures were negative in three patients with frank erosion. No patient required an open heart procedure for lead extraction, the seven patients with early infection required a simple extraction with no specific tools, whereas the six patients with late infections required specialized locking stylets (cook system). All DRI including the device and the leads were extracted.

Univariate and multivariate analysis

Crude associations between covariates and DRI are shown in Table 3. Only men developed a DRI. By crude Cox model, predictive factors of DRI were as follows: procedure time (skin to skin: median of 85 vs. 57.5 min; P = 0.03), re-intervention (54% vs. 6.5%; P < 0.0001), haematoma (31 vs. 8.6% P = 0.01), lead dislodgement (23 vs. 6.2%; P = 0.03), dialysis (23.1 vs. 1.72%; P = 0.003), and procedure type [CRT-ICD (8.6%) vs. CRT PM (1.6%) and system upgrade (1.5%); P = 0.03]. In the multivariate model, four independent predictive factors of DRI remained significant: procedure time (P = 0.0002); dialysis (P = 0.0001); re-intervention (P = 0.006); and procedure type (CRT-ICD vs. other procedures; P = 0.01). Interactions between covariates were not significant. Significant correlations were found between re-intervention and lead dislodgement (r = 0.8; P < 0.001), haematoma (r = 0.2; P < 0.001), procedure time (r = 0.2; P = 0.002) (Tables 3 and 4).

Discussion

Major findings

This study found that the prevalence of DRI in the setting of CRT implants is high, 4.3% at 2.5 years time point, a 1.7% per annum incidence. Four independent predictive factors have been identified in this study: re-intervention, procedure time, dialysis, and primary CRT-ICD indication.

Cardiac resynchronization therapy complications and infection incidence

Complications after CRT implantation were reported to be high, varying from 5 to 18%. Complications described were death, coronary sinus perforation or dissection, tamponnade, inadvertent occurrence of third-degree AV block, ventricular arrhythmias, LV lead dislodgement, high LV pacing threshold, phrenic nerve stimulation, ventricular oversensing, and infections requiring removal of...
the entire system. Kautzner et al. reported 4.3% subintimal CS dissection, 1.1% leak of contrast liquid into the pericardial space (non-significant), 5.4% lead dislodgement or phrenic nerve stimulation, 4.3% third-degree AV block during introducer handling, and 2.2% of infections. In the Multicenter Insync Randomized Clinical Evaluation study, the authors reported two deaths, 4% coronary dissection, 2% coronary-sinus perforation needing pericardocentesis, 5.7% lead dislodgement, and 1.3% infections after

**Table 3** Comparison of patients’ characteristics according to device-related infection in the overall population

<table>
<thead>
<tr>
<th>Device-related infection (n = 13)</th>
<th>No infection group (n = 290)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>66 ± 11</td>
<td>70 ± 10</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>0%</td>
<td>19%</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.1 ± 0.3</td>
<td>3.1 ± 0.3</td>
</tr>
<tr>
<td>Weight</td>
<td>73.4 ± 10</td>
<td>74.9 ± 16</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4/13 (30.7%)</td>
<td>64/290 (22%)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>3/13 (23.1%)</td>
<td>5/290 (1.72%)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>123.0 (107–173)</td>
<td>110.0 (96–130)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2/13 (15.4%)</td>
<td>103/290 (35.5%)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>8/13 (61.5%)</td>
<td>194/290 (66.9%)</td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy</td>
<td>5/13 (38.5%)</td>
<td>96/290 (33.1%)</td>
</tr>
<tr>
<td>LVEF</td>
<td>25.8 ± 5</td>
<td>26.3 ± 6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antithrombotic agent</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>7/13 (53.9%)</td>
<td>115/290 (39.7%)</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>6/13 (46.1%)</td>
<td>163/290 (56.2%)</td>
</tr>
<tr>
<td>No anticoagulant</td>
<td>—</td>
<td>12/290 (4.1%)</td>
</tr>
</tbody>
</table>

| Procedure time (skin to skin; min)$^a$ | 85.0 (68–125) | 57.5 (50–68) | 0.03   |
| X-ray exposure (min)$^a$              | 22.0 (13–35)    | 11.3 (8–17)  | 0.08   |
| Lead dislodgement                   | 3/13 (23%)      | 18/290 (6.2%) | 0.03   |
| Re-intervention                     | 7/13 (54%)      | 19/290 (6.5%) | <0.0001|
| Haematoma                           | 4/13 (30.7%)    | 25/290 (8.6%) | 0.01   |
| Generator replacement               | 2/13 (15.4%)    | 20/290 (6.8%) | 0.2    |

<table>
<thead>
<tr>
<th>Procedure type</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-PM</td>
<td>2/13 (15.4%)</td>
<td>121/290 (41.8%)</td>
</tr>
<tr>
<td>CRT-D</td>
<td>10/13 (77%)</td>
<td>106/290 (36.5%)</td>
</tr>
<tr>
<td>Up-grading</td>
<td>1/13 (7.6%)</td>
<td>63/290 (21.7%)</td>
</tr>
</tbody>
</table>

CRT, cardiac resynchronization therapy; PM, pacemaker; D, defibrillator.

$^a$Median (interquartile).

**Table 4** Univariate and multivariate analysis by Cox model

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>P-value</th>
<th>Multivariate analysis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>13.15 (3.60–48.03)</td>
<td>&lt;0.001</td>
<td>13.39 (2.73–65.62)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Procedure time$^a$</td>
<td>1.02 (1.01–1.04)</td>
<td>0.0007</td>
<td>1.03 (1.01–1.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>Lead dislodgement</td>
<td>4.08 (1.12–14.84)</td>
<td>0.03</td>
<td>1.51 (0.28–8.22)</td>
<td>0.64</td>
</tr>
<tr>
<td>Re-intervention</td>
<td>13.61 (4.56–40.61)</td>
<td>&lt;0.001</td>
<td>7.99 (1.83–34.98)</td>
<td>0.006</td>
</tr>
<tr>
<td>Haematoma</td>
<td>4.50 (1.38–14.60)</td>
<td>0.01</td>
<td>0.99 (0.23–4.25)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedure type</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-PM</td>
<td>1 (Referent)</td>
<td></td>
</tr>
<tr>
<td>CRT-D</td>
<td>5.48 (1.20–25.00)</td>
<td>0.03</td>
</tr>
<tr>
<td>Up-grading</td>
<td>0.96 (0.09–10.55)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

$^a$Hazard ratio for DRI for an increase in procedure time of +1SD (min).
6 months of follow-up. More recently, Knight et al. published that 10% of LV capture were lost, 1% of acute infection occurred, and a long-term retention of CRT was only available in 83% of patients. Daoud et al. reported 3% DRI in a series of 66 patients; the same figure was estimated by Alonso et al. in an expert centre reported a high rate of CRT infection (7%) with a CRT system upgrade. When all main studies were pooled together, the mean risk was close to 2.9%, although follow-ups were quite different (mean follow-up of 13.1 months). The antibiotic prophylactic value at the time of device implantation reduces significantly the risk of DRI. Infectious risk, however, remains close to 1% per annum for standard PM or ICD implantation has been recently measured in a large French prospective study. The incidence of infection was 0.68% at 1 year, with difference noted between de novo and a long-term retention of CRT was only available in 83% of patients. Daoud et al. reported 3% DRI in a series of 66 patients; the same figure was estimated by Alonso et al. in an expert centre reported a high rate of CRT infection (7%) with a CRT system upgrade. When all main studies were pooled together, the mean risk was close to 2.9%, although follow-ups were quite different (mean follow-up of 13.1 months). The antibiotic prophylactic value at the time of device implantation reduces significantly the risk of DRI. Infectious risk, however, remains close to 1% per annum for standard PM or ICD implantation has been recently measured in a large French prospective study. The incidence of infection was 0.68% at 1 year, with difference noted between de novo and put to skin (min) — 162 151 136 ± 50 — 132 ± 51 134 ± 43 ND

Follow-up (months) 12 6 6 — 30 17 15 6

Long term success (%) — 91.2 91 91 83 86 88 82

Table 5 All main studies reporting the percentage of cardiac resynchronization therapy infection

<table>
<thead>
<tr>
<th>Klug et al.10 (n = 117)</th>
<th>Miracle21 (n = 517)</th>
<th>Leon et al.26 (n = 2078)</th>
<th>Kautzner27 (n = 92)</th>
<th>Knight22 (n = 512)</th>
<th>Daoud28 (n = 66)</th>
<th>Alonso29 (n = 116)</th>
<th>Leclercq23 (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of initial success</td>
<td>—</td>
<td>92.4 91.6</td>
<td>91</td>
<td>87</td>
<td>89</td>
<td>88</td>
<td>82.2</td>
</tr>
<tr>
<td>Procedure time (skin to</td>
<td>—</td>
<td>162 151</td>
<td>136 ± 50</td>
<td>—</td>
<td>132 ± 51</td>
<td>134 ± 43</td>
<td>ND</td>
</tr>
<tr>
<td>skin (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
<td>—</td>
<td>33 31</td>
<td>20.2</td>
<td>—</td>
<td>41 ± 29</td>
<td>45 ± 24</td>
<td>ND</td>
</tr>
<tr>
<td>Infections (%)</td>
<td>1.77</td>
<td>1.3 2.2</td>
<td>2.2</td>
<td>1.1</td>
<td>3</td>
<td>2.9</td>
<td>7</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>12</td>
<td>6 6</td>
<td>—</td>
<td>30</td>
<td>17</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Long term success (%)</td>
<td>—</td>
<td>91.2 91</td>
<td>91</td>
<td>83</td>
<td>86</td>
<td>88</td>
<td>82</td>
</tr>
</tbody>
</table>

Risk factors of device infections

The antibiotic prophylactic value at the time of device implantation reduces significantly the risk of DRI. Infectious risk, however, remains close to 1% per annum for standard PM or ICD implantation. The identification of CRT DRI risk factors would guide preventive measures. Studies identified several risks of DRI in standard procedures (PM and ICD implantation). The largest prospective study identified five independent predictive factors including fever and temporary pacing before implantation, re-intervention, device replacement or revision, and absence of antibiotic prophylaxis. To our knowledge, no prospective study reported the factors affecting DRI in a CRT population. Our study found four independent predictive factors of infections which include re-intervention, procedure time, dialysis, and primo CRT-ICD implantation.

Re-intervention represents a classic infectious risk factor for PM and ICD standard procedures. Re-interventions were predominantly due to both haematoma and lead dislodgement. In our hands, both are associated to DRI by univariate analysis but not multivariate analysis. This emphasizes the risk of re-intervention procedures. Five recently published studies examined the risk of complications associated with generator replacement, above all the infectious risk. Accordingly, patients requiring re-intervention for haematoma or lead dislodgement should be considered more at risk. It is not surprising to find this factor in CRT population because of the high (10%) lead dislodgement rates. Haematomas or lead dislodgements should not be sufficient cause for systematic re-interventions since not all haematomas require evacuation and not all leads are critical for the patient’s survival. Suspension or management of anticoagulant therapy in patients planning CRT interventions should support oral anticoagulant agents without heparin and drainage system.

Our study demonstrates that longer implant times increase infection risk. This factor underlines that CRT implantation is not a benign intervention, where experienced physicians are needed. Material improvements of the material (leads, delivery systems, over-the-wire lead technology) could significantly reduce procedure duration and consequently should reduce significantly the infectious risk.

Dialysis represents a state in which the ability of the body’s immune system to respond is decreased. Terminal renal insufficiency was previously associated with the risk of infection from PMs and ICDs surgery by univariate analysis, but no previous report identified this variable as an independent infectious risk factor. Results of the current study suggest that terminal renal insufficiency appears to be a clinically significant component of susceptibility to infection. This should be part of the risk–benefit consideration in patients selected for CRT’s implantation.

It is well known that the cumulative probability of device infection is higher among patients with defibrillators compared with those with PMs. The complexity of CRT-ICD device implants with their larger defibrillator leads, connectors and size may increase the risk of local infections despite a similar implant time (CRT-D and CRT-P, 70 ± 32 and 65 ± 26 min, respectively, P = 0.4). The skin overlying a larger generator pocket may be stretched relatively thin and predispose to erosion. This variation in surface area and lead material may affect the adherence properties of bacteria which are the host of inflammatory response to the device and subsequent risk of infection. Pocket bleeding and infectious
risk tend to be more frequent with a larger incision. Thus, in light of our results, which match those of CARE-HF study, special attention should be given to the selection of patients needing a CRT-ICD or CRT-PM device.\textsuperscript{41,42}

**Clinical implications**

Implantation of a special pacing leads for LV-based resynchronization therapy for CHF is a rather technical procedure associated with a high rate of complications including DRI. Prevention of device infections depends on multiple factors including antibiotic prophylaxis, operators’ experience and technique, and instrument availability.\textsuperscript{19–29} In this clinical setting, the prevalence of CRT DRI seems to be high, close to 4.3% at 2.5 years (1.7% per year incidence), and the risk is two-fold higher compared with a standard PM infection risk. Four independent predictive factors of DRI were detected in our study: these include re-intervention, procedure time, dialysis, and primo CRT-ICD implantation. Two major factors are confirmed here for the first time: procedure time and primo-CRT-ICD implantation. These findings should help identify patients who are at increased risk of developing CRT DRI. Subsequent work should be dedicated to the development of strategies to minimize the modifiable risk variables and to determine whether such modification impacts future infectious complication for the CRT population.

**Study limitations**

Despite the inclusion of all cases corresponding to DRI definitions, the rate of infections might nevertheless have been underestimated, with our long-term rigorous follow-up, likely reducing this risk at its lower level. The inclusion of three patients with frank erosions without identifiable microorganism might be debatable, although it is generally admitted that the erosion mechanism is mainly due to an infectious process requiring a complete system removal.\textsuperscript{5,13,35} All devices were implanted subcutaneously which may be a reason for the incidence of infection: such risk factor has not been identified in the literature and all patients have been implanted with the same subcutaneous procedure. A single centre experience is clearly a limitation for this kind of study. Our overall infection rate in 2007 was similar to the incidence in a French multicentre study,\textsuperscript{10} 0.75% (two infections of 351 standard PM procedures and two infections of 178 standard ICD procedures; 529 procedures per year). A technical limitation of CRT therapy is short battery life, where generator replacement could play an important role. This was not the case in our study, with a low rate of generator CRT replacement (7.3%) similar between both groups (Table 3). Usually, the multivariate analysis should be applied when the rate of events is sufficient: 10 events per covariate, this phenomenon might affect our study’s results.\textsuperscript{43} On the other hand, landmark studies in this field reported low rate of events and applied multivariate analysis.\textsuperscript{10} Moreover, multivariate analysis allowed us to test the interactions between the covariates. Furthermore, we found concordant results by using correlations, with a significant correlation between re-intervention, lead lodgement, and haematoma.

**Conclusions**

This study found that the prevalence of CRT DRI is close to 4.3% at 2.6 years, an incidence of 1.7% per annum. Four independent predictive factors of infections were identified including surgical re-intervention, procedure time, dialysis, and primo CRT-ICD implantation. These parameters should be part of the risk–benefit evaluation in patients selected for CRT implantation.

**Conflict of interest:** M.M. is a full time employee of the Bakken Research Centre, a wholly owned division of the device manufacturer Medtronic Inc. Other authors have no other disclosures to declare.

**References**


