Incidence and predictors of heart failure hospitalization and death in permanent pacemaker patients: a single-centre experience over medium-term follow-up

Andrea Mazza1*, Maria Grazia Bendini1, Massimo Leggio2, Umberto Riva3, Carmine Ciardiello3, Sergio Valsecchi3, Raffaele De Cristofaro1, and Giampiero Giordano1

1Cardiology Division, Santa Maria della Stella Hospital, Località Ciconia, 05018 Orvieto (TR), Italy; 2Clinica Salus Infirorum, San Filippo Neri Hospital, Rome, Italy; and 3Boston Scientific Italy, Milan, Italy

Received 2 November 2012; accepted after revision 31 January 2013; online publish-ahead-of-print 26 February 2013

Aim

The aim of this study was to assess the incidence and clinical predictors of the development of new-onset heart failure (HF) over medium-term follow-up, in patients treated with permanent pacing in daily clinical practice.

Methods and results

We retrospectively enrolled all consecutive patients who underwent single- or dual-chamber pacemaker implantation at the study centre. Patients with a left ventricular ejection fraction (LVEF) ≤ 35% or a prior diagnosis of HF were excluded. Ventricular leads were routinely implanted in the right apex. Pacemakers were implanted in 490 patients with a standard pacemaker indication and LVEF > 35%. Left bundle-branch block (LBBB) was reported in 30 (8%) patients, and an LVEF < 50% in 64 (13%) patients. During a follow-up of 27 + 21 months, 32 (7%) patients reached the combined endpoint of HF death or hospitalization. On multivariate analysis, LBBB (HR, 3.50; 95% CI, 1.1–11.1; P = 0.033) and LVEF < 50% (HR, 5.1; 95% CI, 1.9–14.2; P = 0.002) were confirmed as independent predictors of HF death or hospitalization. Patients with LVEF < 50% and/or LBBB displayed significantly higher rates of HF death or hospitalization (log-rank test, all P < 0.001).

Conclusion

The majority of patients with a standard indication for permanent pacing and normal LV function remained in a clinically stable condition after pacemaker implantation. However, ~7% of patients developed new-onset HF over a period of follow-up of 27 months, and the presence of LBBB and LVEF < 50% at the baseline predicted HF death or hospitalization.

Keywords

Pacemaker • Heart failure • Hospitalization • Mortality

Introduction

With the progressive ageing of the population, both the incidence of heart failure (HF) and the use of permanent pacemakers for the treatment of cardiac rhythm disturbances have increased over the years.1,2

Among the different possible ventricular pacing sites, the right ventricular (RV) apex has been selected as the standard site for lead positioning. This is because intravenous RV apical lead placement is relatively simple and provides the necessary lead stability and reliability. However, RV apical pacing has been shown to impair left ventricular (LV) function by inducing dyssynchronous contraction and relaxation.3 Moreover, chronic RV apical pacing contributes to the development of HF, and is associated with an increased risk of morbidity and even mortality.4–8 In patients with preserved LV function, this seems to occur over long-term follow-up, but not in the medium term.9

The aim of this study was to assess the incidence and clinical predictors of the development of new-onset HF over medium-term follow-up in patients treated with permanent pacing in daily clinical practice.

* Corresponding author. Tel: +39 0763301021; fax: +39 0763307361. E-mail: and.mazza_m@libero.it

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2013. For permissions please email: journals.permissions@oup.com.
What’s new?

- The majority of patients with a standard indication for permanent single- or dual-chamber pacing and normal left ventricular function remain in clinically stable condition over a medium-term follow-up after implantation of a pacemaker.
- About 7% of patients develop new-onset heart failure (HF) over a period of follow-up of 2–3 years.
- The only independent predictors of HF death or hospitalization are basal left bundle-branch block and left ventricular ejection fraction <50%.

Methods

We retrospectively enrolled all consecutive adult patients in whom pacemaker implantation or replacement had been performed from 2003 to 2010 at the Santa Maria della Stella Hospital in Orvieto, Italy. Patients were required to have standard indications for permanent single- or dual-chamber pacing. Patients with evidence of systolic dysfunction [LV ejection fraction (LVEF) ≤ 35%] or a prior diagnosis of HF were excluded from the analysis. The study was approved by the Local Ethics Committee and informed consent was obtained from all patients.

Devices (models Insignia and Altrua, Boston Scientific Inc) and pacing leads were implanted by means of standard techniques. Atrial leads were routinely implanted in the right atrial appendage and ventricular leads in the right apex.

Baseline evaluation included demographics and medical history, clinical examination, 12-lead electrocardiogram, and echocardiographic evaluation of LVEF, calculated by means of Simpson’s equation.

For the purpose of the study, left bundle-branch block (LBBB) was defined as: native QRS duration ≥ 120 ms; broad (frequently notched or slurred) R waves in leads I, aVL, V5, or V6; absent q waves in leads I, V5, and V6; R peak time > 60 ms in leads V5 and V6 but normal in leads V1, V2, and V3; when small initial r waves can be discerned in the above leads.11 Similarly, right bundle-branch block (RBBB) required native QRS duration ≥ 120 ms; rs′, rs′, or rSR′ in leads V1 or V2; occasionally, a wide and notched R wave in leads V1 and/or V2; S wave of greater duration than R wave or > 40 ms in leads I and V6.11 In patients requiring continuous ventricular pacing, intrinsic conduction was searched by slowing down the pacing rate. In case of pacemaker dependency, patients were excluded from the QRS analysis. Pacemaker dependency was defined as the absence of intrinsic conduction for at least 30 s after gradual slowing down of the pacing rate to 30 bpm.12

Optimization of pacing parameters and pharmacological treatments were based on clinical evaluation by the attending physicians. During follow-up, patients returned for regular clinic visits every 6 months. At each scheduled or unscheduled visit, the pacemaker was interrogated and stored data were retrieved. The cumulative ventricular pacing percentage was determined from long-term pacemaker counters.

In the present analysis, we measured the combined endpoint of HF death and hospitalization. The diagnosis of HF was based on the presenting symptoms, clinical findings, and appropriate investigations, in accordance with the guidelines for the diagnosis and treatment of acute and chronic HF.13 Mortality data were obtained by means of hospital file review or direct telephone contact, and hospitalizations were collected from medical records.

Statistical analysis

Continuous data were expressed as means ± standard deviation. Categorical data were expressed as percentages. Mortality rates were summarized by constructing Kaplan–Meier curves, and the distributions of the groups were compared by means of a log-rank test. Cox regression was used to analyse possible predictors of death. All variables associated to a P value < 0.05 on univariate analysis were entered into the multivariate regression analysis. A P value < 0.05 was considered significant for all tests. All statistical analyses were performed by using STATISTICA software, version 7.1 (StatSoft, Inc.).

Results

From 2003 to 2010, a total of 490 consecutive patients with a standard indication for permanent single- or dual-chamber pacing underwent pacemaker implantation in our centre. Patients included in the present analysis had no history of HF and had an LVEF > 35%. Of these, 352 patients underwent de novo pacemaker implantation, while the remaining 138 patients were referred to the centre for device replacement. Table 1 shows baseline clinical variables. The baseline 12-lead electrocardiogram revealed an LBBB in 30 (8%) patients, and the absence of intrinsic rhythm was reported in 5 patients. An LVEF < 50% was measured in 64 (13%) patients on echocardiographic evaluation. The association between primary pacemaker indication and pacing mode is summarized in Table 2.

During a mean follow-up of 27 ± 21 months, 32 (7%) patients reached the combined endpoint of HF death or hospitalization. In detail, 8 (2%) patients died and 29 (6%) were hospitalized for HF; both endpoints occurred in 5 patients.

The mean cumulative ventricular pacing percentage during follow-up was 65 ± 36%.

Baseline parameters and ventricular pacing percentage were evaluated by means of univariate and multivariate analyses to assess their ability to predict the occurrence of HF death or hospitalization during follow-up, as reported in Table 3. On univariate analysis, the factors that showed a significant association with the combined endpoint were: older age, LBBB, chronic obstructive pulmonary disease, and hypertension. Table 3 demonstrates the factors associated with the primary endpoint (HF death or hospitalization). On multivariate analysis, older age, LBBB, and hypertension were the only independent predictors of HF death or hospitalization. The only independent predictors of HF death or hospitalization were the absence of intrinsic rhythm, hypertension, and LBBB.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(n = 490)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>291 (59)</td>
</tr>
<tr>
<td>Age, years</td>
<td>77 ± 8</td>
</tr>
<tr>
<td>Left bundle-branch block, n (%)</td>
<td>30 (8)</td>
</tr>
<tr>
<td>Right bundle-branch block, n (%)</td>
<td>45 (12)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>67 (14)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>343 (70)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>98 (20)</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>99 (20)</td>
</tr>
<tr>
<td>Chronic kidney disease, n (%)</td>
<td>67 (14)</td>
</tr>
<tr>
<td>LV ejection fraction &lt; 50%, n (%)</td>
<td>64 (13)</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; LV, left ventricular.
pulmonary disease, chronic kidney disease, and LVEF < 50%. On multivariate analysis, only LBBB (hazard ratio, 3.50; 95% confidence interval, 1.1 to 11.1; P = 0.033) and LVEF < 50% (hazard ratio, 5.1; 95% confidence interval, 1.9 to 14.2; P = 0.002) were confirmed as independent predictors of HF death or hospitalization.

Figure 1 shows the survival curves for HF death or hospitalization obtained by means of Kaplan–Meier analysis, and stratified by LVEF <50% or ≥50% and presence or absence of LBBB. Patients with LVEF <50% and patients with LBBB displayed significantly higher rates of events. In particular, the presence of both conditions was associated with the highest rate of HF death or hospitalization (log-rank test, all P < 0.001).

**Discussion**

In this study, 7% of patients with a standard indication for permanent single- or dual-chamber pacing and normal or moderately depressed LV function developed new-onset HF over a period of follow-up of 27 months after implantation of a pacemaker. In the present population of patients with no history of HF and no indication for cardiac resynchronization therapy, the only independent predictors of HF death or hospitalization were basal LBBB and LVEF < 50%. The presence of one or both conditions identified patients with shorter time to the first HF event.

Right ventricular pacing has been shown to impair the cardiac performance, owing to the abnormal conduction of the paced depolarization through the ventricular myocardium and the consequent dyssynchronous ventricular contraction, followed by impaired ventricular systolic and diastolic functions. However, the acute effects of RV pacing on LV function may be more evident in patients with pre-existing LV dysfunction. These effects may contribute to the development of HF after chronic RV apical pacing. Although most patients who undergo implantation remain in a clinically stable condition long after the procedure and have a good quality of life, an HF incidence varying between 3 and 12% over a mean follow-up of 3 years has been reported. In previous trials of pacemaker therapy, in which most patients had normal systolic function, the time to the first HF event attributed to RV apical pacing was between 3 and 5 years. By contrast, in defibrillator trials enrolling patients with pre-existing systolic dysfunction, the adverse response to RV apical pacing was accelerated, resulting in manifest HF after 1 year.

A summary of the cited literature is reported in Table 4.
In the Mode Selection Trial (MOST), \textsuperscript{16} \( \approx 10\% \) of 2010 patients who received pacemakers for standard bradycardia indications experienced at least one HF hospitalization during a median follow-up of 3 years; this is in agreement with our findings. In that study, HF was explained as the interaction between a substrate and promoters. Patients with a very high-risk substrate had a dramatically increased risk of HF events that could be attributed to ventricular desynchronization (ventricular pacing percentage) and atrioventricular desynchronization (pacing mode). In contrast, patients with a low-risk substrate (normal LVEF, no history of HF or myocardial infarction, and normal baseline QRS duration) well tolerated ventricular desynchronization due to RV apical pacing and had a correspondingly low risk of new-onset HF. Along the same line, Park et al.\textsuperscript{10} found no association between constant RV apical pacing and HF hospitalization over a 3-year follow-up in patients with complete AV block and normal LV function. In a similar population, Zhang et al.\textsuperscript{9} found up to 26\% of patients developing HF after constant RV apical pacing, but over a far longer timeframe (median 8 years). Our results over the medium-term follow-up are in agreement with these findings. Indeed, in our population of patients with no history of HF and LVEF >35\%, the pacing mode and the ventricular pacing percentage did not predict HF events, which were predicted only by LVEF <50\% and native LBBB. Similar results were also reported in the Danish Multicenter Randomized trial on single-lead atrial pacing vs. dual-chamber pacing in sick sinus syndrome (DANPACE),\textsuperscript{17} in which no association was found between the development of HF and pacing mode or ventricular pacing percentage.

Regardless of pacing, previous studies have shown that the presence of LBBB is associated with an increased risk of HF. In the Framingham study, LBBB was significantly associated with new-onset HF over long-term follow-up and in the presence of impaired LV systolic function of ischaemic aetiology.\textsuperscript{18} Left bundle-branch block is also an established risk factor for HF progression in patients with cardiac disease.\textsuperscript{19} In the long term, isolated LBBB has been associated with an increase in cardiac mortality\textsuperscript{20} and HF progression.\textsuperscript{21} Despite comparable QRS duration and pattern, LBBB and RV pacing cause depolarization and mechanical LV activation abnormalities at different segmental locations. In the presence of LBBB, the left intraventricular dyssynchrony affects the interventricular septum in the majority of cases, whereas during RV pacing, the LV lateral wall is the most frequent dysynchronous segment.\textsuperscript{22,23} Therefore, LBBB and RV pacing represent two different entities with non-overlapping effects on ventricular kinetics; these effects are, however, potentially harmful in both cases.

Currently, cardiac resynchronization therapy is a highly recommended therapeutic option for mildly to severely symptomatic HF patients with LVEF <35\% and LBBB QRS morphology.\textsuperscript{13} In addition, comparable benefits, in terms of significant LV reverse remodelling, have been reported on upgrading chronically paced patients to cardiac resynchronization therapy.\textsuperscript{24–27} Moreover, preliminary investigations have reported possible clinical and structural benefits of cardiac resynchronization therapy in patients with LVEF >35\%, NYHA Class III–IV status, and LBBB,\textsuperscript{28} and the Pacing to Avoid Cardiac Enlargement (PACE) study showed that biventricular pacing may prevent the adverse LV remodelling resulting from conventional RV apical pacing in patients with normal systolic function.\textsuperscript{29}

Therefore, in the light of this evidence, the results of our study support a possible preventive role of cardiac resynchronization therapy in patients with indications for permanent pacing, LVEF<50\%, and LBBB.

---

**Figure 1** Kaplan–Meier estimates of time to HF hospitalization or death, stratified by LVEF <50\% or \( \geq 50\% \) (A), presence or absence of LBBB (B), and simultaneous presence or absence of both conditions (C).
Table 4 Summary of the findings in the literature

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Device/study arm</th>
<th>Ventricular pacing %</th>
<th>Follow-up duration</th>
<th>Heart failure hospitalization rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTOPP 3</td>
<td>Pacemaker-DDD</td>
<td>–</td>
<td>3 years</td>
<td>3.1%*</td>
</tr>
<tr>
<td>MOST 6</td>
<td>Pacemaker-DDD</td>
<td>–</td>
<td>33 months</td>
<td>12.3%</td>
</tr>
<tr>
<td>UK-PACE 15</td>
<td>Pacemaker-DDD</td>
<td>–</td>
<td>4.6 years</td>
<td>3.3%*</td>
</tr>
<tr>
<td>DANPACE 17</td>
<td>Pacemaker-DDD</td>
<td>85%</td>
<td>5.4 years</td>
<td>26%</td>
</tr>
<tr>
<td>DAVID 7</td>
<td>ICD-Dual Chamber</td>
<td>60%</td>
<td>8.4 months</td>
<td>22.6%b</td>
</tr>
<tr>
<td>MADIT II 8</td>
<td>ICD-Dual Chamber</td>
<td>1:VP% ≤50%; 2: &gt;50%</td>
<td>2 years</td>
<td>1: 17%; 2: 30%</td>
</tr>
<tr>
<td>INTRINSIC RV 4</td>
<td>ICD-Dual Chamber</td>
<td>10%</td>
<td>10 months</td>
<td>6.4%a</td>
</tr>
<tr>
<td>Present study</td>
<td>Pacemaker</td>
<td>65%</td>
<td>27 months</td>
<td>7%c</td>
</tr>
</tbody>
</table>

*aAnnual rates.
*bAt 1-year follow-up.
*cCombined endpoint of HF hospitalization or death.

Limitations

The main limitation of the present study is the retrospective design of the analysis. Moreover, as the study sample was not large, the number of patients with HF events during follow-up was small. However, previous studies investigating the incidence of HF in patients on permanent RV pacing have involved comparable sample sizes. Moreover, systematic echocardiographic assessments of LV function during follow-up would have enhanced the validity of the present findings.

Conclusions

The present study showed that the majority of patients with a standard indication for permanent single- or dual-chamber pacing and normal LV function remained in a clinically stable condition after implantation of a pacemaker. However, ~7% of patients developed new-onset HF over a period of follow-up of 27 months, and the presence of LBBB and LVEF <50% at the baseline predicted HF death or hospitalization.

Conflict of interest: U.R., C.C. and S.V. are employees of Boston Scientific, Inc. No other conflicts of interest exist.

References

13. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.
17. Rahi S, Nielsen JC, Hjortshøj S, Thomsen PE, Højberg S, Møller M et al. Heart failure in patients with sick-sinus syndrome treated with single lead atrial or dual-chamber pacing; no association with pacing mode or right ventricular pacing site. Europace 2012;14:1475–82.
Bachmann block pattern resulting from inexcitable areas peripheral to the Bachmann’s bundle: controversial name or concept?

Rocio Hinojar1*, Agustin Pastor1,2, and Francisco G. Cosio1,2

1Cardiology Department, Hospital Universitario de Getafe, Ctra de Toledo, km 12, 5, 28905 Getafe, Madrid, Spain and 2Cardiology Department, Universidad Europea de Madrid, 28670 Madrid, Spain

* Corresponding author. Tel: +34 91 683 0781, E-mail: rociohinojar@gmail.com

The electrocardiographic (ECG) P-wave pattern, >120 ms, and bimodal (±) in inferior leads has been attributed to Bachmann’s bundle block. We have mapped left atrial (LA) activation in a patient with mild mitral stenosis, displaying this pattern, and with history of recurrent atrial flutter. Failure of multiple antiarrhythmic drugs prompted an electrophysiological study with transseptal access to the LA.

Electroanatomic map during flutter disclosed a large low-voltage area in the posterior–superior LA and macro-reentrant activation around the left superior pulmonary vein (LSPV). Ablation of an isthmus between the LSPV and the low-voltage area interrupted the tachycardia. Electrocardiogram in sinus rhythm displayed a wide ± P-wave, identical to pre-ablation recordings. Left atrial activation started at the superior-septal wall (presumed insertion of Bachmann’s bundle) (Figure), but it was blocked along the LA roof and therefore, high lateral activation was delayed in an ascending pattern from the postero-inferior LA wall, explaining the pattern.

Bachmann block pattern can be caused by non-excitable low-voltage areas peripheral to the insertion of Bachmann’s bundle in the high septal LA. This concept would fit well with the frequent association of the ± P-wave pattern with LA macro-reentrant tachycardia.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/Bachmann-block-pattern.pdf

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2013. For permissions please email: journals.permissions@oup.com.