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CLINICAL INVESTIGATIONS

Prevalence and clinical significance of left bundle branch block according to classical or strict definition criteria in permanent pacemaker patients

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Background: Previous studies have shown that the presence of left bundle branch block (LBBB) is associated with an increased risk of cardiac mortality and heart failure (HF). Recently, new criteria to define strict LBBB have been proposed: QRS duration ≥140 ms for men and ≥130 ms for women, along with mid-QRS notching or slurring in ≥2 contiguous leads.

Hypothesis: We assessed the prevalence and prognostic significance of LBBB according to classical (QRS duration ≥120ms) and strict criteria in permanent pacemaker patients.

Methods: We retrospectively enrolled 723 consecutive patients who had undergone single- or dual-chamber pacemaker implantation at the study center from July 2002 to December 2014. Patients with a left ventricular ejection fraction ≤35% or a prior diagnosis of HF were excluded.

Results: LBBB was reported in 54 (7%) patients, and strict-LBBB in 15 (2%) patients. During a median follow-up of 48 months (range, 18–92 months), 147 (20%) patients reached the combined endpoint of death or HF hospitalization. Patients with LBBB and those with strict-LBBB displayed significantly higher rates of death or HF hospitalization (log-rank test, all $P < 0.0001$). In particular, strict-LBBB was associated with the worst outcome. The presence of LBBB according to classical definition criteria (hazard ratio [HR] = 1.98, confidence interval [CI]: 1.23-3.19, $P = 0.005$) and to strict criteria (HR = 2.20; CI: 1.04-4.65; $P = 0.039$) were both confirmed as independent predictors of death or HF hospitalization after adjustment for relevant clinical covariates.

Conclusions: Among patients who had undergone standard pacemaker implantation, the prevalence of LBBB was 7% according to classical definition criteria and 2% according to strict criteria. The presence of LBBB, and particularly of strict-LBBB, at the baseline predicted a poor outcome in terms of death or HF hospitalization.

KEYWORDS

Left Bundle Branch Block, Pacemaker, Heart Failure, Hospitalization, Mortality

1 | INTRODUCTION

Left bundle branch block (LBBB) is a conduction disorder that results in intra- and inter-ventricular mechanical dyssynchrony and consequently causes impairment of systolic and diastolic left ventricular (LV) function.[1] LBBB has been shown to have a negative impact on prognosis, particularly in the context of structural heart disease, whether of ischemic[2] or non-ischemic etiology.[3]

In patients who receive permanent pacemakers for the treatment of cardiac rhythm disturbances, right ventricular (RV) pacing mimics an LBBB and has been shown to equally impair LV function

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by inducing dyssynchronous contraction and relaxation.[4] Over long-term follow-up, chronic RV pacing contributes to the development of heart failure (HF) and is associated with an increased risk of morbidity and even mortality.[5] Moreover, even in patients with normal LV function and an indication for permanent pacing, the presence of a native LBBB has been shown to predict HF death or hospitalization.[6]

Recently, new electrocardiographic (ECG) criteria have been proposed for the diagnosis of LBBB.[7] These criteria are stricter than the current criteria[8] and thus increase the specificity of LBBB diagnosis.[9] However, the prognostic significance of these new criteria has not yet been investigated in patients with indications for permanent pacing.

The aim of this study was to assess the prevalence and prognostic significance of LBBB according to classical and strict criteria in permanent pacemaker patients.

2 | METHODS

2.1 | Patient selection, pacemaker implantation, and follow-up

We retrospectively enrolled all consecutive adult patients in whom pacemaker implantation had been performed from July 2002 to December 2014 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 to allow data handling and access to the medical records for research and clinical reporting purposes. Devices 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.

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.

2.2 | 12-lead ECG

A standard ECG was recorded at the time of pacemaker implantation in the supine position during quiet respiration, at a paper speed of 25 and 50 mm/s and at a standard gain of 1 mV/cm. For the purpose of the study, LBBB was defined according to classical and strict definitions. Classical LBBB was defined according to the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society recommendations[8]: 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. Strict-LBBB was defined according to the criteria proposed by Strauss et al.[7]: QRS duration ≥140 ms for men and ≥130 ms for women, QS or rS in V1–V2, mid-QRS notching or slurring in at least 2 contiguous leads (V1, V2, V5, V6, I, and aVL). In patients requiring continuous ventricular pacing, intrinsic conduction was sought by slowing down the pacing rate. In the 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 seconds after gradual slowing down of the pacing rate to 30 beats/minute.[10] The ECGs were reviewed by an observer blinded to the patients' clinical course and outcome.

2.3 | Clinical events and patient outcome

In the present analysis, we measured the combined endpoint of death and HF 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.[11] Mortality data were obtained by means of hospital file review or direct telephone contact, and hospitalizations were collected from medical records.

2.4 | Statistical analysis

Continuous data were expressed as mean ± standard deviation. Categorical data were expressed as percentages. Event rates were summarized by constructing Kaplan-Meier curves. The log-rank test was applied to evaluate differences between trends (level of significance adjusted for multiple testing by Bonferroni correction). Cox regression was used to analyze possible predictors of death and HF hospitalization. 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 means of STATISTICA software, version 7.1 (StatSoft, Inc., Tulsa, OK).

3 | RESULTS

3.1 | Study population and baseline evaluation

From July 2002 to December 2014, a total of 723 consecutive patients with a standard indication for permanent single- or dual-chamber pacing underwent pacemaker implantation in our center. Patients included in the present analysis had no history of HF and had an LVEF >35%. Table 1 shows baseline clinical variables and the indications for pacemaker implantation. The baseline 12-lead ECG revealed an LBBB in 54 (7%) patients, and a strict-LBBB in 15 (2%) patients; the absence of intrinsic rhythm was recorded in 122 patients.

3.2 | Follow-up

During a mean follow-up of 48 months (range, 18-92 months), 147 (20%) patients reached the combined endpoint of death or HF hospitalization. In detail, 100 (14%) patients died, 47 (7%) were hospitalized for HF, and 26 (4%) experienced both events. All-cause death was reported in 87 patients without LBBB, 6 patients with strict-LBBB, and 7 patients with LBBB but no-strict-LBBB. The Figure 1 shows the Kaplan-Meier survival curves regarding death or HF hospitalization, stratified by the presence or absence of LBBB according to classical and strict definitions (no-LBBB = 0; LBBB and no-strict-LBBB = 1; strict-LBBB = 2). Patients with LBBB or strict-LBBB displayed significantly higher rates of death or HF hospitalization (14 and 8 combined events, respectively) than those without LBBB (125 combined events) (log-rank test, all $P < 0.0001$), strict-LBBB being associated with the worst outcome.

At the time of the last follow-up visit, the mean cumulative ventricular pacing percentage was 59% ± 39%. The percentage pacing was 59% ± 39% in the no-LBBB group and 55% ± 36% in the LBBB group ($P = 0.371$). In the 2 groups, the number of patients who received ≥80% of pacing was 297 (44%) and 18 (33%), respectively ($P = 0.115$).

Baseline parameters and ventricular pacing percentage were evaluated by means of univariate and multivariate analyses to assess their ability to predict the occurrence of death or HF hospitalization during follow-up, as reported in Table 2. On univariate analysis, the factors that showed a significant association with the combined endpoint were: older age, presence of LBBB according to either definition, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, LVEF <50%, and the percentage of ventricular pacing. Therefore, the presence of LBBB according to classical definition criteria and to strict criteria were separately tested by multivariate analysis. In model 1, the LBBB according to the classical definition was confirmed as an independent predictor of death or HF hospitalization (hazard ratio [HR] = 1.98, confidence interval [CI]: 1.23-3.19, $P = 0.005$). Similarly, the strict-LBBB, included in model 2, was independently associated with the endpoint (HR = 2.20, CI: 1.04-4.65, $P = 0.039$). Additional variables confirmed as independent predictors of death or HF hospitalization in both models were older age, chronic kidney disease, and LVEF <50%.

4 | DISCUSSION

In the present study we demonstrated that in patients who had undergone standard pacemaker implantation the prevalence of native LBBB was 7% according to classical definition criteria and 2% according to strict criteria. The presence of LBBB, and in particular of strict-

TABLE 1 Demographics, baseline clinical parameters, and indications for pacing

Parameter	All Patients, N = 723	no-LBBB, N = 669	LBBB, N = 54	*P*
Male gender, n (%)	413 (57)	386 (58)	27 (50)	0.272
Age, y	77 ± 9	77 ± 9	79 ± 8	0.186
Left bundle branch block				
Classical definition, n (%)	54 (7)	0 (0)	54 (100)	–
Strict definition, n (%)	15 (2)	0 (0)	15 (28)	–
Atrial fibrillation, n (%)	196 (27)	190 (28)	6 (11)	0.006
Coronary artery disease, n (%)	119 (16)	113 (17)	6 (11)	0.271
Hypertension, n (%)	538 (74)	499 (75)	39 (72)	0.701
Diabetes mellitus, n (%)	158 (22)	143 (21)	15 (28)	0.273
COPD, n (%)	135 (19)	127 (19)	8 (15)	0.450
Chronic kidney disease, n (%)	107 (15)	94 (14)	13 (24)	0.046
LV ejection fraction <50%, n (%)	94 (13)	78 (12)	16 (30)	<0.001
Clinical indication for pacing				
Sick sinus syndrome	317 (44)	304 (45)	13 (24)	0.002
Atrioventricular block	229 (31)	210 (31)	19 (35)	0.564
AF with slow ventricular response	127 (18)	112 (17)	15 (28)	0.040
Carotid sinus syndrome	44 (6)	37 (6)	7 (13)	0.028
Vasovagal syncope	6 (1)	6 (1)	0 (0)	1.000
Pacing mode				
AAI	4 (1)	4 (1)	0 (0)	1.000
DDD	459 (63)	428 (64)	31 (57)	0.335
DDDR	108 (15)	105 (16)	3 (6)	0.046
VDD	7 (1)	6 (1)	1 (2)	0.421
VVI	102 (14)	88 (13)	14 (26)	0.010
VVIR	43 (6)	38 (6)	5 (9)	0.285
Cumulative ventricular pacing percentage, %	59 ± 39	59 ± 39	55 ± 36	0.371

Abbreviations: AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; LBBB, left bundle branch block; LV, left ventricular.

TABLE 2 Univariate and multivariate analyses of factors predicting heart failure hospitalization and death in the study population

	Univariate Analysis			Multivariate Analysis (1)			Multivariate Analysis (2)		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Male gender	1.14	0.82-1.58	0.451	—	—	—	—	—	—
Age	1.07	1.05-1.10	<0.001	1.08	1.05-1.10	<0.001	1.08	1.05-1.10	<0.001
LBBB, classical definition	3.00	1.91-4.71	<0.001	1.98	1.23-3.19	0.005	—	—	—
LBBB, strict definition	4.63	2.27-9.43	<0.001	—	—	—	2.20	1.04-4.65	0.039
Hypertension	0.99	0.69-1.41	0.948	—	—	—	—	—	—
Diabetes mellitus	1.64	1.16-2.34	0.006	1.39	0.97-2.00	0.078	1.43	0.99-2.05	0.056
COPD	2.18	1.56-3.06	<0.001	1.43	0.98-2.07	0.063	1.43	0.99-2.08	0.057
Chronic kidney disease	3.05	2.15-4.34	<0.001	1.87	1.25-2.80	0.002	1.95	1.31-2.90	0.001
LV ejection fraction <50%	4.50	3.21-6.32	<0.001	2.85	1.96-4.13	<0.001	2.84	1.95-4.13	<0.001
% of ventricular pacing	1.62	1.03-2.56	0.039	1.17	0.72-1.89	0.526	1.13	0.70-1.83	0.610

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LBBB, left bundle branch block; LV, left ventricular.

LBBB, at the baseline predicted a poor outcome in terms of death or HF hospitalization.

Conduction disorders have been shown to have a negative impact on prognosis. Right bundle branch block is associated with an increased risk of mortality in general population and patients with heart disease.[12] LBBB is associated with new-onset HF over long-term follow-up in the general population and in the presence of impaired LV systolic function of ischemic etiology.[13] LBBB is also an established risk factor for HF progression in patients with cardiac disease.[14] In the long term, isolated LBBB has been associated with an increase in cardiac mortality and HF progression.[15]

However, the ECG criteria adopted to accurately define LBBB are debated. A prolonged QRS complex may reflect a block within the right bundle branch or an intraventricular conduction delay caused by delays primarily in the ventricular myocardium (ie, left ventricular dilation or hypertrophy). By contrast, in the presence of LBBB, there is a significant delay between activation of the interventricular septum and activation of the LV free wall. Endocardial mapping studies have shown that approximately one-third of patients diagnosed as having a complete LBBB may actually have delayed conduction throughout the LV because of underlying hypertrophy or left anterior fascicular block.[7,9,16]

Recently, Strauss et al[7] proposed stricter diagnostic criteria for LBBB, including longer QRS duration (≥140 ms in men, ≥130 ms in women) and the presence of mid-QRS notching/slurring in more than 2 contiguous leads. These criteria derive from electrical mapping and echocardiographic studies in humans,[7] and should allow to identify the characteristic inverted activation of septum.

The importance of identifying LBBB has been emphasized in the perspective of cardiac resynchronization therapy (CRT) for patients with severe systolic dysfunction. Prespecified subgroup analyses of data collected in large CRT trials[17] have suggested that, in terms of morbidity/mortality, patients with complete LBBB benefit more from CRT than patients with nonspecific intraventricular conduction delay or right bundle branch block. On the basis of this evidence, current class I recommendations are restricted to patients with complete LBBB.[18]

Despite ECG similarities, recent studies have demonstrated that LBBB is associated with different LV dyssynchrony patterns from those observed in patients on right apical pacing, both when the most delayed activated region of the LV is considered, and when the activation pattern is taken into account.[19]

Chronic RV pacing was shown to worsen HF in patients with preexisting systolic dysfunction enrolled in defibrillator trials. The

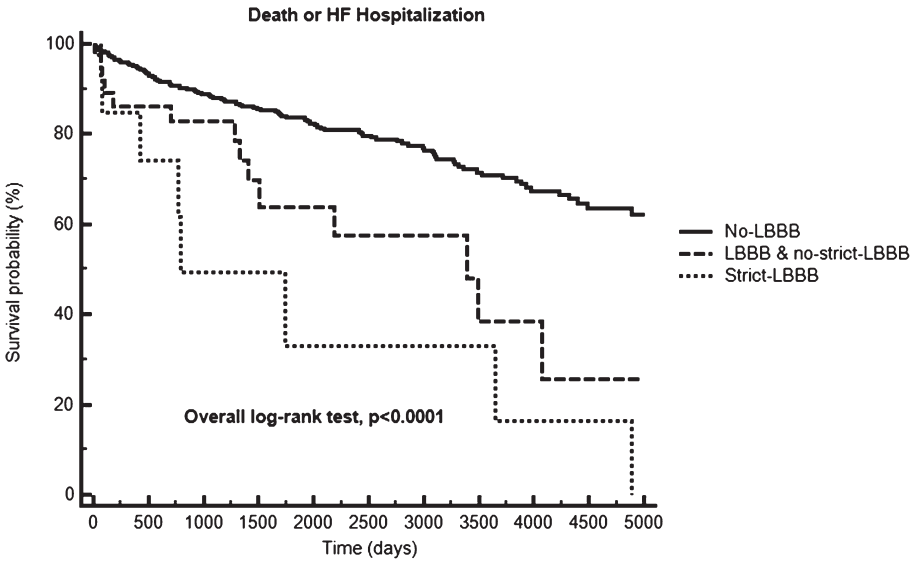

FIGURE 1 Kaplan-Meier estimates of time to HF hospitalization or death, stratified by presence or absence of LBBB according to classical and strict definitions (no-LBBB = 0; LBBB & no-strict-LBBB = 1; strict-LBBB = 2). Abbreviations: HF, heart failure; LBBB, left bundle branch block.

adverse response to pacing was fast and resulted in HF events after 1 year.[20] By contrast, in previous trials of pacemaker therapy,[21,22] the time to the first HF event attributed to RV apical pacing was between 3 and 5 years. Similarly, our patients with a low-risk substrate (normal LVEF, no history of HF or myocardial infarction) tolerated ventricular desynchronization due to RV apical pacing and had a correspondingly relatively low risk of new-onset HF. In agreement with previous studies on patients with normal LV function,[5] on multivariate analysis we did not find an association between ventricular pacing percentage and HF events, which were predicted only by native LBBB, LVEF <50%, and chronic kidney disease. Similar results were also reported in the DANPACE (Danish Multicentre Randomized Trial on Single-Lead Atrial (AAIR) Pacing versus Dual-Chamber (DDDR) Pacing in Sick Sinus Syndrome) trial,[22] in which no association was found between the development of HF and the pacing mode or ventricular pacing percentage.

In our population, patients with normal baseline conduction and those with LBBB had a similar electrical activation during pacing that moved from the RV to the LV resulting in electrical dyssynchrony. The reason for the observed divergence in outcomes is difficult to ascertain. However, 2 factors may play a role. First, in this study population the cumulative ventricular pacing percentage was about 60%, and perhaps the dyssynchronous activation in the natively conducted beats in the LBBB patients contributes to the difference in outcomes. Second, as previously shown in patients with systolic dysfunction, intrinsic LBBB and RV pacing may have an additive effect and induce greater mechanical dyssynchrony and further impair LV function.[23]

In the present analysis, the association between the development of HF during follow-up and the presence of native LBBB, especially when it is defined according to strict criteria, matches with recent evidence of the greater benefit of CRT in patients with LBBB defined according to the criteria proposed by Strauss et al.[7] These findings seem to suggest that, in the presence of an accurately diagnosed LBBB, CRT could be considered as a therapeutic option for patients with indications for pacemaker implantation, especially in the presence of moderate LV dysfunction (LVEF <50%).

The BLOCK HF (Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block) trial investigated the effect of CRT in patients with pacemaker indications and LVEF <50%.[24] The absolute reduction in the risk of death or hospitalization due to HF was 4.8% over a mean follow-up of 37 months in patients treated with CRT vs apical pacing. The expected benefits of CRT were therefore limited in the overall population considered in the trial, especially in light of the anticipated higher risk of complications in patients with CRT devices. However, according to our results, in the presence of LBBB and, in particular strict-LBBB, the implantation of a CRT system could be appropriate to reduce the risk of HF progression. The current class of recommendation for de novo CRT implantation in HF patients with reduced EF and an expected high percentage of ventricular pacing is IIa.[18] By contrast, only a class I indication is provided for upgrade from conventional pacemaker therapy to CRT in patients with LVEF <35% in New York Heart Association functional class III–IV. In light of the well-known higher rate of complications in device upgrade procedures,[25] and the economic implications of premature device replacement,[26] the early implantation of a CRT system seems justified in patients with LBBB. In our event-free survival analysis, the curves diverged early, with about 50% of strict-LBBB patients experiencing HF events within 2 years of pacemaker implantation.

4.1 | Limitations

The main limitation of the present study is the retrospective design of the analysis. Some variability in the selection or management of patients during the inclusion period may have influenced the results. However, the study was carried out in a single center; the operators in charge of patient selection, device implantation, and clinical management did not change during the study period; and all the patients included were consecutive. Moreover, the evaluation of changes in ECG or systematic echocardiographic assessments of LV function during follow-up would have enhanced the validity of the present findings. In addition, due to the retrospective design of the study, accurate adjudication of the mode of death was not possible, and only all-cause death was considered as a component of the combined study endpoint of death and HF hospitalization.

5 | CONCLUSION

In patients with standard pacemaker indications, the prevalence of native LBBB was 7% according to classical definition criteria and 2% according to strict criteria. The presence of LBBB, and in particular of strict-LBBB, at the baseline predicted a poor outcome in terms of death or HF hospitalization. In these patients, the implantation of a de novo CRT system could help to prevent HF. However, prospective studies are required to demonstrate this.

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