Differential clinical characteristics and prognosis of intraventricular conduction defects in patients with chronic heart failure

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Aims
Intraventricular conduction defects (IVCDs) can impair prognosis of heart failure (HF), but their specific impact is not well established. This study aimed to analyse the clinical profile and outcomes of HF patients with LBBB, right bundle branch block (RBBB), left anterior fascicular block (LAFB), and no IVCDs.

Methods and results
Clinical variables and outcomes after a median follow-up of 21 months were analysed in 1762 patients with chronic HF and LBBB (n = 532), RBBB (n = 134), LAFB (n = 154), and no IVCDs (n = 942). LBBB was associated with more marked LV dilation, depressed LVEF, and mitral valve regurgitation. Patients with RBBB presented overt signs of congestive HF and depressed right ventricular motion. The LAFB group presented intermediate clinical characteristics, and patients with no IVCDs were more often women with less enlarged left ventricles and less depressed LVEF. Death occurred in 332 patients (interannual mortality = 10.8%): cardiovascular in 257, extravascular in 61, and of unknown origin in 14 patients. Cardiac death occurred in 230 (pump failure in 171 and sudden death in 59). An adjusted Cox model showed higher risk of cardiac death and pump failure death in the LBBB and RBBB than in the LAFB and the no IVCD groups.

Conclusion
LBBB and RBBB are associated with different clinical profiles and both are independent predictors of increased risk of cardiac death in patients with HF. A more favourable prognosis was observed in patients with LAFB and in those free of IVCDs. Further research in HF patients with RBBB is warranted.

Keywords
Heart failure • Bundle branch block • Outcomes • Prognosis

Introduction
Intraventricular conduction defects (IVCDs) can probably impair the clinical course and outcomes of patients with chronic heart failure (HF) since delayed activation of either the right or left ventricle shortens the duration of the ventricular diastolic filling period, and this in turn reduces the stroke volume and cardiac output.1,2 Moreover, the systolic and diastolic ventricular asynchrony originating due to the abnormal cardiac activation sequence3,4 will worsen the already depressed cardiac output and favour further ventricular volume remodelling.5,6
Clinical registries that have analysed the prognostic implications of bundle branch block in patients with HF\textsuperscript{7–12} reported different results. Whereas the presence of LBBB emerges as an independent prognostic marker in some studies\textsuperscript{7,10}, others found a higher mortality linked to the presence of right bundle branch block (RBBB).\textsuperscript{11,12} Differences in the length of the follow-up period (from 1 up to 5 years)\textsuperscript{7,10} may account to some extent for the reported prognostic differences, although the categorization of patients and the analysis of the causes of death would certainly play an important role. Indeed, vital status or all-cause mortality instead of a more precise assessment of different causes of cardiac death are presently determined in most studies. On the other hand, the clinical characteristics associated with different IVCDs cannot be well established because echocardiographic data are not reported in all studies and, moreover, they lack information on relevant features such as LV and left atrial size, or mitral valve assessment.\textsuperscript{7,10,12,13}

This study was therefore undertaken to determine the clinical characteristics and 21-month follow-up outcomes of chronic HF in relation to the presence of LBBB, RBBB, and LAFB, and the absence of IVCDs.

**Methods**

**Study population**

We screened 2254 patients with chronic HF entered in the Spanish Network for the Study of Heart Failure (REDINSCOR).\textsuperscript{14} Patients were consecutively recruited between January 2007 and January 2011 at HF units in 18 hospitals. Inclusion criteria were: (i) age older than 18 years; and (ii) prior hospital admission (≥24 h) due to HF and at least one echocardiographic abnormality (LVEF <40%, LV end-diastolic diameter ≥60 mm, altered LV relaxation indicating diastolic dysfunction, or thickness of interventricular septum/LV posterior wall ≥14 mm). All patients were symptomatic (functional NYHA class II–IV) and were treated according to the established clinical guidelines. Exclusion criteria were: (i) reversible acute HF; (ii) severe valvular disease amenable to surgical repair; (iii) right HF secondary to chronic cor pulmonale; and (iv) concomitant terminal disease. The investigation conforms with the principles outlined in the Declaration of Helsinki. The protocol was approved by the ethics committees of all centres, and all patients gave written informed consent to participate in the study.

**Study variables**

Data were collected using specifically designed web forms, and quality control was carried out every month. We recorded 93 clinical variables at study inclusion, and standard criteria were used to define them. Cardiovascular risk factors were eventually coded as dichotomous variables (yes/no). Central obesity was defined as abdominal circumference ≥88 cm in women and ≥102 cm in men.\textsuperscript{15} Body mass index (kg/m$^2$) was entered as a continuous variable. Anaemia was defined as haemoglobin <120 g/L for women and <130 g/L for men.\textsuperscript{16} The plasma levels of NT-proBNP and BNP were dichotomized because echocardiographic data are not reported in all studies and, moreover, they lack information on relevant features such as LV and left atrial size, or mitral valve assessment.\textsuperscript{7,10,12,13}

Plasma levels of cardiac troponin I or T were considered ‘high’ according to the reference cut-off value for each hospital.

Left bundle branch block was defined by a prolonged QRS duration of ≥0.12 s associated with a broad, notched R wave without q waves in leads I, aVL, and V6, and an rS pattern in lead V1. RBBB was characterized by prolonged QRS duration of ≥0.12 s associated with an R, rSR’, or qR wave in lead V1; wide, slurred S waves in leads I, aVL, V5, and V6; and a wide terminal r wave in aVF. LAFB was defined by leftward axis deviation of ≤−45° or more associated with qR wave in leads I and aVL and an rS pattern in leads II, III, and aVF.

**Follow-up**

Follow-up data were obtained from the outpatient annual visits or from the readmission and event reports. Total mortality included all cardiac and non-cardiac deaths. Cardiac mortality included death due to pump failure and sudden death. Pump failure death included patients dying because of refractory HF and patients undergoing urgent cardiac transplantation. Sudden death was defined as an unexpected natural death with no apparent cause occurring <1 h after the onset of symptoms. Patients lost to follow-up and those submitted to non-emergency heart transplant were censored for the analysis. The reported deaths were reviewed by an ad hoc committee.

**Statistical analysis**

Continuous variables were expressed as the mean ± standard deviation (SD) and the categorical variables are presented as frequency and percentage. Differences in the categorical variables were assessed by the χ$^2$ test or Fisher’s exact test, and differences in continuous variables were analysed by analysis of variance (ANOVA). A multivariate analysis (Cox model) was built to assess the influence of the different IVCDs on survival, and a Cox proportional hazard regression model was used to identify independent predictors of readmissions and cardiac death for each IVCD. Variables showing a significant level in the univariate model ($P<0.1$) were thereafter included in the multivariate Cox model following a backward stepwise approach. The final model was adjusted for those variables categorized as clinically relevant. Moreover, confounding variables were included when they carry a change of the effect on the hazard ratio >10%.\textsuperscript{22} The proportionality assumption of the models was verified using time-dependent variables. Variables with >10% of missing data were not included in the Cox models, and a multivariate regression imputation was applied, whenever necessary.\textsuperscript{23} A two-sided $P<0.05$ was considered statistically significant. All analyses were performed using SPSS (v 19.0) software.

**Results**

**Clinical characteristics**

Among the 2254 patients screened, 532 (23.6%) presented LBBB, 134 (6%) RBBB, 154 (6.8%) LAFB, and 942 (41.8%) no IVCDs at inclusion. The remaining 492 patients (21.8%) presented left posterior fascicular block ($n=14$), combined BBB ($n=87$), non-specific intraventricular conduction ($n=131$), and ventricular pacing rhythm ($n=260$), and they were not included in the analysis. Thus, the final study population consisted of 1762 patients (mean age 66 years, 68% men, 57% in NYHA class III–IV, mean LVEF of 36%).

As shown in Table 1, there were significant clinical differences between the study groups. Patients with LBBB had a more frequent history of dilated cardiomyopathy and presented with the most
Table 1  Baseline clinical characteristics of 1762 patients with and without intraventricular conduction defects

| Variables                        | LBBB  (n = 532, 30.2%) | RBBB  (n = 134, 7.6%) | LAFB  (n = 154, 8.7%) | No IVCDs  (n = 942, 53.5%) | P-value |
|----------------------------------|-------------------------|-----------------------|-----------------------|-----------------------------|---------|
| Age, years                       | 66.8 ± 11.6             | 67.6 ± 12.6           | 68.5 ± 13.8           | 64.7 ± 13.7                 | <0.001  |
| Sex, male                        | 380 (71%)               | 101 (75%)             | 108 (70%)             | 610 (65%)                   | 0.011   |
| Diabetes mellitus                | 209 (39%)               | 58 (43%)              | 53 (34%)              | 406 (43%)                   | 0.146   |
| Hypertension                     | 351 (66%)               | 98 (73%)              | 111 (72%)             | 639 (68%)                   | 0.282   |
| Prior AMI                         | 176 (33%)               | 59 (44%)              | 49 (29%)              | 352 (37%)                   | 0.023   |
| Ischaemic heart disease          | 228 (43%)               | 70 (52%)              | 61 (40%)              | 450 (48%)                   | 0.047   |
| Dilated cardiomyopathy           | 210 (39%)               | 21 (16%)              | 49 (32%)              | 215 (23%)                   | <0.0001 |
| BMI, kg/m²                       | 28.3 ± 4.6              | 29.3 ± 5.8            | 28.7 ± 4.2            | 29.2 ± 5.4                  | 0.011   |
| Central obesity                  | 299 (56%)               | 91 (68%)              | 87 (56%)              | 586 (62%)                   | 0.025   |
| NYHA class, III–IV               | 316 (59%)               | 75 (56%)              | 98 (64%)              | 512 (54%)                   | 0.081   |
| Orthopnoea                       | 222 (42%)               | 64 (48%)              | 76 (49%)              | 348 (37%)                   | 0.004   |
| Nocturnal dyspnoea               | 102 (19%)               | 38 (28%)              | 36 (23%)              | 176 (19%)                   | 0.042   |
| Third heart sound                | 95 (18%)                | 23 (17%)              | 14 (9%)               | 104 (11%)                   | <0.001  |
| Lower limb oedema                | 137 (26%)               | 58 (43%)              | 54 (35%)              | 270 (29%)                   | <0.001  |
| Jugular ingurgitation            | 129 (24%)               | 37 (28%)              | 43 (28%)              | 168 (18%)                   | <0.001  |
| Hepatomegaly                     | 76 (14%)                | 32 (24%)              | 17 (11%)              | 108 (11%)                   | <0.001  |
| Hepatoglujar reflex              | 91 (17%)                | 27 (20%)              | 33 (21%)              | 124 (13%)                   | 0.011   |
| Ascites                          | 27 (5%)                 | 16 (12%)              | 10 (9%)               | 48 (5%)                     | 0.013   |
| RR interval, ms                  | 826 ± 168               | 801 ± 169             | 817 ± 162             | 808 ± 175                   | 0.223   |
| QTc duration, ms                 | 148 ± 28                | 135 ± 28              | 111 ± 25              | 98 ± 20                     | <0.0001 |
| AF/flutter                       | 125 (23%)               | 44 (33%)              | 37 (24%)              | 260 (28%)                   | 0.098   |
| LV mass, mm                      | 404 ± 123               | 351 ± 103             | 372 ± 119             | 348 ± 121                   | <0.0001 |
| LV mass index, g/m²              | 212 ± 62                | 182 ± 55              | 196 ± 60              | 181 ± 64                    | <0.0001 |
| LA, mm                           | 48 ± 9                  | 49 ± 9                | 48 ± 7                | 46 ± 8                      | <0.0001 |
| Indexed LA, mm/m²                | 25 ± 5                  | 25 ± 6                | 25 ± 5                | 24 ± 5                      | <0.0001 |
| Septal thickness, mm             | 11 ± 3                  | 12 ± 3                | 12 ± 3                | 12 ± 3                      | <0.0001 |
| LV posterior wall, mm            | 11 ± 2                  | 11 ± 3                | 11 ± 2                | 11 ± 2                      | 0.126   |
| Mitral regurgitation, III/IV     | 141 (27%)               | 18 (13%)              | 20 (13%)              | 145 (15%)                   | <0.0001 |
| Normal RV motion                 | 393 (74%)               | 93 (69%)              | 111 (72%)             | 764 (81%)                   | <0.0001 |
| Abnormal LV relaxation           | 157 (36%)               | 41 (34%)              | 46 (37%)              | 337 (40%)                   | 0.351   |
| Pseudonormal LV relaxation       | 66 (15%)                | 18 (15%)              | 14 (11%)              | 114 (13%)                   | 0.696   |
| Restrictive LV relaxation        | 101 (23%)               | 25 (21%)              | 25 (20%)              | 166 (20%)                   | 0.587   |
| Haemoglobin, g/L                 | 131 ± 20                | 131 ± 21              | 130 ± 18              | 132 ± 21                    | 0.779   |
| eGFR (mL/min/1.73 m²)            | 67 ± 25                 | 68 ± 29               | 66 ± 27               | 70 ± 27                     | 0.052   |
| NT-proBNP or BNP high³           | 292 (70%)               | 69 (64%)              | 83 (72%)              | 438 (60%)                   | 0.003   |
| ACE inhibitor                    | 356 (67%)               | 93 (69%)              | 107 (69%)             | 618 (66%)                   | 0.684   |
| ARB                              | 118 (22%)               | 27 (20%)              | 29 (19%)              | 206 (22%)                   | 0.799   |
| RAAS blockade                    | 462 (87%)               | 117 (87%)             | 135 (88%)             | 805 (85%)                   | 0.792   |
| Beta-blockers                    | 442 (83%)               | 102 (76%)             | 115 (75%)             | 755 (80%)                   | 0.067   |
| Aldosterone antagonists          | 332 (62%)               | 71 (53%)              | 94 (61%)              | 467 (50%)                   | <0.0001 |
| Digoxin                          | 132 (25%)               | 36 (27%)              | 43 (28%)              | 191 (20%)                   | 0.042   |
| Loop diuretics                   | 468 (88%)               | 116 (87%)             | 141 (92%)             | 748 (79%)                   | <0.0001 |
| Antithrombotics                  | 271 (51%)               | 79 (59%)              | 71 (46%)              | 542 (58%)                   | 0.009   |
| Anticoagulants                   | 226 (42%)               | 62 (46%)              | 74 (48%)              | 368 (39%)                   | 0.090   |
| Erythropoietin stimulation       | 2 (0.37%)               | 1 (0.74%)             | 3 (1.94%)             | 7 (0.74%)                   | 0.257   |
dilated and weighted LV, more advanced mitral valve regurgitation, larger QRS duration, and most depressed LVEF. Patients with RBBB had a more frequent history of ischaemic heart disease and prior myocardial infarction, a greater proportion of central obesity, signs of left and right HF, and abnormal RV motion at echocardiography. Patients with LAFB presented an intermediate proportion of risk factors and degree of structural and functional cardiac involvement, and had a lower prevalence of previous myocardial infarction than patients with LBBB or RBBB. However, deterioration of the NYHA functional class and presence of signs of left and right HF remained highly expressed in patients with LAFB.

Patients free of IVCDs were more often women, with less enlarged left ventricles and less depressed LVEF. The mean haemoglobin values were normal, but anaemia was present in 673 patients (38%). Anaemic patients were distributed similarly among the study groups, and had lower GFR (61 vs. 73 mL/min/1.73 m²) and received more antithrombotics (63% vs. 49%) and diuretics (88% vs. 81%) than non-anaemic patients ($P < 0.001$). Erythropoietin-stimulating agents were administered in 13 patients (0.73%). The percentage of drug prescription varied among the study categories. Patients with LBBB tended to receive more beta-blockers, whereas loop diuretics were used more in patients with RBBB or LAFB. At the end of the follow-up, the total percentage of patients with ACE inhibitors changed from 68% at inclusion to 63% ($P < 0.001$), aldosterone antagonists from 54% to 51% ($P = 0.012$), and diuretics from 82% to 78% ($P < 0.001$), but the percentage of renin–angiotensin–aldosterone system (RAAS) blockers

| Table 1 Continued |
|-------------------|
| Variables | LBBB | RBBB | LAFB | No IVCDs |
| IC | 59 (11%) | 12 (9%) | 13 (8%) | 70 (7%) |
| CRT/CRT-D | 26 (5%) | 4 (3%) | 9 (6%) | 12 (1%) |

Qualitative data are presented as absolute frequencies and percentages. Quantitative data are expressed as mean ± SD.

| Table 2 Readmissions and mortality rates in heart failure patients with and without intraventricular conduction defects after a median follow-up of 21 months |
|-------------------|
| Variables | LBBB | RBBB | LAFB | No IVCDs |
| All-cause readmission | 219 (41%) | 52 (39%) | 46 (30%) | 282 (30%) |
| Heart failure | 128 (24%) | 36 (27%) | 37 (24%) | 197 (21%) |
| Myocardial ischaemia | 35 (7%) | 12 (9%) | 6 (4%) | 59 (6%) |
| Arrhythmias | 102 (19%) | 16 (12%) | 13 (8%) | 63 (7%) |
| ICD | 23 (4%) | 4 (3%) | 7 (5%) | 36 (4%) |
| CRT/CRT-D | 72 (14%) | 5 (4%) | 2 (1%) | 10 (1%) |
| Cardiac transplantation | 23 (4%) | 5 (4%) | 7 (5%) | 23 (2%) |
| All-cause mortality | 125 (23%) | 36 (27%) | 31 (20%) | 140 (15%) |
| Cardiovascular death | 99 (19%) | 27 (20%) | 25 (16%) | 106 (11%) |
| Cardiac death | 94 (18%) | 24 (18%) | 21 (14%) | 91 (10%) |
| Pump failure | 66 (12%) | 23 (17%) | 18 (12%) | 64 (7%) |
| Sudden | 28 (5%) | 1 (1%) | 3 (2%) | 27 (3%) |
| Vascular | 5 (1%) | 3 (2%) | 4 (3%) | 15 (2%) |
| Extravascular | 21 (4%) | 5 (4%) | 6 (4%) | 29 (3%) |
| Unknown cause | 5 (0.9%) | 4 (3.0%) | 0 (0%) | 5 (0.5%) |

Readmissions*<br>

| Mortality | LBBB | RBBB | LAFB | No IVCDs |
| All-cause mortality | 125 (23%) | 36 (27%) | 31 (20%) | 140 (15%) |
| Cardiovascular death | 99 (19%) | 27 (20%) | 25 (16%) | 106 (11%) |
| Cardiac death | 94 (18%) | 24 (18%) | 21 (14%) | 91 (10%) |
| Pump failure | 66 (12%) | 23 (17%) | 18 (12%) | 64 (7%) |
| Sudden | 28 (5%) | 1 (1%) | 3 (2%) | 27 (3%) |
| Vascular | 5 (1%) | 3 (2%) | 4 (3%) | 15 (2%) |
| Extravascular | 21 (4%) | 5 (4%) | 6 (4%) | 29 (3%) |
| Unknown cause | 5 (0.9%) | 4 (3.0%) | 0 (0%) | 5 (0.5%) |

*One or more readmissions for the same cause.
(88%) and beta-blockers (82%) remained the same. Similar trends were observed in all four study groups.

An implantable cardioverter-defibrillator (ICD) was inserted in 154 patients before inclusion (Table 1), and 70 devices (Table 2) were implanted during the follow-up (65 new implants and 5 reimplants). The proportion of implanted ICDs among the four groups did not differ significantly. CRT was applied to 140 patients (51 before inclusion and 89 during the follow-up), and in 117 of them (83%) an ICD was added to the CRT (CRT-D). Thus, the total number of patients with ICD either alone or in combination with CRT was 330 (19% of the study cohort). The percentage of implantation of a CRT/CRT-D was 18% in LBBB, 7% in RBBB, 7% in LAFB, and 2% in the no IVCD group \( (P < 0.001) \). In 69% of cases, the ICD was implanted for primary prevention and 18% of patients received appropriate shocks to treat severe ventricular arrhythmias.

Outcomes

Patients were followed for a median of 21 months (interquartile range 11–33) and 15 of them (0.9%) were lost to follow-up. Non-emergency heart transplant was performed in 43 patients (2.4%). There were 666 readmissions due to decompensated HF, 148 due to myocardial ischaemia, and 222 due to arrhythmias. Death occurred in 332 patients (interannual mortality rate of 10.8%). Causes of death were: cardiovascular in 257 (77.4%), extravascular in 61 (18.4%), and of unknown origin in 14 (4.2%) patients. Among the cardiac deaths, 171 were due to pump failure and 59 occurred suddenly. As shown in Table 2, patients with RBBB or LBBB had the highest rates of readmissions and mortality, followed by patients with LAFB, and finally by patients free of IVCDs. After adjustment for age, prior myocardial infarction, diabetes, central obesity, mitral valve regurgitation, signs of left and right HF, LVEF, left atrial size, LV mass, haemoglobin, renal function, ICD, CRT, and drug therapy, the Cox model showed that RBBB and LBBB had the highest rates of readmissions and mortality, followed by patients with LAFB, and finally by patients free of IVCDs. After adjustment for age, prior myocardial infarction, diabetes, central obesity, mitral valve regurgitation, signs of left and right HF, LVEF, left atrial size, LV mass, haemoglobin, renal function, ICD, CRT, and drug therapy, the Cox model showed that RBBB and LBBB had the highest rates of readmissions and mortality, followed by patients with LAFB, and finally by patients free of IVCDs (Figure 1, Table 3). Although not significant, the hazard ratio for readmission, cardiac death, and pump failure death tended to be higher in the RBBB than in the LBBB group. In the multivariate analysis, the most prevailing predictors of these events were diabetes mellitus, prior myocardial infarction, presence of signs of left and right HF, anaemia, and decreased GFR (Supplementary material, Table S1). The beneficial effect of ICD and CRT on cardiac death and pump failure death did not reach

![Figure 1](image_url) Adjusted Cox model survival curves for readmissions (A), cardiac death (B), and pump failure death (C) in patients with chronic heart failure with and without intraventricular conduction defects (IVCDs) after a median follow-up of 21 months. LAFB, left anterior fascicular block; LBBB, left bundle branch block; RBBB, right bundle branch block.

Table 3 Hazard ratios for readmissions and cardiac mortality in heart failure patients with and without intraventricular conduction defects after a median follow-up of 21 months

| Hazard Ratios | P-value | HR  | 95% CI for HR |
|--------------|---------|-----|---------------|
| All-cause readmission |          |     |               |
| LBBB vs. no IVCD | 0.123   | 1.172 | 0.958 1.433   |
| RBBB vs. no IVCD | 0.018   | 1.433 | 1.063 1.930   |
| LAFB vs. no IVCD | 0.459   | 0.887 | 0.646 1.218   |
| Cardiac death |          |     |               |
| LBBB vs. no IVCD | 0.005   | 1.579 | 1.149 2.169   |
| RBBB vs. no IVCD | 0.007   | 1.894 | 1.192 3.008   |
| LAFB vs. no IVCD | 0.336   | 1.266 | 0.783 2.049   |
| Pump failure death |          |     |               |
| LBBB vs. no IVCD | 0.015   | 1.600 | 1.097 2.335   |
| RBBB vs. no IVCD | 0.0001  | 2.620 | 1.603 4.283   |
| LAFB vs. no IVCD | 0.139   | 1.492 | 0.878 2.535   |

AMI, acute myocardial infarction; CI, confidence interval; eGFR, estimated glomerular filtration rate (MORD method); HR, hazard ratio; ICD, implantable cardioverter-defibrillator; IVCD, intraventricular conduction defect; LA, left atrial; LAFB, left anterior fascicular block; RAAS blockade: renin–angiotensin–aldosterone system blockade; RBBB, right bundle branch block.

aAdjusted for: age, ICD, CRT, signs of left HF, signs of right HF, LVEF, diabetes mellitus, prior AMI, LV mass index, haemoglobin, eGFR, and loop diuretics.

bAdjusted for: age, ICD, CRT, signs of left HF, signs of right HF, LVEF, diabetes mellitus, prior AMI, LV mass index, indexed LA diameter, mitral valve regurgitation III/IV, haemoglobin, beta-blockers, and RAAS blockade.

cAdjusted for: age, ICD, CRT, signs of left HF, signs of right HF, LVEF, diabetes mellitus, LV mass index, indexed LA diameter, haemoglobin, eGFR, beta-blockers, and RAAS blockade.
statistical significance. In contrast, prescription of beta-blockers and RAAS blockers predicted significant benefit on mortality risk (Supplementary material, Table S1).

During the follow-up, 65 de novo cases of IVCDs were recorded: 26 LBBB, 20 RBBB, and 19 LAFB. Patients with new onset of IVCDs continued to be ascribed to the free of IVCDs group because patient categorization was done according to the inclusion ECG.

Discussion

This study provides integrative information on the clinical and prognostic influence of the most frequent IVCDs in a cohort of patients with chronic HF. Differences in the clinical profile and 2-month risk of readmissions and cause of death were observed among patients with LBBB, RBBB, and LAFB, and in those without IVCDs.

Clinical characteristics

A clinical phenotype characterized by LV dilation with markedly depressed systolic function, advanced mitral valve regurgitation, and history of dilated cardiomyopathy was more often observed in patients with LBBB. In contrast, patients with RBBB presented with overt signs of right and left HF, more depressed RV motion at echocardiography, and more frequently reported a history of coronary heart disease. On the other hand, patients with LAFB showed intermediate degrees of structural LV derangements with respect to LBBB and RBBB, although they still presented marked signs of left and right HF and advanced NYHA functional class. Patients free of IVCDs were more often women with less enlarged left ventricles and less depressed LVEF, suggesting a predominance of a diastolic rather than a systolic dysfunctional substrate. The clinical–ECG associations described in this study have not been previously recognized, due to the lack of studies analysing more than two IVCDs in the same cohort. On the other hand, not all studies assessing the prognostic value of LBBB and RBBB in the same series of patients \(^{8,10-12}\) have provided echocardiographic information, and, moreover, specific data on relevant structural cardiac features such as LV mass, LV diameter, or LA size, or resynchronization therapies were not reported in these studies. However, specific findings such as the observation of a more advanced mitral valve regurgitation in patients with LBBB in one study,\(^{9}\) or the higher prevalence of previous myocardial infarction in HF patients with RBBB reported in three studies\(^ {8,11,12}\) are in agreement with the clinical patterns found in our patients. Furthermore, there is a coherence between the pharmacological treatment instituted in our patients and their clinical phenotype, since, in accordance with the predominance of LV dilation in patients with LBBB, they received more CRT and beta-blockers. Likewise, patients with RBBB received more loop diuretics in consonance with their advanced signs of congestive HF and greater percentage of depressed RV motion at echocardiography. It is therefore unlikely that the clinical associations observed in our study were fortuitous as they share clinical and pathophysiological plausibility. The mechanistic foundation for the association between LBBB and LV dilation is provided by experimental observations demonstrating that LBBB itself is able to induce LV dilation.\(^ {7}\) On the other hand, LV dilation could secondarily induce LBBB because the increased wall stress linked to the dilated cavity\(^ {25}\) may overstretch the left bundle branch fibres and then impair conduction through them. An example of impairment of bundle branch conduction secondary to ventricular dilation is the occurrence of RBBB in the course of pulmonary thrombo-embolism.\(^ {25}\)

Outcomes

The prognosis of LBBB has been assessed in several clinical registries\(^ {7-12,26,27}\) and although most of them found a worse outcome in patients with LBBB, other studies reported a more unfavourable prognosis linked to RBBB. In a cohort of 5517 patients with congestive HF,\(^ {7}\) patients with LBBB (n = 1391) showed a higher 1-year all-cause mortality and sudden death than controls free of LBBB. An unfavourable prognosis of LBBB was also observed in a cohort of patients with acute HF 1 year after admission.\(^ {9}\) However, studies simultaneously comparing the prognosis of LBBB and RBBB in the same cohort of patients have not afforded consistent results since some of these studies report a more unfavourable prognosis in LBBB, whereas others found increased mortality risk in patients with RBBB. Indeed, in a series of 9082 hospitalized HF patients with LBBB (n = 1480) and RBBB (n = 651) followed for 5 years, the adjusted risk of death was higher in patients with LBBB than in those with RBBB.\(^ {10}\) Likewise, in a cohort of 110 000 subjects free of cardiovascular disease followed up for 9.5 years, 310 subjects developed BBB (LBBB, 112; RBBB, 198), and those with LBBB presented increased prevalence of cardiovascular disease and higher cardiac mortality than age- and sex-matched controls.\(^ {13}\) In contrast, a study including 3200 hospitalized patients with acute HF showed that rehospitalization and death occurred more frequently in patients with RBBB (n = 118) than in those with LBBB (n = 107).\(^ {12}\) Likewise, in a cohort of 1888 patients with HF and LVEF <50%, RBBB (n = 193) had a 4-year all-cause mortality higher than LBBB (n = 306).\(^ {11}\) Finally, a comparable all-cause mortality of LBBB and RBBB was observed in patients with decompensated HF 23 months after being admitted to an intensive care unit.\(^ {8}\)

Over the last 10 years, randomized trials have consistently demonstrated a significant reduction in morbidity and mortality in patients with mild to advanced HF and prolonged QRS complex duration treated with CRT,\(^ {28,29}\) particularly when an ICD is added to the CRT.\(^ {25}\) In our study, the beneficial effect of CRT on mortality in the Cox model did not reach statistical significance even though 83% of the 140 CRT-implanted patients had an added ICD and, therefore, an optimal therapy. A rate of CRT implantation higher than ours could theoretically mitigate the worse prognosis of IVCD, but this cannot be ascertained because the CRT implantation rate is not reported in the above-reviewed studies on the prognosis of BBB. Moreover, CRT implantation rates were largely heterogeneous across the European countries: in 2006 (our study began in January 2007), > 80 devices per million inhabitants were implanted in six countries, whereas < 40 devices per million inhabitants were implanted in another four, including Spain.\(^ {30}\)

In summary, our study reveals that both LBBB and RBBB are associated with a higher 21-month incidence of cardiac death and pump failure death than for patients with LAFB and patients free of IVCDs. Thus, in addition to the advanced therapies that are currently applied to patients with LBBB (i.e. LV...
Conflict of interest:
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Appendix 1. REDINSCOR

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References
1. Xiao HB, Lee CH, Gibson DG. Effect of left bundle branch block on diastolic function in dilated cardiomyopathy. Br Heart J 1991;66:443–447.
2. Grines CL, Bashore TM, Boudoulas H, Olson S, Shaffer P, Woolsey CF. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation 1989;79:845–853.
3. Kang SJ, Song KJ, Yang HS, Song JM. Parkinson’s disease and left bundle-branch block: a prospective study. Jpn J Med 2009;48:220–224.
4. Li CH, Carreras L, Arribas F. Clinical implications of left bundle branch block: a meta-analysis of 23 studies. J Am Coll Cardiol 2003;41:1425–1435.
5. Vernooy K, Verbeek XA, Peschar M, Crijns HJ, Arts T, Cornelussen RN, Prinzen FW. Left bundle branch block induces ventricular remodelling and functional septal hypoperfusion. Eur Heart J 2005;26:91–98.
