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Left bundle branch block in dilated cardiomyopathy with intermediate left ventricular dysfunction: Clinical phenotyping and outcome correlates

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ABSTRACT

Background: Left bundle branch block (LBBB) negatively affects prognosis in heart failure patients with a reduced left ventricular ejection fraction (LVEF). Less is known about the prognostic role of LBBB in dilated cardiomyopathy (DCM) with intermediate LVEF (between 36% and 50%). We sought to assess the role of LBBB in optimally treated DCM patients with mildly to moderately reduced LVEF and to determine the possible variables associated with subsequent LVEF reduction.

Methods: We retrospectively analyzed DCM patients with LVEF >35% after 3-to-9 months of optimal medical treatment (OMT) consecutively evaluated from 1990 to 2010. All-cause mortality or heart transplantation (D/HTx) and sudden cardiac death (SCD) or major ventricular arrhythmias (MVA) were considered as outcome measures. LVEF deterioration during follow-up was also considered.

Results: Among 280 (49%) patients that met the study criteria, 76 had LBBB (27%). During a mean follow-up of 151 months, the rates of D/HTx and SCD/MVA were similar between LBBB and not LBBB patients (p value = 0.52 and $p = 0.39$, respectively). Twenty-six out of 76 (34%) patients with LBBB experienced LVEF deterioration below 36%. The persistence of moderate-severe mitral regurgitation (MR), left atrial end-systolic area index and LV end-diastolic volume index emerged as independent predictors of LVEF deterioration and were associated with an increased risk of D/HTx during follow-up.

Conclusions: LBBB does not affect mortality in DCM patients with intermediate LVEF after OMT. However, among these patients those with persistent significant MR, left atrial and LV remodeling carries a higher risk of LVEF deterioration during follow-up.

1. Introduction

Dilated cardiomyopathy (DCM) is a heart muscle disease characterized by reduced ejection fraction (LVEF) in absence of abnormal loading conditions or coronary artery disease which can explain the dysfunction [1]. Structural and morpho-functional ventricular remodeling is often associated with delayed electrical activation and prolongation of QRS, ultimately leading to left bundle branch block (LBBB) [2]. In patients with DCM, LBBB has been largely associated with higher morbidity and mortality [3]. Cardiac resynchronization-therapy (CRT) on top of OMT demonstrated the potential to reverse the negative effects of LBBB [4]. However, current guidelines recommend CRT only for heart failure (HF) patients with LBBB and persistent severe systolic dysfunction (LVEF ≤35%) [5,6] after 3-to-9 months of OMT. Nevertheless, the impact of LBBB in patients with HF and intermediate LVEF (i.e. 36–50%) remains still debated. Despite recent analysis suggesting a possible prognostic role of LBBB in this subgroup [7], specific data in DCM patients are lacking.

Therefore, the present study aimed to investigate the prognostic role of LBBB in patients with DCM and intermediate LVEF, and to

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characterize the patients exposed to higher risk of late LVEF deterioration within this subgroup of DCM with LBBB and intermediate impairment of systolic function.

2. Methods

2.1. Study population and study design

DCM patients consecutively evaluated in the Heart Muscle Disease Registry of Trieste from 1 January 1990 to 31 December 2010 were retrospectively analyzed. Study population consisted of patients with LVEF between 36% and 50% after 3-to-9 months of OMT (i.e. enrolment). Furthermore, no patients had a pacemaker or a CRT at the time of enrolment.

DCM was defined as previously described excluding ischemic or hypertensive heart diseases, active myocarditis, alcoholic cardiomyopathy, significant organic valve diseases, tachycardia-induced cardiomyopathy, peripartum cardiomyopathy, congenital heart diseases, sarcoidosis, and advanced systemic diseases affecting short-term prognosis [1,8,9].

Left bundle branch block was defined as QRS duration ≥120 ms with the presence of established morphological criteria [10].

OMT was defined as ACE inhibitors/ARBs and beta-blockers titrated to the highest tolerated dose, if not contraindicated. Moreover, since 1998, ICDs were introduced for primary prevention of sudden cardiac death (SCD) in high-risk patients (persistent LVEF ≤35% and NYHA functional class II–III despite optimal medical therapy) [11]. Since 2005 CRT was systematically implanted in symptomatic patients with LBBB and LVEF ≤35% despite 3-to-9 months of OMT [10].

The study analyzed the incidence of all-cause mortality and heart transplantation (D/HTx) and of arrhythmic outcomes, defined as SCD or major ventricular arrhythmias (MVA) (sustained ventricular tachycardia, aborted SCD or appropriate ICD interventions), in patients with or without LBBB [12]. Furthermore, LVEF deterioration during follow-up was considered in the analysis in order to identify possible predictors of adverse remodeling during the follow-up.

Follow-up started from 3-to-9 months after the initial evaluation and ended on 31 December 2016 or at the event time.

The institutional ethics board approved the study and informed consent was obtained under the institutional review-board policies of the hospital administration.

2.2. Echocardiographic study

Left ventricular dimensions, systolic and diastolic function were assessed according to international guidelines [13]. Specifically, LV volumes and LVEF were calculated by Simpson's biplane method. All volumes were indexed according to body surface area. Transmitral E and A wave velocities were measured using pulsed wave Doppler at the level of the mitral leaflet tips. The LV filling pattern was classified as restrictive (RFP) in the presence of E-wave deceleration time <120 ms or E/A ≥2 associated with E-wave deceleration time ≤150 ms [10]. Right ventricular dysfunction was defined by a right ventricular fractional area change <35%. Left atrial end-systolic area was calculated from apical view. Mitral regurgitation (MR) was assessed using a multiparametric approach, by measuring the effective regurgitant volume or orifice area measured by the proximal isovelocity surface area, whenever feasible, or the vena contracta width at color-flow Doppler, and graded on a 3-point scale according to current recommendations. Significant mitral regurgitation was considered if the regurgitant jet was classified as moderate to severe [14,15].

2.3. Statistical analysis

Summary statistics of clinical and instrumental variables were expressed as mean and standard deviation, median and interquartile range, or counts and percentage, as appropriate. Comparisons between groups were made by the analysis of variance (ANOVA) test on continuous variables, using the Brown–Forsythe statistic when the assumption of equal variances did not hold, or by the non-parametric median test when necessary; the Chi-square test was calculated for discrete variables. Kaplan-Meier survival curves for survival free from death and HTx were estimated and compared between groups by means of the Log-rank test. Cumulative incidence curves of SCD/MVAs were estimated and compared between groups taking into account death for other cause or HTx as a competing risk. A stepwise uni- and multivariable cause-specific Cox regression was performed in order to find best predictors of EF worsening (EF ≤ 35%) during follow-up, starting from the list of significant and clinically relevant parameters which emerged at univariable analysis. In order to check for multicollinearity, Spearman rho correlation coefficient was computed among predictors selected by the stepwise procedure. In the cause-specific Cox regression model, the outcome of interest was EF worsening (i.e. EF ≤35%) during follow-up among patients with LBBB. In the Kaplan-Meier analysis, the outcome of interest was death or HTx. Finally, in the cumulative incidence curves, the outcome of interest was SCD/MVAs vs. death for other causes or HTx, treated as competing risks. Percentages of censoring corresponded to patients that did not experience the outcome of interest for each of the above-defined end-points until the administrative study closure date (i.e. 31 December 2016). The IBM-SPSS statistical software version 19 and the software R (R Foundation for Statistical Computing, Vienna, Austria; URL https://www.r-project.org/) were used for the analyses.

3. Results

3.1. Persistent LBBB in intermediate LV dysfunction: characterization and prognostic role

Among 572 patients initially evaluated, 285 (50%) were excluded because of persistent severe LV dysfunction (LVEF ≤ 35%) despite OMT and 7 (1%) were excluded for the occurrence of death or heart transplantation before re-evaluation. The analysis was performed on 280 patients with intermediate LVEF after 3-to-9 months of OMT. Among them, 27% of patients (n = 76) had persistent LBBB (Supplementary Fig. 1). They were older, with more impaired LVEF, larger left ventricular volume and left atrial area compared to those without LBBB (Table 1). There was no cross-over of patients with initial non-LBBB pattern on their ECG that went on to develop LBBB or require pacing in the 3-to-9 months of OMT. After a median follow-up of 151 months (interquartile range [IQR] 97–233) 16 patients (21%) in the LBBB group died or underwent HTx (14 died, 2 underwent HTx), while 51 patients (25%), in the group without LBBB, died or underwent HTx (37 died, 14 underwent HTx) (p value = 0.52) (Fig. 1). Furthermore, only 2 patients with LBBB experienced SCD/MVAs (2.6%, n = 1 SCD and n = 1 MVA) vs. 10 non-LBBB (4.9%; n = 8 SCD and n = 2 MVA) (p value = 0.39, Supplementary Fig. 2). In the Kaplan-Meier analysis, censored patients were 213, 76%. In the competing risk analysis, patients that survived free from HTx and MVAs until the administrative study closure date were 212 patients, 76%.

3.2. Persistent LBBB in intermediate LV dysfunction: identification of CRT candidates

Among patients with LBBB (n = 76), 34% of patients (n = 26) during the follow-up experienced LVEF worsening below 36%. Percentage of censoring (i.e. patients that did not experience the EF worsening in this subgroup or that die or were transplanted during follow-up) was 66% (50 patients). At 3-to-9 months evaluation, those patients presented longer QRS duration, larger LV volumes and left atrial area and lower LVEF compared to those who didn't experience worsening LVEF (Supplementary Table 1).

At multivariable analysis, the persistence of moderate-to-severe mitral regurgitation (MR) [hazard ratio (HR) 3.004; 95% confidence interval (CI) 1.130–7.989, $p = 0.027$], left atrial end-systolic area index [HR 1.233; 95% CI 1.038–1.464, $p = 0.017$] and left ventricular end-diastolic volume index [HR 1.027; 95% CI 1.008–1067, $p = 0.017$] emerged as independent predictors of LVEF worsening below 36% (Table 2 and Fig. 2). The presence of those predictors is additively associated with higher risk of D/HTx (Supplementary Fig. 3). The highest degree of positive linear correlation between predictors in the multivariable model was a Spearman rho = 0.33 (between left atrial area and moderate to severe MR), indicating a moderate grade of linear association.

Moreover, after a median follow-up of 151 months (IQR 97–233), patients who experienced LVEF worsening had a trend towards a higher rate of D/HTx compared to the others, 35% and 14% respectively ($p = 0.07$). Notably, 13 patients (50%) in the LBBB group who developed severe LV dysfunction underwent CRT implantation.

4. Discussion

4.1. Main findings

DCM is often considered as a distinct form of reduced ejection fraction HF, due to its specific characteristics [16]. In this setting, LBBB may be either causative or secondary to the underlying disease. Indeed, LBBB may be the cause of non-ischemic cardiomyopathy and, in selected patients, resynchronization is often associated with disease control and LVEF normalization [17,18]. On the other hand, impairment of

the conduction system and intraventricular conduction delay, often leading to LBBB, are frequently bystanders in DCM patients [2].

In DCM, the new onset of LBBB during follow-up has been related with worse outcomes due to progressive cardiac remodeling [3]. The clinical role of newly acquired LBBB was prospectively examined also using the Framingham Study population, in which the appearance of intraventricular conduction delays independently contributed to an increased risk of cardiovascular mortality [19]. As a consequence, CRT has rapidly become a pivotal treatment in those patients [20,21]. The LBBB pattern is currently the main conduction abnormality and the most robust ECG criterion for the selection of candidates to CRT [22].

Nevertheless, the role of LBBB in patients with LVEF >35% remains debated, also due to the heterogeneity of the populations included in the studies [7,22]. Specifically, in DCM this issue is still widely unexplored. In our cohort of patients with DCM and intermediate left ventricular dysfunction, LBBB was not associated with worse prognosis though a consistent number of patients (35%) experienced significant deterioration of LVEF during follow-up. However, persistence of moderate-to-severe mitral regurgitation, significant left ventricular and atrial enlargement despite OMT emerged as independent predictors of disease progression and possible tools for early identification of CRT candidates in patients with intermediate LVEF after an adequate period of OMT.

4.2. Prognostic role of persistent LBBB in intermediate left ventricular dysfunction in DCM patients

The prognostic role of LBBB in patients with mild-to-moderate LV dysfunction was recently observed in a large DCM population [7]. Witt et al. demonstrated that patients with LBBB and LVEF >35% have poorer clinical outcomes compared to those without LBBB, suggesting a possible CRT positive effect regardless of the severity of LV dysfunction [7]. However, the study was conducted mostly in patients with ischemic DCM (81%), narrowing the results in this specific population of DCM patients. Our results, conducted on a well selected non ischemic DCM population, did not confirm the role of LBBB in DCM patients with intermediately depressed LVEF, suggesting a different mechanism underlining the condition and the need of considering differently the patients on the basis of their HF etiology. During follow-up, 50% of the LBBB group who developed significant LV dysfunction underwent CRT implantation. It is interesting that this treatment can drive better outcomes and may have modified the natural course of the disease process in our study population.

4.3. Persistent LBBB in intermediate left ventricular dysfunction in DCM patients: identification of possible CRT candidates

Despite the apparently neutral effect of LBBB in DCM patients with intermediately depressed LVEF, specific subgroups of patients may develop a worse ventricular function during the follow-up. Furthermore, the development of severely depressed LVEF was associated with an increased mortality rate in our cohort. In those patients, the early identification of other predictors, beyond conduction abnormalities, appears fundamental to guide the best tailored treatment, including CRT. Indeed, LVEF and LBBB, when considered alone, appear insufficient for the risk stratification in DCM patients [23]. From our analysis, persistent moderate to severe mitral regurgitation, significant left ventricular and atrial enlargement were able to identify high-risk subgroups in terms of both LVEF decrease and D/HTx during follow-up (see Fig. 2 and Supplementary Fig. 3). Those patients could represent potential early CRT candidates regardless to intermediate LVEF. They in fact could experience greater benefit of device implantation. This hypothesis deserves obviously future focused, possibly prospective, studies.

The persistence of left ventricular dilatation despite optimal medical treatment, as well as the presence of either moderate to severe mitral regurgitation or enlarged left atrium might indicate a more advanced

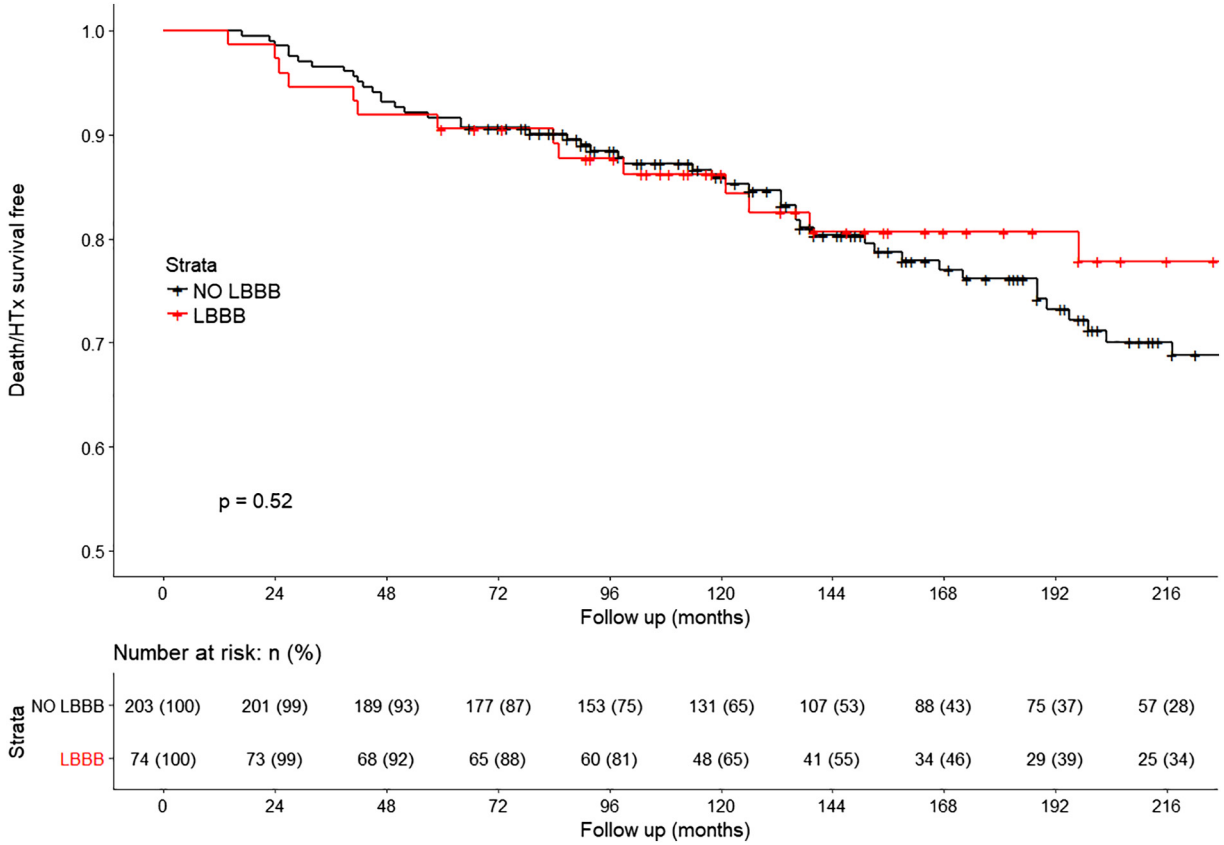

Fig. 1. Kaplan-Meier curve of survival free from death/HTx in DCM patients according to LBBB presence on ECG. HTx = heart transplantation; LBBB, left bundle branch block.

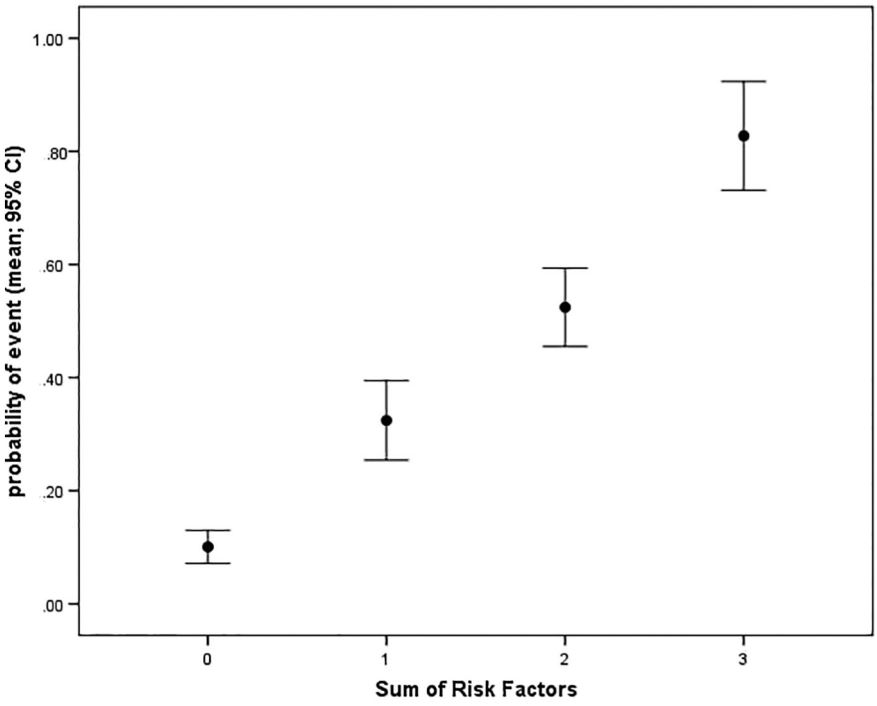

Fig. 2. Estimated risk of development of severe LV dysfunction on the basis of number of independent predictors in our population with left bundle branch block. Note that patients presenting persistent moderate to severe mitral regurgitation, enlarged left ventricular end-diastolic volume [>79 ml/m^2, i.e. median value of our population] and enlarged left atrial end-systolic area [>13 cm^2/m^2, i.e. median value of our population] carried a risk of LVEF worsening during follow-up >70%.

myocardial damage. Particularly, significant mitral regurgitation appears to be an independent predictor of progressive adverse remodeling [24] and a rapid improvement of functional mitral regurgitation after CRT implantation in DCM patients has already been reported [25]. Furthermore, left atrial dilation despite therapy may indicate persistent diastolic dysfunction and elevated filling pressures secondary to advanced myocardial disease with high probability of adverse progression towards poor long-term outcomes [26]. Resynchronization of the papillary muscle, modification of mitral-annulus contraction and increasing ventricular contractility seem to be the underlying positive effects of CRT implantation in those subgroups of patients [27]. Notably, longer QRS duration was significantly associated with the subsequent LVEF deterioration at the univariate analysis. However, its prognostic implication was less strong when combined in the multivariable analysis. Those findings seem to confirm literature data for which the presence of LBBB per se is a poorer predictor than QRS duration secondary to LBBB, both in terms of prognosis and response to CRT [28]. Lastly, since a moderate grade of positive linear correlation was present between predictors selected by the stepwise algorithm, a certain degree of overfitting in the estimates from the multivariable model cannot be excluded. As it is expected, correlation between measures is unavoidable in this kind of data, and our results need to be validated in external populations.

Table 1
Patient characterization at 3-to-9 months evaluation stratified by the persistence of LBBB.

	Total population 280	No LBBB 204 (73%)	LBBB 76 (27%)	*p*
Age (years)	46 ± 14	43 ± 13.5	52 ± 12	<0.001
Male sex, n (%)	190 (68)	136 (67)	46 (61)	0.43
SBP (mm Hg)	128 ± 17	125 ± 16	133 ± 17	<0.001
Heart rate (bpm)	68 ± 10	68 ± 10	67 ± 10	0.33
QRS length (ms)	109 ± 29	95.6 ± 17	146 ± 23	<0.001
NYHA III–IV, n (%)	8 (3)	6 (3)	2 (3)	0.46
LVEF (%)	43.4 ± 4.5	43.8 ± 4.6	42.5 ± 4.2	0.037
LVEDDI (mm/m^2)	31.9 ± 4.9	32 ± 4.6	31.9 ± 5.7	0.59
LVEDVI (ml/m^2)	74.9 ± 22.9	73.4 ± 22	79 ± 24.4	0.061
LAESAI (cm^2/m^2)	11.9 ± 2.9	11.7 ± 2.8	12.4 ± 3.2	0.03
sPAP (mm Hg)	25.9 ± 8.2	24.6 ± 5.8	29.2 ± 12.2	0.07
RVD, n (%)	12 (4)	11 (5)	1 (1)	0.13
Moderate-severe MR, n (%)	48 (17)	35 (17)	13 (17)	0.93
RFP, n (%)	10 (4)	6 (3)	4 (5)	0.35
Beta-blockers, n (%)	255 (91)	188 (92)	68 (89)	0.29
ACE-inhibitors-ARBs, n (%)	264 (94)	180 (88)	68 (89)	0.59
Mineralocorticoid receptor antagonist, n (%)	16 (6)	14 (7)	2 (3)	0.34
Diuretics, n (%)	83 (30)	61 (30)	22 (29)	0.87

Values are expressed as mean ± SD or median with interquartile range as appropriate, and as percentage. All reported parameters have been evaluated at 3-to-9 months follow-up.
Legend: SBP, systolic blood pressure; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVEDDI, left ventricular end-diastolic diameter index; LVEDVI, left ventricular end-diastolic volume index; LAESAI, left atrial end-systolic area index; RVD, right ventricular dysfunction; MR, mitral regurgitation; RFP, restrictive filling pattern; sPAP, systolic pulmonary arterial pressure.

Table 2
Univariate and multivariate Cox regression analysis: predictors of LVEF worsening ≤35% in patients with LBBB and intermediate systolic dysfunction at 3-to-9 months evaluation.

	Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*
Age[a]	1.023	0.987–1.059	0.209			
SBP[a]	0.999	0.985–1.013	0.925			
NYHA III–IV	0.048	0.000–5965	0.716			
QRS length[a]	1.021	1.005–0.038	0.012			
QRS length ≥ 150 ms	1.486	0.642–3.439	0.354			
QRS length ≥ 180 ms	3.495	1.490–8.199	0.004			
NSVT	3.952	1.505–10.379	0.005			
LVEDVI[a]	1.022	1.005–1.039	0.010	**1.027**	**1.008–1.067**	**0.017**
LVEDDI[a]	1.027	0.978–1.079	0.287			
LVEF[a]	0.894	0.807–0.992	0.034			
RVD	0.047	0.000–4670	0.603			
Moderate to severe MR	2.720	1.131–6.541	0.025	**3.004**	**1.130–7.989**	**0.027**
RFP	6.103	1.217–30.600	0.028			
LAESAI[a]	1.260	1.078–1.473	0.004	**1.233**	**1.038–1.464**	**0.017**

Legend: SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; LVEDDI, left ventricular end-diastolic diameter index; LVEDVI, left ventricular end-diastolic volume index; LAESAI, left atrial end-systolic area index; RVD, right ventricular dysfunction; MR, mitral regurgitation; RFP, restrictive filling pattern.
Bold values indicate statistically significance at $p < 0.05$.
[a] Hazard ratio estimation is referred to every unit increase or decrease for continuous variables.

4.4. Limitations

This retrospective study needs an external validation to be confirmed. Enrollment of patients in a tertiary referral Centre for cardiomyopathies and HF may constitute selection bias of the population analyzed. Furthermore, the results may be influenced by the low percentages of mineralcorticoid antagonists and NYHA III–IV patients and the relatively low event rate in the very long term, as previously described in non-ischemic DCM patients [29]. Systematic data on natriuretic peptides, genetics, 3D-echocardiography, strain and strain rate, cardiac magnetic resonance were not available. They are needed for future larger studies. Regarding left atrial measures, the left atrial end-systolic volume has been systematically recorded in our Center only since 2013.

Regarding the statistical analysis, since the low number of events, we verified results from the stepwise algorithm with those from a penalized Cox model [30], and the same variables were selected.

Finally, we acknowledge the small sample size, particularly concerning the risk of development of LV dysfunction. However, to the best of our knowledge this is one of the largest DCM population in which the impact of LBBB in patients with intermediate systolic dysfunction under optimal medical treatment has been investigated. Further investigations are required to confirm our data in larger cohorts of patients.

5. Conclusions

LBBB does not affect mortality in DCM patients with intermediate LVEF after optimal medical therapy. However, in those patients, persistent significant mitral regurgitation and enlarged left chambers emerged as pivotal features for the identification of higher risk patients with LVEF deterioration during the follow-up, which may benefit from an early resynchronization regardless the systolic function.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.005.

Conflict of interest

None.

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