


# Prevalence, clinical and instrumental features of left bundle branch block-induced cardiomyopathy: the CLIMB registry

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## Abstract

**Aims** Although increasingly recognized as a distinct pathological entity, left bundle branch block-induced cardiomyopathy (LBBB-ICMP) is not included among the possible aetiologies of acquired dilated cardiomyopathies (DCM). While diagnostic criteria have been proposed, its recognition remains principally retrospective, in the presence of clinical and instrumental red flags. We aimed to assess the prevalence and clinical and instrumental features of LBBB-ICMP in a large cohort of patients with DCM.

**Methods and results** We analysed a cohort of 242 DCM patients from a two-centre registry. Inclusion criteria were age > 18, non-ischaemic or non-valvular DCM, and LBBB on electrocardiogram. LBBB-ICMP was defined according to previously proposed diagnostic criteria: (i) neither family history nor clinically identifiable potential causes for DCM; (ii) negative genetic testing; (iii) echocardiographic features including non-severe chamber dilation, normal absolute and relative wall thickness, marked dyssynchrony, and normal right ventricular function; and (iv) absence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR). From the entire cohort, we identified 30 subjects (similar in terms of New York Heart Association class I or II in 80% vs. 75%,  $P = 0.56$ ; QRS width of  $150 \pm 22$  vs.  $151 \pm 24$  ms,  $P = 0.82$ ; and cardiac remodelling of baseline end-diastolic diameter  $66 \pm 8$  vs.  $65 \pm 10$  mm,  $P = 0.53$ ) with a comprehensive dataset including CMR and genetic testing, required to verify the presence of the diagnostic criteria proposed for LBBB-ICMP. The main characteristics of this subgroup were 73% males, age  $45 \pm 13$  years, left ventricular ejection fraction (LVEF)  $30 \pm 10\%$ , LGE in 38% of patients, and QRS complex of  $150 \pm 22$  ms. Patients were under guideline-directed medical therapy, and 57% of them were treated with cardiac resynchronization therapy (CRT). Two patients (6.67%, 50% males, age  $53 \pm 13$  years) fulfilled the diagnostic criteria proposed for LBBB-ICMP. After a follow-up of 44 (12–76) months, LVEF was normal and QRS width significantly reduced (from  $154 \pm 25$  to  $116 \pm 52$  ms) in patients with LBBB-ICMP. Both patients were under optimal medical treatment, and one was implanted with CRT-D. Neither of the two patients experienced death, malignant ventricular arrhythmia, or heart failure hospitalization at follow-up.

**Conclusions** Left bundle branch block-induced cardiomyopathy emerges as a distinct pathological entity, promptly identifiable in a minority but not negligible proportion of patients with newly diagnosed DCM and LBBB, using a series of diagnostic criteria including CMR and genetic testing. Further studies are needed to better elucidate the clinical course of LBBB-ICMP.

**Keywords** Dilated cardiomyopathy; Left bundle branch block; Left bundle branch block-induced cardiomyopathy

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## Background

Left bundle branch block-induced cardiomyopathy (LBBB-ICMP) is an increasingly recognized pathological entity with potentially distinct therapeutic implications.<sup>1,2</sup> Nevertheless, it is not included among the possible aetiologies of acquired dilated cardiomyopathies (DCM), nor among the unclassified cardiomyopathies.<sup>3,4</sup> Although diagnostic criteria have been proposed,<sup>2,5</sup> its recognition remains principally retrospective, in the presence of clinical and instrumental red flags. LBBB-ICMP prevalence, clinical course, and early management strategies are therefore largely unknown.

## Aims

We sought to assess the prevalence of LBBB-ICM according to our previously proposed diagnostic criteria<sup>2</sup> in two cohorts of patients with DCM and to investigate the clinical course of the disease including potential differences as regards other aetiologies.

## Methods

We analysed a cohort of DCM patient participants of a two-centre Italian registry study named CLIMB (CLInical registry of dilated cardioMyopathies with left Bundle branch block). Patients had been consecutively recruited since 1995. Inclusion criteria were age > 18, non-ischaemic or non-valvular DCM [defined by the presence of left ventricular (LV) or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions or coronary artery disease sufficient to cause global systolic impairment],<sup>3</sup> and LBBB on electrocardiogram (ECG) (defined according to American Heart Association<sup>6</sup> criteria and those proposed by Strauss).<sup>7</sup> The study aimed to assess the prevalence and clinical and instrumental features of LBBB-ICMP. We defined LBBB-ICMP according to the diagnostic criteria previously proposed: (i) neither family history nor clinically identifiable potential causes for DCM; (ii) negative genetic testing; (iii) echocardiographic features including non-severe chamber dilation according to international recommendations,<sup>8</sup> normal absolute and relative wall thickness, marked dyssynchrony on echocardiography defined as the presence of visually assessed septal flash or apical rocking,<sup>9</sup> or as a significant septal-to-lateral wall delay with colour-coded tissue Doppler imaging,<sup>10</sup> and normal right ventricular function; and (iv) absence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR).<sup>2</sup>

## Results

From the entire cohort of 242 patients, we identified 30 subjects (similar in terms of New York Heart Association class, cardiac remodelling, and QRS width) with a comprehensive dataset including CMR and genetic testing, required to verify the presence of the diagnostic criteria<sup>2</sup> proposed for LBBB-ICMP. The characteristics of this subgroup are reported in *Table 1* [73% males, age  $45 \pm 13$  years, left ventricular ejection fraction (LVEF)  $30 \pm 10\%$ , LGE in 38% of patients, and QRS complex of  $150 \pm 22$  ms]. Patients were under guideline-directed medical therapy, and 57% of them were treated with cardiac resynchronization therapy (CRT).

Two patients (6.67%, 50% males, age  $53 \pm 13$  years) fulfilled the diagnostic criteria proposed for LBBB-ICMP<sup>2</sup> (*Table 1*). To be precise, their ECG was characterized by 'true' LBBB,<sup>6,7</sup> already present at diagnosis. They presented non-severe LV dilation, normal relative wall thickness, absence of severe diastolic dysfunction, and normal right ventricular function, according to international echocardiographic cut-off values. Moreover, no LGE or likely pathogenic genetic variants were found. After a follow-up of 44 (12–76) months, LVEF was normal and QRS width significantly reduced (from  $154 \pm 25$  to  $116 \pm 52$  ms) in patients with LBBB-ICMP. Both were under optimal medical treatment, and one was implanted with CRT-D. During the follow-up period, neither of the two patients experienced death, malignant ventricular arrhythmia, or heart failure hospitalization.

## Discussion

Our findings suggest that the diagnostic criteria proposed for LBBB-ICMP<sup>2</sup> seem to (i) identify LBBB-ICMP in a minority (almost 7%) of patients presenting with both DCM and LBBB, apparently carrying a benign outcome, and (ii) be highly specific when applied to large cohorts of patients with DCM and LBBB.

Although preliminary, the present data are new, due to the lack of a universal consensus regarding diagnostic criteria for LBBB-ICMP. Previous studies reported differences in prevalence of LBBB-ICMP. Vaillant *et al.* reported 1.6% in their retrospective analysis,<sup>5</sup> while other studies focusing on the response to treatments in patients with LBBB and LV dysfunction did not provide significant data.<sup>11,12</sup> Moreover, the inclusion criteria of those studies were less strict as they mainly considered echocardiographic data, while CMR and genetic features were not available.<sup>5,11,12</sup>

Our study has some limitations. First, the retrospective analysis over a long enrolment period and the strict diagnostic criteria proposed limited the sample size. However, to the best of our knowledge, this is one of the largest cohorts of

**Table 1** Characteristics of the study population and the two left bundle branch block-induced cardiomyopathy patients

Variable	Entire cohort <sup>a</sup> (n = 242)	Patients with both CMR and genetic data (n = 30)	LBBB-induced cardiomyopathy (n = 2; 7%)
Males, n (%)	164 (68)	22 (73)	1 (50)
Age (years)	53 ± 13.5	45 ± 13	53 ± 13
NYHA functional class I or II, n (%)	182 (75)	24 (80)	2 (100)
Chronic kidney disease, n (%)	15 (6)	1 (3)	0 (0)
<b>Favouring factors/possible aetiologies</b>			
<b>None ('idiopathic')</b>	123 (52)	17 (59)	2 (100)
Familial (Gen +)	11 (5)	5 (17)	0 (0)
Arterial hypertension	59 (25)	3 (10)	0 (0)
Inflammatory	20 (8.5)	4 (14) <sup>b</sup>	0 (0)
Toxins (e.g. alcohol and chemotherapy)	20 (8.5)	0 (0)	0 (0)
Tachycardia induced	5 (2)	1 (3) <sup>b</sup>	0 (0)
<b>Family history of DCM, n (%)</b>	41 (17)	7 (23)	0 (0)
<b>Genetic mutation (none/ VUS/pathologic), n (%)</b>	14 (22)/21 (32)/30 (46)	6 (20)/10 (33)/14 (47)	2 (100)/0 (0)/0 (0)
<b>ECG</b>			
Sinus rhythm, n (%)	197 (93)	29 (97)	2 (100)
Baseline QRS in V2/aVL (ms)	151 ± 24	150 ± 22/143 ± 24	154 ± 25/159 ± 23
<b>LBBB (AHA/Strauss criteria), n (%)</b>	133 (64)/132 (64)	16 (53)/15 (50)	2 (100)/2 (100)
<b>LBBB already present at diagnosis, n (%)</b>	186 (82)	23 (82)	2 (100)
<b>Device therapies</b>			
AICD/CRT-D/CRT-P, n (%)	49 (20)/84 (35)/6 (2)	4 (13)/17 (57)/0 (0)	0 (0)/1 (50)/0 (0)
<b>Medical therapies</b>			
ACE-I or ARB or ARNi, n (%)	220 (92)	28 (97)	2 (100)
Beta-blockers, n (%)	210 (88)	27 (93)	2 (100)
MRA, n (%)	61 (68)	13 (45)	2 (100)
<b>Imaging features</b>			
<b>Late gadolinium enhancement on CMR, n (%)</b>	28 (38)	11 (38)	0 (0)
<b>Basal echocardiogram</b>			
IVSd (mm)	10 ± 2	10 ± 2	10.5 ± 0.7
EDD (mm)	65 ± 10	66 ± 8	67 ± 10
RWT	0.30 ± 0.07	0.26 ± 0.05	0.28 ± 0.13
EDV (mL)	179 ± 78	191 ± 56	187 ± 83
LVEF (%)	34 ± 11	30 ± 10	28 ± 6
<b>Follow-up echocardiogram</b>			
EDD (mm)	61 ± 11	61 ± 8	52 ± 6
RWT	0.32 ± 0.07	0.30 ± 0.06	0.34 ± 0.07
EDV (mL)	159 ± 68	156 ± 44	92 ± 7
LVEF (%)	40 ± 11	40 ± 11	51 ± 0.7
LVEF ≥ 50% at follow-up	50 (25)	8 (27)	2 (100)
ΔLVEF ≥ 10% and ΔESV ≥ 15% at follow-up	58 (31)	12 (43)	2 (100)
ΔLVEF ≥ 10% and ΔEDDi ≥ 10% at follow-up	61 (31)	12 (41)	2 (100)
Cardiovascular events at follow-up, n (%)	56 (24)	8 (27)	0 (0)

ACE-I, angiotensin-converting enzyme inhibitors; AICD, automatic implantable cardioverter defibrillator; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor neprilysin inhibitors; CMR, cardiac magnetic resonance; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; DCM, dilated cardiomyopathy; ECG, electrocardiogram; EDD, end-diastolic diameter; EDDi, end-diastolic diameter indexed for body surface area; EDV, end-diastolic volume; ESV, end-systolic volume; IVSd, interventricular septum thickness diastole; LBBB, left bundle branch block [AHA (American Heart Association) criteria: (i) QRS duration ≥ 120 ms; (ii) broad notched or slurred R wave in leads I, aVL, V5, and V6; (iii) absent q waves in leads I, V5, and V6; and (iv) R peak time greater than 60 ms in leads V5 and V6, ST and T waves usually opposite in direction to QRS; and Strauss criteria: (i) QRS duration ≥ 140 ms (men) or 130 ms (women); (ii) QS or rS in leads V1 and V2; and (iii) mid-QRS notching or slurring in ≥ 2 of leads V1, V2, V5, V6, I, and aVL]; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; RWT, relative wall thickness; VUS, variant of uncertain significance.

In bold, all the variables used to define LBBB-induced cardiomyopathy, as previously suggested,<sup>2</sup> including the following echocardiographic features: LVEDD ≤ 61 mm in females and ≤ 68 mm in males, RWT ≥ 0.22 in females and 0.24 in males, absence of severe diastolic dysfunction defined as E/A ratio > 2 and/or E/e' ratio > 15, left atrial volume index ≤ 41 mL/m<sup>2</sup> and/or LA area ≤ 40 cm<sup>2</sup>, and tricuspid annular plane systolic excursion ≥ 17 mm.

<sup>a</sup>The percentages in this column are expressed on the total observations of 242 cases.

<sup>b</sup>Combined aetiology in one case.

patients with DCM and LBBB deeply phenotypically characterized so far. The present study opens the way to larger, multicentre, prospective confirmatory registries with the aim of addressing an early diagnosis and proper management of LBBB-ICMP. In fact, even if the proposed criteria for LBBB-ICMP<sup>3</sup> might be associated with a good outcome, the presence of LBBB has been reported as an ominous sign. In this perspective, future research studies on the natural history of LBBB-ICMP in comparison with other forms of non-ischæmic DCM are warranted. Retrospective diagnosis, after LBBB resolution, is actually a complex matter. Spontaneous resolution of LBBB has rarely been described, and, on the other hand, CRT effectiveness can be influenced by many variables, such as venous anatomy and lead positions. Moreover, we still do not know if LBBB is only responsible for 'dyssynchronopathy' or if it is able *per se* to trigger a cardiomyopathic process in all cases of suspected LBBB-ICMP. Finally, although some authors<sup>11,12</sup> have suggested earlier CRT implantation, at the present time, there is no evidence that this should be considered the best treatment strategy. The latter remains largely speculative because several variables might potentially influence the complex phenotype of LBBB-ICMP. Moreover, the retrospective analysis of a few cases could be only hypothesis generating.

In our study, some quantitative echocardiographic parameters on cardiac dyssynchrony were not systematically

available; however, their clinical impact and superiority over qualitative assessment has not yet been definitively established.

## Conclusions

Left bundle branch block-induced cardiomyopathy emerges as a distinct pathological entity, promptly identifiable in a minority but not negligible proportion of patients with newly diagnosed DCM and LBBB, using a series of diagnostic criteria including CMR and genetic testing. Further studies are needed to better elucidate the clinical course of LBBB-ICMP.

## Conflict of interest

All authors (G.D.S., A.D.B., M.Z., E.B., P.C., E.M., M.E.C., G.P., G.S., and M.M.) have nothing to disclose.

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