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Left bundle branch block-induced cardiomyopathy: a diagnostic proposal for a poorly explored pathological entity☆,☆☆

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ABSTRACT

Despite being increasingly recognized as a specific disease, at the present time left bundle branch block (LBBB)-induced cardiomyopathy is neither formally included among unclassified cardiomyopathies nor among the acquired/non-genetic forms of dilated cardiomyopathy (DCM). Currently, a *post-hoc* diagnosis of LBBB-induced cardiomyopathy is possible when evaluating patients' response to cardiac resynchronization therapy (CRT). However, an early detection of a LBBB-induced cardiomyopathy could have significant clinical and therapeutic implications. Patients with the aforementioned form of dyssynchronopathy may benefit from early CRT and overall prognosis might be better as compared to patients with a primary muscle cell disorder (i.e. "true" DCM). The real underlying mechanisms, the possible genetic background as well as the early identification of this specific form of DCM remain largely unknown. In this review the complex relationship between LBBB and left ventricular non-ischaemic dysfunction is described. Furthermore, a multiparametric approach based on clinical, electrocardiographic and imaging *red flags*, is provided in order to allow an early detection of the LBBB-induced cardiomyopathy.

1. Introduction

Dilated cardiomyopathy (DCM) is usually phenotypically defined by the presence of left ventricular (LV) or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions (e.g. arterial hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment [1].

Despite the clear definition, DCM encompasses a broad range of disorders. The causes of DCM can be classified as either genetic or non-genetic (acquired). The phenotypic expression of DCM may be the result of the combination of a genetic predisposition with environmental factors such as myocardial inflammation, drugs (e.g. chemotherapy agents), toxics (e.g. alcohol), nutritional deficiencies or endocrine disorders [2]. Some forms of DCM are "arrhythmia-induced cardiomyopathies" that could be caused by sustained supraventricular arrhythmias (tachy-induced) or by the dyssynchrony induced by frequent ventricular ectopic beats [3]. With regard to the last mechanism, a frequent dyssynchronous ventricular activation, may be the cause of reduced efficiency of ventricular contraction which may be responsible for a dyssynchrony-related cardiomyopathy. The relationship between DCM and left bundle branch block (LBBB) is well known, as well as the non-negligible quota of super-responders to cardiac resynchronization therapy (CRT). Furthermore, the asynchrony in the left ventricular (LV) contraction and the impairment in the systolic ventricular function induced by complete LBBB [4] have previously been described. Nevertheless, LBBB is not included in the acquired "electrical" possibly reversible causes of DCM. As a consequence, the "LBBB-induced cardiomyopathy" diagnosis, prognosis and management remain unclear.

The aim of this review is to describe the complex relationship between LBBB and LV non-ischaemic dysfunction and to investigate the possible early features of LBBB-induced cardiomyopathy that could help in distinguishing this condition from other forms in the spectrum of DCM with clear prognostic and therapeutical implications.

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2. LBBB-induced cardiomyopathy: the state of art

The definition and electrocardiographic (ECG) criteria for LBBB have changed over the years [5]. The 2009 AHA/ACCF/HRS remains the most commonly used definition for LBBB in clinical practice [6]. The prevalence of isolated LBBB in the general population appears low; in a screened population of 110.000 subjects it was 0.1% [7]. Patients with DCM frequently present a prolonged QRS duration (> 120 msec) due to intraventricular conduction delay or LBBB. In a retrospective analysis of 608 patients with DCM, LBBB was found at baseline in 31% of cases [8]. However, studies specifically addressing this issue are lacking and difficult to conceive, since LBBB may appear at different timing in the course of the disease. On the other hand, the prevalence of DCM in patients with LBBB in a recent small CMR study was found to be 21%, thus emphasizing the complex relationships between LBBB and DCM [9]. Independently from the associated disease [10] and the severity of LV dysfunction, LBBB represents per se a pathologic hallmark being associated with poor clinical outcomes [11]. In LBBB, the electrical activation of the LV is altered, leading to delay and inhomogeneity of depolarization and repolarization. The electrical activation of the interventricular septum commences on the right, then propagates inferiorly, to the left and slightly anteriorly [12]. LBBB is characterized by a significant prolongation of LV activation time and a marked delay in the activation of the basal free wall. The LV activation sequence seems to be more homogeneous in patients with isolated LBBB and much more heterogeneous in those with the conduction disturbance associated with structural heart disease [13]. The net result on LV mechanics is a global discoordination of the contraction/relaxation process, usually defined as intraventricular and interventricular dyssynchrony. The deleterious effects of LBBB on mechanical synchrony involve the entire cardiac cycle. The leftward septal pre-ejectional shift, followed by a paradoxical movement to the right, significantly differs from the normal heart. Furthermore, the delayed deformation of the lateral wall has consequences on papillary muscles and mitral valve apparatus kinetics. Finally, diastolic filling is shortened [13]. All these may cause LV remodeling (e.g. dilatation and increased mass) together with impaired systolic and diastolic function.

The effects of dyssynchrony on LV geometry and function were investigated in several canine models [14]. The most simple explored the effects of LBBB, LV or right ventricular (RV) pacing, while the most complex added myocardial infarction, or valvular heart diseases (e.g. mitral regurgitation) in order to have a model resembling as close as possible to the pathophysiology of CRT patients [14]. In one of the most cited preclinical experimental studies using a canine model, the asynchronous ventricular activation during LBBB (induced by radio frequency ablation) leads to redistribution of circumferential shortening and myocardial blood flow (i.e. decreased perfusion in the septum and increased in LV lateral wall) and, in the long run, LV remodeling (dilatation and increased mass) [15]. It was noteworthy that the hypertrophy developed by the dogs was most likely due to the redistribution of workload [15]. Human studies showed reversible perfusion defects (e.g. in the interventricular septum) in the absence of obstructive coronary artery disease in patients with LBBB, and some patients with intermittent LBBB develop angina coincident with the onset of LBBB [16]. In humans, apart from the "isolated" LBBB-induced cardiomyopathy (theme of the present discussion), two other models of dyssynchronopathy can be observed, both iatrogenic: chronic RV pacing and the acute model of new-onset LBBB after aortic valve interventions (i.e. transcatheter aortic valve implantation – TAVI, or surgical aortic valve replacement – AVR). However, both iatrogenic models show important differences compared to LBBB-induced cardiomyopathy. The model of chronic RV pacing, although leading often to LV dysfunction, significantly differs from LBBB-induced cardiomyopathy (the site of stimulation induced-breakthrough differs from that of intrinsic breakthrough, resulting in a depolarization through the interventricular septum different from that induced by LBBB). The iatrogenic model of LBBB after TAVI [13] is worth noting for its pathophysiology (similar to some extent to that of "spontaneous isolated LBBB" according to the ECG criteria) and its clinical implications [17]. New LBBB complicates a significant percentage of TAVI procedures [17]. LBBB after TAVI is associated with adverse clinical outcomes [18]. Despite some similarities, the iatrogenic model of LBBB after TAVI is not comparable to LBBB-induced cardiomyopathy. In fact, ventricles submitted to a chronic pressure overload, such as in patients with aortic stenosis (usually severely remodeled before the interventional procedure), may not have necessarily the same mechanical behaviour as hearts with LBBB-induced cardiomyopathy.

Despite the experimental studies, the relationship between LBBB and LV dilatation and dysfunction is complex and still poorly understood; thus, the chicken or the egg causality dilemma seems to be unsolved. Different scenarios should be taken into account: 1) LBBB may appear in the natural course of DCM, representing a marker of disease severity and being associated with an increased risk of all-cause mortality [8]; 2) LBBB may play a causative role in the development of a "dyssynchronopathy". An approach based on the perceived causal contributions of LBBB toward the overall cardiomyopathic process should be advisable, avoiding a monolith interpretation [19]. Over the last two decades several reports appeared concerning the causative link between LBBB and LV dilatation and dysfunction in patients with heart failure (HF). In 2005 Blanc et al. introduced the concept of left ventricular dyssynchrony-induced cardiomyopathy [20]. Five among the 29 studied patients (17%) had both complete normalization of LV function and clinical improvement following CRT. Similar percentages of normalized LV function have been subsequently reported in other DCM series [21,22]. In 2013, Vaillant and colleagues better defined the characteristics of the so-called LBBB-induced cardiomyopathy: 1) normal sinus rhythm and >5-year history of typical LBBB; 2) LV EF > 50% at the time of diagnosis of LBBB; 3) progressive decrease in LV EF to ≤40%; LV end-diastolic diameter ≥ 55 mm and development of NYHA functional class II to IV; 4) presence of LV mechanical dyssynchrony; 5) no other identifiable cause of cardiomyopathy; and 6) indication for and super-response to CRT. By using these pre-defined and strict diagnostic criteria, they found 6 patients (1.6%, probably underestimated due to the retrospective data collection and missing data) over 375 candidates for CRT with this syndrome [23]. The NEOLITH [24] and NEOLITH II[25] studies showed that guideline-directed medical therapy (GDMT) did not significantly improve LV ejection fraction (EF) in new-onset LBBB-associated idiopathic non-ischaemic cardiomyopathy at 3 months, and that earlier CRT implantation (i.e. before 3 months of GDMT) was associated with more favorable cardiac remodeling. The Authors suggested that delaying CRT may miss a critical period to halt and reverse progressive myocardial damage [25]. Similarly, Merlo et al. found that LBBB was a negative predictor of LV reverse remodeling in patients with idiopathic DCM receiving GDMT [26].

More recently, Sze et al. supported these results and challenged the order of action recommended in the guidelines. The Authors suggested shortening medication time in favor of earlier consideration of CRT in patients with cardiomyopathy accompanied or induced by LBBB. In a large Duke echocardiography dataset including 659 cardiomyopathy patients, they found that those with LBBB and GDMT did not show any significant improvement in LVEF over 3 to 6 months in comparison with those not on GDMT [27]. The hypothesis of a CRT at an earlier stage should be confirmed in prospective studies. However, the findings of the study by Sze et al. indirectly corroborate the notion of dyssynchronopathy as a specific pathophysiological entity.

3. LBBB-induced cardiomyopathy: work-up for an "a priori" diagnosis

The criteria of LBBB-induced cardiomyopathy proposed by Valliant et al. [21] are poorly applicable in clinical practice. First of all, a new

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diagnosis of DCM with associated LBBB is not unusual, and clinicians do not have data regarding the possible causative or consequence role of LBBB. Second, the diagnosis of LBBB-induced cardiomyopathy is a "*a-posteriori*" diagnosis, on the basis of LVEF normalization after removing LBBB. Furthermore, there are no randomized trials on this topic and, despite some studies suggested a benefit from earlier CRT than guidelines currently recommend [24,25,27], we do not have sufficient data yet.

Nevertheless, due to the aetiological heterogeneity of DCM that portends its clinical heterogeneity, a precise aetiological definition seems to be crucial. In fact, the withdrawal of the presumed causative factor (e.g. alcohol, sustained supraventricular arrhythmias) may induce reverse LV remodeling with significant beneficial prognostic implications. This could be true also in selected patients with LBBB-induced cardiomyopathy that should be addressed to early CRT implantation, despite the severity of LV dysfunction. In this perspective, we propose a number of clues that should be taken into account when approaching a patient with a newly diagnosed DCM and LBBB (Table 1). We are aware about the lack of studies specifically investigating this pathological entity. By consequence, we only propose a number of *red flags* mainly based on clinical observation, acknowledging that our proposal requires to be confirmed in large future patients' cohorts.

Bearing in mind these limitations, the following points appear of relevant significance (Fig. 1):

3.1. Presence of true LBBB

The strict definition proposed by Strauss et al. includes a QRS duration ≥140 ms in men and ≥130 ms in women, QRS notching or slurring in two or more contiguous leads of V1, V2, V3, V4, V5, V6, I and aVL, and a QS or rS in V1 and V2 [28]. It is reasonable that the larger the QRS, the higher the probability of a causative effect of LBBB on LV remodeling. In fact, guidelines recommend a QRS duration >150 ms and previous experiences suggested that super-responders to CRT might be identified among those carrying the largest QRS [29]. However, it is still unclear whether there might be a threshold for QRS duration indicating such a severe remodeling that normalization after correction of LBBB is unlikely.

3.2. Exclusion of other possible causes of DCM

LBBB-induced cardiomyopathy includes "pure" patients. In this perspective, other possible triggers of dysfunction should be identified prior to confirm the exclusive causative role of LBBB. Therefore, DCM

Table 1
Useful features in the early diagnostic work-up of "LBBB-induced cardiomyopathy". Proposal based on current literature and expert clinical observations in patients not fulfilling the criteria for a primary DCM.

Criteria	DCM	"LBBB-induced cardiomyopathy" or "dyssynchronopathy"
Clinical		
Absence of significant coronary artery disease	+	+
- Family history of DCM	+	−
- Muscular dystrophies		
- Mitochondrial diseases		
- Myocarditis		
- Drugs		
- Toxics		
- Endocrine disorders		
- Peripartum		
Genetics		
- Pathogenic or likely pathogenic mutations	+ in 30–50% of cases	−
- Genetic-environment interactions	+ but largely unknown	? completely unknown
Imaging		
Presence of "true" LBBB on ECG since disease presentation	+/−	+
LV dilatation > 2SD	Frequent	Possible
Relative wall thickness (RWT)	Lower limits/reduced	Usually within normal range
Wall thickness	Usually within normal range (toward lower limits)	Usually within normal range (sometimes increased, especially lateral wall)
LV systolic dysfunction	+	+
LV mechanical dyssynchrony by echocardiography	+/− Variable degree	+ Usually marked with septal flash, rocking motion of the apex, etc.
Diastolic dysfunction	+/− (often grade II or III)	+/− (usually lesser degree i.e. grade I)
LA dilatation	+/− (often severe)	+/− (often within normal limits or mild dilatation)
Persistent RV systolic dysfunction after optimal medical therapy	+/−	−
Presence of late gadolinium enhancement on CMR imaging	+/−	−
Clinical course and prognosis		
Overall prognosis	Variable (sometimes poor with the need for heart transplant)	To be defined but expected better in comparison with true DCM
Response to resynchronization therapy (CRT-P or CRT-D)	Usually (but not always) good (sometimes poor - e.g. patients with extremely impaired systolic function – EF < 20%)	Expected super-response (sometimes excellent with reverse remodeling and almost complete normalization of LV systolic function)

DCM (dilated cardiomyopathy); LBBB (left bundle branch block); LV (left ventricle); LA (left atrium); RV (right ventricle); CMR (cardiovascular magnetic resonance).

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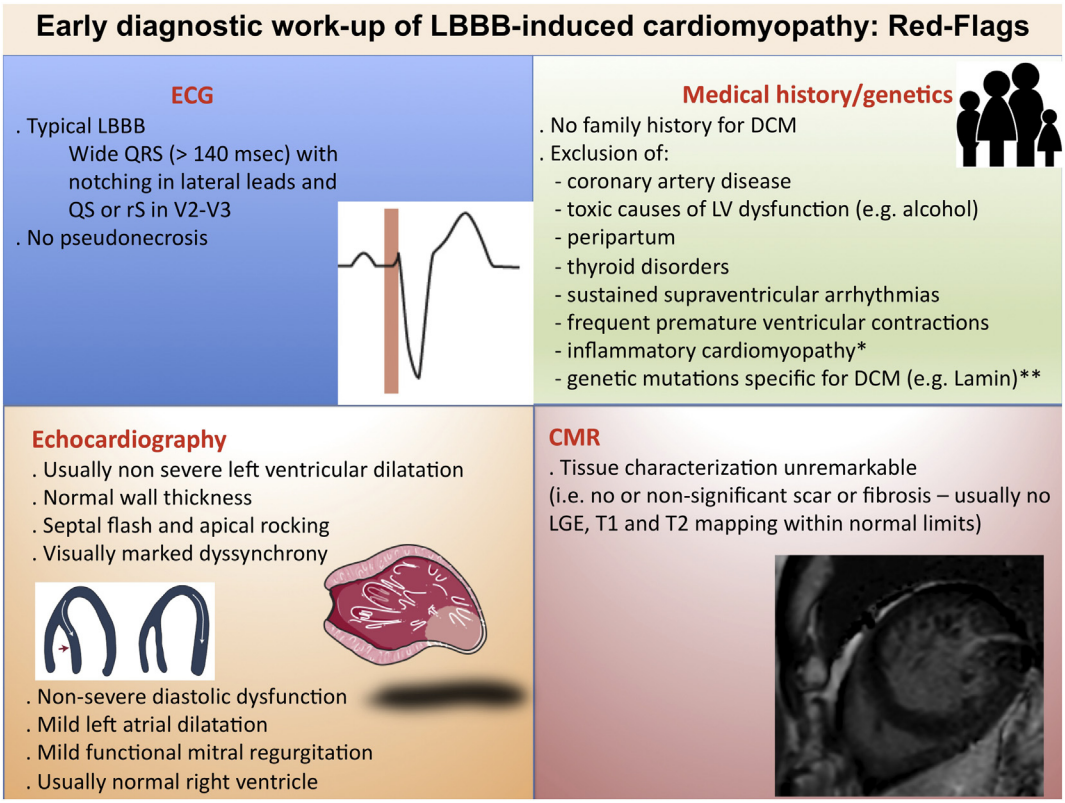

Fig. 1. Relevant *red-flags* in order to early identify LBBB-induced cardiomyopathy. *By CMR or EMB when clinically indicated; **by genetic testing when indicated (see text).

patients should not be considered for early CRT in presence of clear family history for sudden cardiac death or DCM, acute stress situations, peripartum, thyroid disorders, history of significant hypertension (i.e. 140/90 mmHg or need of >1 anti-hypertensive drug), alcohol abuse (>100 g/die and >80 g/die for males and females respectively), chemotherapy, sustained supraventricular high-rate (>100 bpm) arrhythmias, very frequent ectopic ventricular beats, or acute myocardial inflammation (detected by cardiac magnetic resonance or endomyocardial biopsy).

3.3. Imaging-derived red-flags

3.3.1. Echocardiography

Echocardiography plays a pivotal role in the diagnosis of DCM [30]. It also provides useful information regarding prognosis and helps guide treatment. The main echocardiographic features include LV chamber dilatation and systolic dysfunction, but RV involvement is not uncommon in familial/genetic forms [30,31]. In patients with DCM, LV usually appears spherical in shape, with a net convexity of the interventricular septum toward the right ventricle, while wall thickness is usually within normal limits and relative wall thickness tends to be reduced (i.e. < 0.26). LV mass is often increased due to LV dilatation. DCM is usually characterized by global hypokinesis and overall systolic impairment. Regional wall motion abnormalities may sometimes suggest the presence of coronary artery disease [31].

In patients with apparent LBBB-induced cardiomyopathy echocardiography shows some characteristic features that might help in distinguishing this condition from other forms in the spectrum of DCM (Table 1). Regarding LV geometry, it is noteworthy the usually non-severe dilatation (less than 2SD) with normal absolute and relative wall thickness, whereas patients with "true" DCM usually exhibit a different shape (i.e. spherical LV with lower-limits or reduced relative wall thickness). However, the amount of LV remodeling in patients with LBBB-induced cardiomyopathy could be highly variable and it is largely unknown. Therefore, proposed diagnostic criteria on LV geometry (mainly based on clinical observations) need to be confirmed in properly designed studies on cardiac imaging. Furthermore, patients with dyssynchonopathy usually have lesser degrees of diastolic dysfunction (often grade I or abnormal relaxation). Left atrium is usually not severely enlarged and not spherical shaped, while functional mitral valve regurgitation is often mild as a consequence of not severely tethered leaflets. Finally, RV is usually spared with normal geometry and function (Table 1).

3.3.2. Evolving concepts: from the electrical and mechanical dyssynchrony to the electromechanical substrate

Despite being largely accepted when selecting patients for cardiac resynchronization therapy (CRT), ECG criteria have several limitations. The strict definition of LBBB proposed by Strauss has been questioned since it seems to not improve the prediction of response to CRT [32].

This is at least partly due to the fact that ECG is able to detect the electromechanical dyssynchrony. However, in failing hearts with LBBB a pivotal role is played by mechanical dyssynchrony (MD). MD should be appreciated with echocardiography and, despite its routine use as an additive tool to the ECG criteria for patient selection to CRT has not gained clinical acceptance, its pathophysiological significance should not be underestimated, being the other side of dyssynchrony [33]. Thus, it is emerging the importance of a unifying dyssynchrony hypothesis considering an overall electromechanical substrate. The myocardial dyssynchronous movement related to LBBB can be identified by echocardiography using visual "eyeballing", M-mode, or strain imaging. Septal flash (SF) [34] and apical rocking (ApRock) [35] are typical signs of dyssynchronopathy and they can be visually appreciated. Indeed, not all LBBBs by ECG reflect a true LV activation delay, which can result in nonresponse to CRT [34,36]. Two-dimensional strain echocardiography may detect true LBBB activation by the contraction pattern assessment (i.e. early terminated shortening in the septal wall, early pre-stretch in the lateral wall and late lateral peak contraction) [37]. In fact, patients

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with chronic right ventricular (RV) pacing have an induced LBBB; however, only a minority of these patients develop LV dysfunction and heart failure symptoms. This should be explained by the absence of mechanical dyssynchrony (MD). In a study including 914 patients eligible for CRT, MD was observed in 51% of patients with RV pacing versus 77% of those with intrinsic LBBB [38].

3.3.3. Cardiac magnetic resonance

Despite its numerous strengths, in most of the cases of "DCM", echocardiography does not provide useful information about aetiology, and this could be defined only gathering clinical, echocardiographic and laboratory tests, plus genetic analyses when available. Tissue characterization by CMR provides additional information in patients with DCM. The presence and patterns of late gadolinium enhancement (LGE) [39,40] may suggest a specific aetiology and have prognostic implications [41,42]. However, the true prevalence of LGE in patients with DCM in the "real world" seems to be much lower in comparison to that reported in the studies. Furthermore, despite some promising results obtained with the new T1 mapping and extracellular volume (ECV) techniques in Lamin A/C (LMNA) mutation carriers [43], for the time being CMR techniques substantially failed to provide significant information about aetiology in most of the cases of DCM. This could be particularly true in patients with LBBB-induced cardiomyopathy. In these patients, tissue characterization is usually unremarkable (i.e. negative), particularly in the interventricular septum, posterior and lateral walls.

Future studies are required to confirm the role of CMR as a tool for arrhythmic prognostic risk stratification in DCM patients [42,44] and in those with LBBB-induced cardiomyopathy.

3.4. Genetics

Recently, the Next Generation Sequencing techniques have impressively widened the genetic landscape of DCM. Currently >50 genes are known to be involved in the pathogenesis of the disease. The most frequent is the TTN gene, followed by genes of lamin A/C, sarcomeric proteins, cytoskeleton, ion channel, desmosome, phospholamban. A genetic basis of DCM should be theoretically excluded before considering a possible LBBB-induced cardiomyopathy; however, genetic testing is not widely available thus making it difficult in clinical practice. Furthermore, the indications for genetic testing in DCM include familial and sporadic forms with specific clues suggesting an inherited genetic basis [45]. The presence of specific mutations, such as cytoskeleton genes or LMNA A/C are demonstrated as associated to a lack of reverse remodeling under GDMT [46], particularly in presence of LBBB [47]. Conversely TTN mutations could be associated to a more favorable remodeling [46].

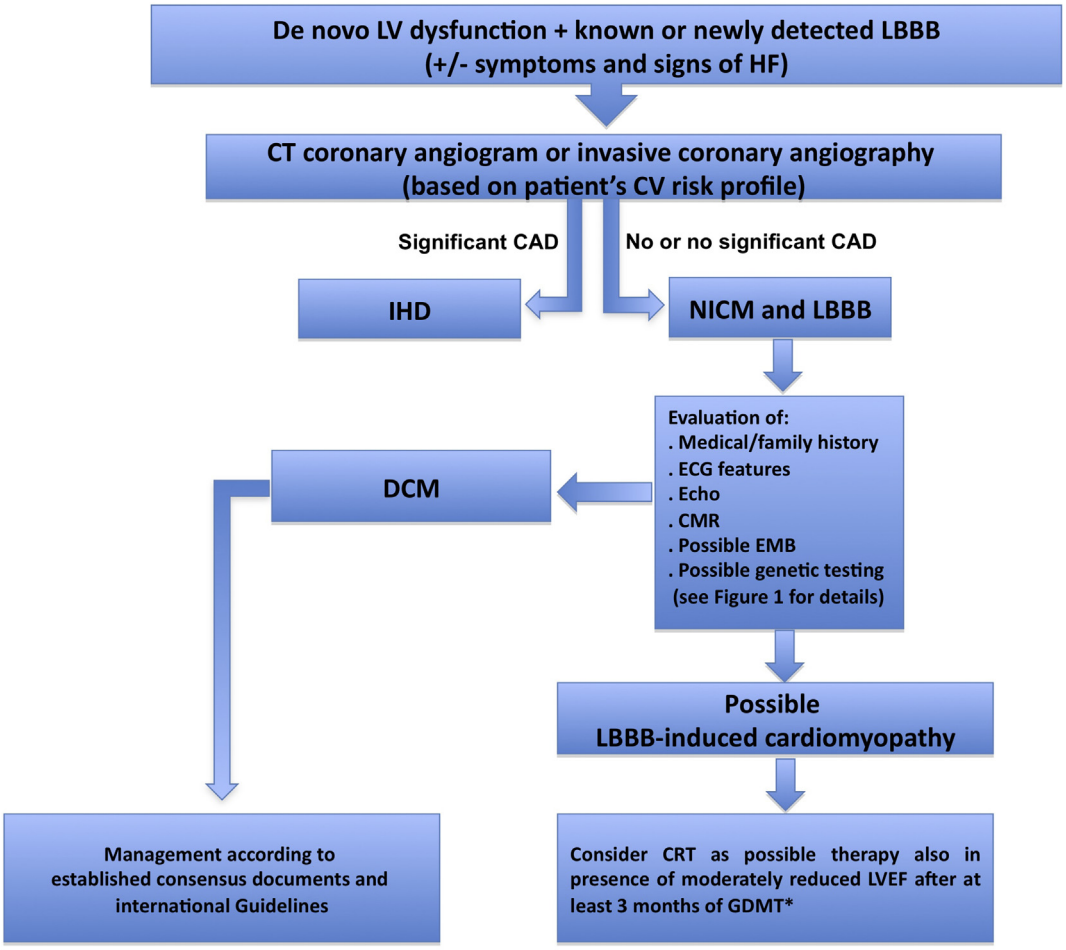

Fig. 2. Proposed algorithm for the management of patients with LBBB-induced cardiomyopathy. LBBB – Left bundle branch block; HF – Heart Failure; CT – Computed tomography; CAD – Coronary artery disease; IHD – Ischaemic heart disease; NICM – Non-ischaemic cardiomyopathy; CMR – Cardiac magnetic resonance; EMB – Endomyocardial biopsy; DCM – Dilated cardiomyopathy; Moderately reduced LVEF (36% to 50%). * No clear evidence. The decision should be based on: 1. Patient clinical status (HF yes/not, NYHA functional class); 2. Imaging features (e.g. marked dyssychrony); 3. Suitable anatomy and local operator expertise; 4. Patients preferences; 5. Early response (in terms of LV geometry/function and patients functional status) to medical therapy and possibility to titrate drugs. Whether or not patients will benefit more from a CRT-P instead of a CRT-D device remains unknown.

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4. Gaps in evidence

LBBB-induced cardiomyopathy is a distinct entity that could be healed by the correction of LBBB. Nevertheless, some important open issues remain and are to be considered.

A) There is a little percentage of patients with LBBB that present a concomitant LV systolic dysfunction and dilatation. This situation suggests a possible genetic individual background that remains largely unknown, particularly regarding its interactions with environmental factors. Furthermore, LBBB may have detrimental effects on intracellular protein homeostasis (e.g. ion channel remodeling and abnormal Ca++ homeostasis within cardiac myocytes) [48].

B) In the presence of suspected LBBB-induced cardiomyopathy, after the above mentioned diagnostic work-up, a CRT approach after 3 months of GDMT [49] regardless the severity of the dysfunction, might be a therapeutic option after a careful comprehensive patient evaluation, and should be investigated in properly designed clinical trials (Fig. 2). The best position of LV electrode remains a crucial issue that has to be implemented in the future. Multimodality imaging may help in guiding optimal LV lead position in order to reduce the quota of non-responders to CRT [50,51]. However, technical issues related to the procedure still represent a potential limitation despite an accurate pre-operative planning. The lack of QRS narrowing after CRT will suggest a failure of resynchronization and the diagnosis of LBBB-induced cardiomyopathy will remain a hypothesis. Recently, promising results in patients with heart failure and LBBB (which does not mean LBBB-induced cardiomyopathy) were obtained with His bundle pacing instead of conventional CRT. The good hemodynamic response observed in the acute setting should be confirmed by randomized controlled trials with long-term follow-up [52]. The limitations in our knowledge of the pathophysiology and natural history of LBBB-induced cardiomyopathy and LBBB itself do not allow us to define a treatment strategy for these patients. For example, cases are described of spontaneous (i.e. without CRT) resolution of LBBB leading to reverse remodeling in dyssynchronopathy [53]. This concept of a possible reversible electrical (and subsequently mechanical) remodeling warrants further investigation, due to the potential therapeutic implications.

C) Prospective and randomized studies are needed to confirm these preliminary hypotheses and to address some unanswered questions such as the role of medical therapy in the context of LBBB-induced cardiomyopathy and the long-term response to CRT. In fact, there are no studies showing that CRT therapy alone may heal the pathology and in a recent review Sze showed that 25% of patients with LBBB and heart failure with reduced ejection fraction may respond to GDMT [54]. On the other hand, it has been highlighted that <15% of DCM patients has an apparent healing under GDMT and in the long-term follow-up a sensible proportion of those patients developed LVEF deterioration [55]. Similarly, there are no definite data revealing if the super-response to CRT is durable over time or not. Despite these limitations, we should acknowledge that there are no studies specifically enrolling subjects with LBBB-induced cardiomyopathy, nor studies investigating the role of Angiotensin Receptor-Neprilysin Inhibitors in this subgroup of heart failure patients.

Table 2 summarizes the main gaps in evidence discussed above.

Table 2
Gaps in evidence (short list of selected issues that deserve to be addressed in future clinical research).

Definition and diagnosis	• Clinical, ECG and imaging criteria (prospective studies are needed to confirm the proposed diagnostic criteria and their usefulness in differentiating LBBB-induced cardiomyopathy from primary DCM).
Epidemiology	• % of patients with heart failure, LBBB associated with LV dysfunction and dilatation. • Gender differences.
Aetiology and pathophysiology	• Potential genetic background and interaction with environmental factors • Changes in protein homeostasis • possible structural changes of cardiomyocites
Natural history and clinical outcomes	• Reversible condition? *- spontaneous resolution of LBBB and LV dysfunction/ dilatation – electrical and mechanical remodeling (Who? When? Why?)* • Long term prognosis *- healing? Comparison with primary DCM and LBBB.*
Cardiac resynchronization therapy (CRT)	• Timing: early (i.e. before 3 months of GDMT) vs delayed strategy (pros and cons) • Potential role for His bundle pacing?
Medical therapy	• Effectiveness (alone or combined with CRT) • Potential efficacy in inducing electrical remodeling • Potential role of ARNi

DCM – dilated cardiomyopathy; LV – left ventricle; GDMT – guideline directed medical therapy; ARNi – angiotensin receptor neprilisin inhibitor.

5. Conclusions

LBBB-induced cardiomyopathy represents a distinct nosological entity, which may derived from a complex potential interaction between genetic background and an electric persistent noxa. Despite specific features and the algorithm here proposed (Fig. 2), currently this intriguing and challenging diagnosis can be made only retrospectively due to the lack of clinical and instrumental findings certainly identifying affected patients. Further observational and possibly prospective studies are needed to better refine the diagnostic criteria together with the natural history of this poorly explored pathology.

References

[1] P. Elliott, B. Andersson, E. Arbustini, et al., Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases, Eur. Heart J. 29 (2008) 270–276.
[2] Y.M. Pinto, P.M. Elliott, E. Arbustini, et al., Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non- dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases, Eur. Heart J. 37 (2016) 1850–1858.
[3] B. Bozkurt, M. Colvin, J. Cook, et al., American Heart Association Committee on Heart Failure and Transplantation of the Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; and Council on Quality of Care and Outcomes Research. Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement From the American Heart Association, Circulation 134 (2016) e579–e646.
[4] C.L. Grines, T.M. Bashore, H. Boudoulas, S. Olson, P. Shafer, C.F. Wooley, Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony, Circulation 79 (1989) 845–853.
[5] J. Kanawati, R.W. Sy, Contemporary review of left bundle branch block in the failing heart - pathogenesis, prognosis, and therapy, Heart Lung Circ 27 (2018) 291–300.
[6] B. Surawicz, R. Childers, B.J. Deal, et al., American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; American College of Cardiology Foundation; Heart Rhythm Society. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology, J. Am. Coll. Cardiol. 53 (2009) 976–981.
[7] G.J. Fahy, S.L. Pinski, D.P. Miller, et al., Natural history of isolated bundle branch block, Am. J. Cardiol. 77 (1996) 1185–1190.
[8] A. Aleksova, C. Carriere, M. Zecchin, et al., New-onset left bundle branch block independently predicts long-term mortality in patients with idiopathic dilated cardiomyopathy: data from the Trieste Heart Muscle Disease Registry, Europace 16 (2014) 1450–1459.
[9] M. Mahmod, T.D. Karamitsos, J.J. Suttie, S.G. Myerson, S. Neubauer, J.M. Francis, Prevalence of cardiomyopathy in asymptomatic patients with left bundle branch block referred for cardiovascular magnetic resonance imaging, Int J Cardiovasc Imaging 28 (2012) 1133–1140.
[10] G. Parodi, C. Salvadori, S. Del Pace, et al., Left bundle branch block as an electrocardiographic pattern on presentation of patients with tako-tsubo cardiomyopathy, J Cardiovasc Med 10 (2009) 100–103.
[11] C.M. Witt, G. Wu, D. Yang, D.O. Hodge, V.L. Roger, Y.M. Cha, Outcomes with left bundle branch block and mildly to moderately reduced left ventricular function, JACC Heart Fail 4 (2016) 897–903.
[12] P. Francia, C. Balla, F. Paneni, M. Volpe, Left bundle-branch block–pathophysiology, prognosis, and clinical management, Clin. Cardiol. 30 (2007) 110–115.

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[13] V. Auffret, R.P. Martins, C. Daubert, et al., Idiopathic/iatrogenic left bundle branch block-induced reversible left ventricle dysfunction: JACC state-of-the-art review, J. Am. Coll. Cardiol. 72 (2018) 3177–3188.

[14] M. Strik, L.B. van Middendorp, K. Vernooy, Animal models of dyssynchrony, J. Cardiovasc. Transl. Res. 5 (2012) 135–145.

[15] K. Vernooy, X.A. Verbeek, M. Peschar, et al., Left bundle branch block induces ventricular remodelling and functional septal hypoperfusion, Eur. Heart J. 26 (2005) 91–98.

[16] L. Littmann, J.D. Symanski, Hemodynamic implications of left bundle branch block, J. Electrocardiol. 26 (2000) 91–98.

[17] V. Auffret, R. Puri, M. Urena, et al., Conduction disturbances after transcatheter aortic valve replacement: current status and future perspectives, Circulation 136 (2017) 1049–1069.

[18] N. Carrabba, R. Valenti, A. Migliorini, et al., Impact on left ventricular function and remodeling and on 1-year outcome in patients with left bundle branch block after transcatheter aortic valve implantation, Am. J. Cardiol. 116 (2015) 125–131.

[19] N.C. Wang, E.C. Adelstein, M. Singh, A.H. Voigt, S. Saba, Left bundle branch block-associated cardiomyopathies and early cardiac resynchronization therapy: conceptualizing a tailored approach, J. Am. Coll. Cardiol. 71 (2018) 1943–1944.

[20] J.J. Blanc, M. Fatemi, V. Bertault, F. Baraket, Y. Etienne, Evaluation of left bundle branch block as a reversible cause of non-ischaemic dilated cardiomyopathy with severe heart failure. A new concept of left ventricular dyssynchrony-induced cardiomyopathy, Europace 7 (2005) 604–610.

[21] L.V. Serdoz, E. Daleffe, M. Merlo, et al., Predictors for restoration of normal left ventricular function in response to cardiac resynchronization therapy measured at time of implantation, Am. J. Cardiol. 108 (2011) 75–80.

[22] P. Castellant, M. Fatemi, E. Orhan, Y. Etienne, J.J. Blanc, Patients with non-ischaemic dilated cardiomyopathy and hyper-responders to cardiac resynchronization therapy: characteristics and long-term evolution, Europace 11 (2009) 350–355.

[23] C. Vaillant, R.P. Martins, E. Donal, et al., Resolution of left bundle branch block-induced cardiomyopathy by cardiac resynchronization therapy, J. Am. Coll. Cardiol. 61 (2013) 1089–1095.

[24] N.C. Wang, M. Singh, E.C. Adelstein, et al., New-onset left bundle branch block-associated idiopathic nonischemic cardiomyopathy and left ventricular ejection fraction response to guideline-directed therapies: the NEOLITH study, Heart Rhythm. 13 (2016) 933–942.

[25] N.C. Wang, J.Z. Li, E.C. Adelstein, et al., New-onset left bundle branch block-associated idiopathic nonischemic cardiomyopathy and time from diagnosis to cardiac resynchronization therapy: the NEOLITH II study, Pacing Clin. Electrophysiol. 41 (2018) 143–154.

[26] M. Merlo, S.A. Pyxaras, B. Pinamonti, G. Barbati, A. Di Lenarda, G. Sinagra, Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment, J. Am. Coll. Cardiol. 57 (2011) 1468–1476.

[27] E. Sze, Z. Samad, A. Dunning, et al., Impaired recovery of left ventricular function in patients with cardiomyopathy and left bundle branch block, J. Am. Coll. Cardiol. 71 (2018) 306–317.

[28] D.G. Strauss, R.H. Selvester, G.S. Wagner, Defining left bundle branch block in the era of cardiac resynchronization therapy, Am. J. Cardiol. 107 (2011) 927–934.

[29] L. Vitali Serdoz, E. Daleffe, M. Merlo, et al., Predictors for restoration of normal left ventricular function in response to cardiac resynchronization therapy measured at time of implantation, Am. J. Cardiol. 108 (2011) 75–80.

[30] B. Pinamonti, G. Cacciatore, Dilated cardiomyopathy: indication and role of non-invasive instrumental evaluation, Ital Heart J 3 (2002) 405–411 Suppl.

[31] B. Pinamonti, G. Sinagra, Clinical Echocardiography and Other Imaging Techniques in Cardiomyopathies, Springer International Publishing Switzerland, 2014 45–56.

[32] E. Bertaglia, F. Migliore, A. Baritussio, et al., Stricter criteria for left bundle branch block diagnosis do not improve response to CRT, Pacing Clin. Electrophysiol. 40 (2017) 850–856.

[33] J. Lumens, B. Tayal, J. Walmsley, et al., Differentiating electromechanical from non-electrical substrates of mechanical discoordination to identify responders to cardiac resynchronization therapy, Circ Cardiovasc Imaging. 8 (2015), e003744.

[34] A. Doltra, B. Bijnens, J.M. Tolosana, et al., Mechanical abnormalities detected with conventional echocardiography are associated with response and midterm survival in CRT, JACC Cardiovasc. Imaging 7 (2014) 969–979.

[35] J.U. Voigt, T.M. Schneider, S. Korder, et al., Apical transverse motion as surrogate parameter to determine regional left ventricular function inhomogeneities: a new, integrative approach to left ventricular asynchrony assessment, Eur. Heart J. 30 (2009) 959–968.

[36] B. Corteville, J. De Pooter, T. De Backer, M. El Haddad, R. Stroobandt, F. Timmermans, The electrocardiographic characteristics of septal flash in patients with left bundle branch block, Europace. 19 (2017) 103–109.

[37] N. Risum, B. Tayal, T.F. Hansen, et al., Identification of typical left bundle branch block contraction by strain echocardiography is additive to electrocardiography in prediction of long-term outcome after cardiac resynchronization therapy, J. Am. Coll. Cardiol. 66 (2015) 631–641.

[38] I. Stankovic, C. Prinz, A. Ciarka, et al., Long-term outcome after CRT in the presence of mechanical dyssynchrony seen with chronic RV pacing or intrinsic LBBB, JACC Cardiovasc. Imaging 10 (2017) 1091–1099.

[39] J.A. McCrohon, J.C. Moon, S.K. Prasad, et al., Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance, Circulation 108 (2003) 54–59.

[40] R.G. Assomull, S.K. Prasad, J. Lyne, et al., Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy, J. Am. Coll. Cardiol. 48 (2006) 1977–1985.

[41] P.G. Masci, R. Schuurman, B. Andrea, et al., Myocardial fibrosis as a key determinant of left ventricular remodeling in idiopathic dilated cardiomyopathy: a contrast-enhanced cardiovascular magnetic study, Circ Cardiovasc Imaging 6 (2013) 790–799.

[42] A. Gulati, A. Jabbour, T.F. Ismail, et al., Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy, JAMA 309 (2013) 896–908.

[43] M. Fontana, A. Barison, N. Botto, et al., CMR-verified interstitial myocardial fibrosis as a marker of subclinical cardiac involvement in LMNA mutation carriers, JACC Cardiovasc. Imaging 6 (2013) 124–126.

[44] M. Merlo, A. Cannatà, M. Gobbo, D. Stolfo, P.M. Elliott, G. Sinagra, Evolving concepts in dilated cardiomyopathy, Eur. J. Heart Fail. 20 (2018) 228–239.

[45] R.E. Hershberger, M.M. Givertz, C.Y. Ho, et al., Genetic evaluation of cardiomyopathy-a Heart Failure Society of America practice guideline, J. Card. Fail. 24 (2018) 281–302.

[46] M. Dal Ferro, D. Stolfo, A. Altinier, et al., Association between mutation status and left ventricular reverse remodleling in dilated cardiomyopathy, Heart 103 (2017) 1704–1710.

[47] M. Merlo, S.A. Pyxaras, B. Pinamonti, et al., Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment, J. Am. Coll. Cardiol. 57 (2011) 1468–1476.

[48] T. Aiba, G.G. Hesketh, A.S. Barth, et al., Electrophysiological consequences of dyssynchronous heart failure and its restoration by resynchronization therapy, Circulation. 119 (2009) 1220–1230.

[49] Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2012;60:1297–313.

[50] Z. Bakos, E. Ostenfeld, H. Markstad, et al., A comparison between radial strain evaluation by speckle-tracking echocardiography and cardiac magnetic resonance imaging, for assessment of suitable segments for left ventricular lead placement in cardiac resynchronization therapy, Europace 16 (2014) 1779–1786.

[51] A. Sommer, M.B. Kronborg, B.L. Nørgaard, et al., Multimodality imaging-guided left ventricular lead placement in cardiac resynchronization therapy: a randomized controlled trial, Eur. J. Heart Fail. 18 (2016) 1365–1374.

[52] A.D. Arnold, M.J. Shun-Shin, D. Keene, et al., His resynchronization versus biventricular pacing in patients with heart failure and left bundle branch block, J. Am. Coll. Cardiol. 72 (2018 18) 3112–3122.

[53] M. Kloosterman, M. Rienstra, I.C. Van Gelder, A.H. Maass, Spontaneous resolution of left bundle branch block and biventricular stimulation lead to reverse remodeling in dyssynchronopathy, J. Electrocardiol. 49 (2016) 696–698.

[54] E. Sze, J.P. Daubert, Left bundle branch block-induced left ventricular remodeling and its potential for reverse remodeling, J. Interv. Card. Electrophysiol. 52 (2018) 343–352.

[55] M. Merlo, D. Stolfo, M. Anzini, et al., Persistent recovery of normal left ventricular function and dimension in idiopathic dilated cardiomyopathy during long-term follow-up: does real healing exist? J. Am. Heart Assoc. 4 (2015), e001504.

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