Left bundle branch block in heart failure: Is it A cause or A consequence?

Bloc de branche gauche dans l'insuffisance cardiaque : cause ou conséquence ?

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SUMMARY

Left bundle branch block (LBBB) in the setting of heart failure (HF) is linked to adverse outcome, it increases the risk of both all-cause of mortality and arrhythmic sudden death. Cardiac dyssynchrony is the recognized mechanism behind such an unfavorable prognosis, however, recent studies have identified this mechanism as a cause rather than a consequence of left ventricular dysfunction and remodeling. In this regard, we aim through this article to try to answer crucial questions about LBBB in HF and to highlight the gaps in the evidence.

MOTS-CLÉS

Heart failure, left bundle branch bloc, Cardiac resynchronization therapy

RÉSUMÉ

Le bloc de branche gauche (BBG) dans le cadre de l'insuffisance cardiaque (IC) est associé à un mauvais pronostic, celle-ci est due à l'augmentation du risque de mortalité de toute cause confondue et aussi par morts subites arythmogène. La désynchronisation cardiaque est le mécanisme derrière ce pronostic défavorable, cependant, des études récentes ont identifié le BBG comme une cause de dysfonction ventriculaire gauche systolique plutôt qu'une conséquence de remodelage cardiaque. Dans ce contexte, essayons grâce à cet article de répondre à des questions cruciales à propos le BBG dans l'IC et d'identifier et réfléchir quant aux lacunes qui existe dans les preuves scientifiques jusqu'à présent.

KEYWORDS

Insuffisance cardiaque, bloc de branche gauche, resynchronisation cardiaque

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INTRODUCTION

Many questions continue to be raised about left bundle branch block (LBBB) in heart failure (HF) mainly about its definition, pathophysiological mechanisms and therapeutic implications.

Traditionally, LBBB was regarded rather as a consequence than a cause of myocardial disease because of the fact that LBBB is associated with mild and long-term poor prognosis proven by numerous studies.

It is important to emphasize that LBBB in HF should be diagnosed early and accurately for a better response to treatment. In addition, it is mandatory to search for the exact location and mechanism behind the conductive block in order to select the appropriate treatment.

In this regard, we will try - through this article- to answer questions about LBBB in heart failure and to highlight the gaps in evidence

LBBB definition and diagnosis

According to American and European guidelines of conduction disturbances and cardiac pacing (1-3). LBBB definition is based on 5 main sets of criteria which are: QRS duration and morphology, R wave peak time, Q waves and concordance between ST-T and QRS complex (Table I resume definition criteria).

Table 1. LBBB diagnosis criterions

Complete or advanced LBBB	American guidelines (1,2)	European guidelines (3)
QRS duration	• ≥120 ms: > 16 years • >100 ms 4-16 years • >90 ms: < 4 years	• QRS >_120 ms.
QRS morphology	• Broad, notched or slurred R wave in leads I, AVL, V5, and V6. • An occasional RS pattern in V5 and V6 attributed to displaced transition of QRS complex • QS pattern in V1 V2 but a small r wave may exist	• Notches or slurring in the middle third of QRS in at least two of the following leads: V1, V2, V5, V6, I, and aVL • **Horizontal plane:** QS or rS in V1 with small 'r' with ST slightly elevated and positive asymmetrical T wave and unique R wave in V6 with negative asymmetric T wave. • **Frontal plane:** exclusive R wave in I and aVL often with a negative asymmetrical T wave, slight ST depression, and usually QS in aVR with positive T wave.
Q wave	• Absent Q waves in leads I, V5, and V6. • In the lead AVL, a narrow Q wave may be present in the absence of myocardial pathology	• Unique R wave in V6. • Exclusive R wave in I and aVL
R peak time	• > 60 ms in V5 V6. • Normal in leads V1, V2, and V3, when small initial R waves can be discerned in the precordial leads	• A prolongation at the delayed peak in R in V5-V6 to longer than 60 ms.
ST-T / QRS concordance	• ST and T waves usually opposite in direction to QRS • Positive T wave in leads with upright QRS may be normal (positive concordance). • Depressed ST segment and/or negative T wave in leads with negative QRS (negative concordance) are abnormal.	• The ST segment is slightly opposed to the QRS polarity, and particularly when it is at least 140 ms and is rapidly followed by an asymmetrical T wave also of opposed polarity. • When the QRS is less than 140 ms, the T wave in V6 may be positive.s

It is important to highlight that a QRS duration < 80 ms cannot no matter the age define a conductive bundle branch block and incomplete LBBB in adults require a QRS duration > 110 ms (1,2).

QRS Frontal axis can be normal or deviated to the left, to the right or to a superior plane which is variable according to the latest depolarized myocardial wall according to the excitation vector (1,3).

Strauss et al. (4) in 2011, suggested more stringent criteria to predict response to cardiac resynchronization therapy (CRT). In his study, Strauss refined the diagnostic criteria according to the pathophysiological mechanism of conduction during LBBB, calling it 'true LBBB.'

Strauss assumes that men have larger ventricles that take longer to depolarize, consequently different QRS duration cutoffs need to be considered (≥140 ms (male), ≥130 ms (female)) (4).

Furthermore, he claims that one third of patients diagnosed with complete LBBB by conventional ECG criteria are misdiagnosed (5). Mainly because of the absence of a delayed septal activation of more than 30 ms (trans-septal activation time) which is essential if there is a right to left septal activation.

Therefore, he gave a second criterion about QRS morphology which is a mid-QRS notching or slurring in at least 2 of the leads I, AVL, V1, V2, V5 or V6 and a terminal negative deflection in V1 / V2 (with a QS or rS pattern) (5).

According to the same article (4), Q waves in leads I, V5, and V6 cannot exclude LBBB diagnosis. Although, Previous studies included LBBB with Q waves in V5 V6 were found to predict response to CRT (anterior and/or apical infarcts can lead to Q waves in lateral leads in the presence of LBBB).

Strauss (4,5) goes on to say that the misdiagnosis of a true LBBB came likely from a combination of left ventricle (LV) hypertrophy, LV dilatation, slowed intraventricular conduction, delayed initiation of LV activation (incomplete LBBB) and left anterior fascicular block.

Indeed, an increase in the wall thickness of the LV leads to an increase in the duration of the QRS (approximately, every 3 to 4 mm of increased LV wall thickness in computer simulations added 10 ms to activation and QRS duration) (5). This represents 1/3 of LBBB and labeled as LBBB-like pattern which usually has a smooth R wave and a less delayed ventricular activation (6).

Accordingly, patients with LV dilation and / or hypertrophy and LBBB should have a very significantly prolonged QRS duration.

All the electrocardiographic changes noted above have their clinical and possibly therapeutic implications, particularly on candidates for CRT.

The revolutionary definition of Strauss et al. (4) is strongly correlated with both the extent of LV asynchrony and response to CRT in several studies. According to Tian et al. (7), multivariate analysis showed that true LBBB is an independent predictor of super-response to CRT along with LV end-diastolic dimension (OR=11.680; 95% CI [1.966–69.390]; P= 0.007).

Unfortunately, CRT in HF patients with Right bundle branch block (RBBB) and nonspecific interventricular conduction delay (IVCD) had poorer response compared to LBBB patients.

Howbeit, the wide range of speculations in the electrophysiological mechanisms of LBBBs has led to atypical patterns which may lead to promoting effects in regard to CRT (RBBB that masks LBB delay, atypical LBBB with delayed transition or axis, LBBB with Q waves in left leads without significant R peak time…) (6).

Pathophysiology and pathogenesis of LBBB in heart failure

In LBBB, conductive block may occur at any level in His-Purkinje system, from the distal part of the atrioventricular (AV) node to the left fascicles. The wide anatomical variation in left bundle branch complicates further the diagnosis of LBBB (8,9).

The fact that His-bundle pacing creates significant narrowing of the QRS complex in some LBBB patients, the origin of the block can only be proximal to the pacing site, thus, a considerable part of LBBBs is induced by a proximal block.

These results were explained by the longitudinal dissociation theory which assumes that the conductive fibers of the right and left branch of his-bundle are histologically isolated within the trunk. Injury of the trunk can lead to complete AV block or bundle branch block (10).

According to studies from the late 1970s, bundle branch blocks are due to functional asynchronous conduction in the His bundle rather than an actual peripheral conductive block in the bundle branch (10).

Upadhyay et al. (11) were the first to highlight the presence of left focal intra-hissian block (not a delay) responsible for a complete LBBB. Although, in this cohort study focal and proximal conduction block within the left-sided His fibers accounted for the majority of LBBB patterns and it was successfully resolved after His bundle pacing.

However, the block site can be pre-divisional (from the distal part of the AV node to the left bundle trunk) or post-divisional (in the two left fascicles). This block can due to an acute or subacute decrease in blood supply (coronary atherosclerosis, coronary fistulas, chronic myocardial infarction sequel), to a mechanical compression (mostly iatrogenic episodes during transcatheter aortic valve implantation or during Occluder implantation in septal defects) or to transient

factor that alters conduction properties of His-Purkinje system (class I antiarrhythmic drugs, pulmonary embolism, exercise-induced LBBB, anesthesia...) (11).

Aberrancy (functional block) is a frequent cause of LBBB, mainly during rate-related LBBB and Bundle Branch Reentry Ventricular Tachycardia (BBRVT), this especially the case of acute HF episodes which may aggravate the prognosis (6).

More often, conduction abnormalities may develop in ischemic/non-ischemic cardiomyopathy due to degeneration/fibrosis process of the conduction system, adverse ventricular remodeling, and/or ischemia, and this is usually associated with increased morbi-mortality (13-17). Consequently, LBBB is a consequence of advanced dilated cardiomyopathy.

Impact of LBBB on patients with heart failure

LBBB in general population represents less than 1% but increases with age. It's more frequently encountered in hypertension, coronary artery disease, valvular heart disease, cardiomyopathies and myocarditis (16).

In heart failure, QRS duration > 120 ms occurs in approximately 30% of cases. LBBB is more common compared to right bundle branch block (RBBB) (25% to 36% vs. 4% to 6%, respectively) (17).

Nevertheless, LBBB can develop without risk factors and may reflect degeneration of the intrinsic conduction system. In non-ischemic cardiomyopathy (NICM), it is thought to be secondary to ventricular remodeling and/or fibrosis of the conduction system. Indeed, in patients with dilated cardiomyopathy, QRS duration progressively prolongs with 5 ms annually (16,17).

HF patients with prolonged QRS duration have high rates of all causes of mortality (13-16) and perhaps a higher incidence of death than those with narrow QRS which significantly increases with QRS duration (QRS <120 ms, QRS 120-160 ms and QRS> 160 ms correlated with 20%, 36% and 58% mortality at 36 months, respectively) (17).

In a MUSTT sub study, LBBB and nonspecific IVCD are significant predictors of mortality and sudden death from arrhythmias compared to RBBB (18,19).

Consequently, LBBB is considered as an independent risk factor of mortality in patients with heart failure, and as a consequence of adverse cardiac remodeling with a diseased conduction system.

CRT emerged in the early 2000s as a new era of treatment which targets ventricular conduction delay (especially LBBB) for a better outcome. But can LBBB be a cause of HF rather than a consequence or an aggravating factor? Can CRT be an "antidote" rather than a simple treatment for HF patients with LBBB?

Can LBBB be a cause of heart failure?

Synchronous ventricular conduction is essential for an efficient cardiac performance, this is achieved by an electrical conduction through an intact His-Purkinje system and a fast and homogeneous impulse conduction in a healthy myocardium (20).

LBBB is responsible for electrical dyssynchrony characterized by a successive (rather than simultaneous) ventricular depolarization with a slow conduction originating from the RV free wall gradually propagating to the LV free wall associated to a significantly prolonged transseptal conduction time (usually > 30 ms) (20).

The rest of the LV is activated in a homogeneous but delayed manner, the last activation site usually occurs in the lateral and basal wall (the direction of the conduction vector defines the delayed zone and therefore the QRS axis) (8,20).

Generally, QRS duration of 120 to 150 ms indicates a delay confined to the specialized conduction system, whereas QRS duration > 150 ms usually indicates additional conduction delay in diseased myocardium (20).

Although, QRS duration cannot distinguish between right or left conduction abnormalities and between inter- and intra-ventricular desynchronization. Moreover, a standard electrocardiogram is prone to subjective interpretation and there are several definitions of specific conduction disturbances such as LBBB (there is a 23% disagreement in LBBB classification was found between the European and American guidelines) (8,20).

Therefore, multiple non-invasive techniques have been developed which allow a more precise analysis of electrical desynchronization by incorporating spatial or temporal information (20).

Assessment of electrical desynchronization helps to better understand the cause of LBBB (differentiation between a diseased conduction system and cardiac adverse remodeling) and the pathophysiological mechanism of electrical dyssynchrony which has a great therapeutic impact (especially on technical as well as programming considerations in CRT).

The close relationship between excitation and contraction makes things conceivable that dyssynchronous electrical

activation leads to dyssynchronous ventricular contraction.

A dyssynchronous ventricular contraction exhibit itself through a reverse coupling between contraction and stretching in different myocardial layers during cardiac cycle and its magnitude is determined by the activation delay between LV walls (8). Usually, septal wall and left ventricle free wall (lateral wall most often) are the typically involved layers in mechanical dyssynchrony.

The right anterior septal region is activated rapidly via an intact right bundle, this early activation during the pre-ejection phase is followed by a systolic rebound stretch, sometimes in a bi- or triphasic pattern (21, 22).

In contrast, the left basal posterolateral region is activated late as excitation propagates slowly via cell-to-cell intra-myocardial conduction followed by a strong systolic shortening that continues into diastole (21,22).

This reciprocal contraction/stretching between the septal and lateral walls of the left ventricle has several mechanical, hemodynamic and metabolic consequences.

The early activated septum (before aortic valve opening) results in forces that are unopposed by a similar activation in lateral walls (which it is in his stretching phase), consequently this delays the rise of intracavitary pressure and extends the isovolumetric contraction phase (22).

As the LV lateral wall starts to shorten (late activated lateral wall), there is rebound stretch of the septum and septal shortening at end-systole is significantly reduced. This creates a loss of energy and an overall decrease in ejection fraction (wasted work concept). In addition, the late activation of the posterior papillary muscle results in a non-optimal mitral closure and mitral regurgitation which further decrease the stroke volume (22).

Wasted work concept and the reduction of stroke volume have a strong impact on the outcome of HF patients.

This mechanical dyssynchrony express itself also through a metabolic energy shift to myocardial walls that experience an important amount of wall stress, resulting in septal wall thinning and lateral wall thickening (8).

However, cardiac dyssynchrony during LBBB is complex but can be induced. RV stimulation shares physiological similarities with LBBB, in that it causes late activation of the LV free wall and therefore electromechanical dyssynchrony.

A number of studies identified subtle differences in activation patterns between the two (trans-septal conduction time appeared to be lower with RV stimulation). While LBBB is associated with a circumferential LV activation pattern, RV stimulation shows a strange heterogeneity in wave propagation due to its propensity to resolve or exaggerate existing conduction barriers (23).

In the DAVID trial, the increased risks of heart failure and death during RV pacing were almost entirely among patients with an initial QRS duration of 110 ms, providing evidence that pacing-induced worsening of a pre-existing ventricular conduction delay contributes to adverse effects and serious clinical consequences (17).

A recent Korean multicenter study showed that a QRS > 140 ms has a very high sensitivity (95%) for pacing-induced cardiomyopathy and a QRS > 167 ms has a very high specificity for this cardiomyopathy (23).

These structural and hemodynamic consequences of LBBB as well as the nearly complete recovery of ventricular function after biventricular pacing in so-called super-responders, suggests that LBBB may be the cause of onset of dilated cardiomyopathy in some patients.

Vaillant et al. (25) in 2013 suggested 5 criteria of LBBB induced cardiomyopathy in a retrospective study through 6 super responders' patients who have common characteristics (a history of typical LBBB > 5 years, initial LVEF > 50%, LV dysfunction <40% with NYHA class II-IV, major mechanical dyssynchrony and no apparent cause for the cardiomyopathy).

The NEOLITH I study is a cohort study that compared LVEF improvement in NICM in patients with and without LBBB. Optimal medical treatment at 3 months could not improve LVEF in non-ischemic cardiomyopathy patients with LBBB compared to patients with narrow QRS complex ($p<0.0001$) (26).

Afterwards, the same team conducted the NEOLITH II study to identify the optimal time for CRT implantation in patients with NICM and LBBB (27). In idiopathic non-ischemic cardiomyopathy with LBBB, earlier CRT implantation (< 9 months from LBBB onset) has been associated with more favorable cardiac remodeling. Furthermore, delaying CRT may miss a critical period for stopping and reversing progressive myocardial damage.

These findings corroborate the notion of dyssynchronopathy as a specific pathophysiological entity, but further

prospective studies are needed to confirm the hypothesis of earlier CRT implantation as a first line treatment along with medical therapy.

Gaps in evidence and further insights

Despite the seemingly rational explanation of LBBB induced cardiomyopathy, many questions remain to be answered.

First, all the discussed studies have established the LBBB induced cardiomyopathy diagnosis in 'a posteriori' approach mainly on the basis of normalization of left ventricle function after CRT. Albeit, the diagnosis must be established as earlier as possible and in a prospective way to manage it effectively.

On the other hand, the broad etiology spectrum of dilated cardiomyopathies basically those with a potentially reversible cause, (alcohol, arrhythmic cardiomyopathy…) complicate further the diagnosis and management (28).

Sanna et al (28) propose an early diagnosis approach to identify these patients based on 4 red flags: 1) True LBBB on electrocardiogram 2) Exclusion of any possible cause for cardiomyopathy (especially ischemic causes) 3) A marked mechanical dyssynchrony in echocardiography without severe LV / LA dilatation 4) the absence significant scars or fibrosis in cardiac magnetic resonance.

In spite of its specific characteristics, LBBB cardiomyopathy is an intriguing and difficult diagnosis that can only be made retrospectively due to the lack of clinical and instrumental results certainly identifying affected patients. Even so, reversible causes of cardiomyopathy and some spontaneously resolved LBBBs (31) that can apparently be cured by CRT, tangle further the "a posteriori" diagnosis.

Additionally, many LBBBs can be misdiagnosed as a nonspecific intraventricular conduction block due to LV dilation or electrical axis deviation which can exclude these patients from CRT candidacy.

Second, in case of a suspected LBBB induced cardiomyopathy, is a waiting period of 3 months to assess medical treatment response necessary? many NICM with LBBB significantly respond to medical therapy, which is the case of 25% of patients in a recent review (29).

A sensible proportion of patients who have an apparent recovery under medical therapy, developed LVEF deterioration in long-term follow-up (30). Given these results and those of the NEOLITH I study (26) (< 15% of patients have an apparent healing after 3 months of medical therapy), guideline directed medical treatment is important but there must be something that stops the LV adverse remodeling.

Indeed, a recent study has investigated the efficacy and safety of withdrawal of HF neurohumoral blockers in patients with normalized ejection fractions after CRT (32). It was feasible to withdraw neurohumoral blockers in almost 2 of 3 subjects without observing changes in clinical condition, LV volume, and natriuretic peptides over a follow-up period of 2 years.

Although, the study was not powered to find significant differences or confirm non-inferiority between the 2 groups. But this may indirectly push further towards the diagnosis of LBBB cardiomyopathy and towards CRT as a potential radical treatment of dyssynchronopathy.

Native QRS complex narrowing (and even resolution of LBBB) after biventricular stimulation (in what is called complete reverse electrical and subsequently mechanical remodeling) was suggested by a few clinical studies conducted with a small number of patients (33-35). In these trials, abbreviation of the duration of native QRS was associated with a favorable response as well as greater improvements in LV size and function.

Consequently, HF with recovered ejection fraction after complete reverse remodeling was the main factor suggesting the LBBB cardiomyopathy diagnosis in HF patients with CRT.

Third, if spontaneous QRS narrowing (and even resolution of LBBB) and complete recovery of LVEF (HF with recovered EF or CRT super-responders) after successful CRT were factors leading to suggest LBBB cardiomyopathy, the diagnosis may be excluded after a no or incomplete response to the CRT?

Given the technical challenges of conventional biventricular stimulation and the absence of spontaneous QRS narrowing after CRT in some patients, can the His bundle pacing strategy be an alternative?

According to Arnold et al (36), His pacing can deliver larger reductions in ventricular activation time, which leads to significantly greater improvements in acute hemodynamic function compared to biventricular stimulation in HF patients.

Authors suggest in this article (36) that we could have recruited an unusually high proportion of "nonresponders" to CRT. Therefore, can His bundle resynchronization expand the circle of patients with LBBB cardiomyopathy?

Forth, Post hoc results from the MADIT-CRT, REVERSE, and RAFT trials suggest a potential benefit from CRT in HF patients with LBBB regardless of QRS duration which can expand CRT indication (3).

Finally, novel heart failure therapy armamentarium (mainly Sacubitril-Valsartan and SGLT2 inhibitors) proved to be effective in improvement of LV size and function and even inducing reverse remodeling.

Abudan et al (37) have conducted a retrospective study of HF patient with LBBB under treatment with Sacubitril-Valsartan, after a median follow up of 9 months, there was a complete resolution of LBBB in a small subset of patients.

This may complicate further the diagnosis of LBBB cardiomyopathy and at the same time enlarge the spectrum of dyssynchronopathy (it is important to think of myocardial depolarization but it is mandatory to study myocardial repolarization for further therapeutic improvement).

CONCLUSION

LBBB cardiomyopathy represent an under diagnosed etiology of heart failure which needs an early and accurate diagnosis for a more specific treatment. More prospective studies are needed to expand our knowledge about this distinct nosological entity.

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