Reevaluation of the electrocardiographic pattern of left bundle branch block for proper patient selection and better survival in cardiac resynchronization therapy

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Abstract. According to the present guidelines, in New York Heart Association Class I-IV heart failure, ejection fraction ≤ 35%, and electrocardiographic (ECG) QRS width ≥ 120 ms and left bundle branch block, cardiac resynchronization therapy is indicated. Reevaluation of the MADIT-CRT data and electrophysiologic and pathologic findings of human left bundle branch block gave evidence that "true" left bundle branch block requires a QRS width of ≥ 130 ms (in woman) and ≥ 140 ms (in man). In true, (not continuously widening, but presenting with at least 40 ms abrupt QRS prolongation) left bundle branch block, the initial (septal) QRS forces lose their original left-to-right direction. After the right ventricular depolarization (30-40 ms) an interventricular (slow, muscular) activation occurs that takes ≥ 40 ms, whereas the final depolarization of the lateral wall of the left ventricle takes also ≥ 50 ms, that is to say the total QRS length ≥ 130 ms, or more. After the 40th ms from the beginning of depolarization, notched/ slurred R waves are characteristic, visible in a minimum two of the leads of the I, aVL, V_1, V_2, V_5 and V_6, and a ≥ 40 ms increase of QRS complex develops, if compared to the pre-LBBB QRS time. In contrast, the slow, continuously widened "LBBB-like" QRS pattern mostly belongs to left ventricular hypertrophy, or it is an ECG sign of a metabolic or infiltrative disease.
Key words: heart failure – cardiac resynchronization therapy (CRT) – MADIT-CRT study – morphology of left bundle branch block

Heart failure (HF) is a major public health problem worldwide, with rising prevalence due to aging and nonetheless improved medical treatment and successful prevention of cardiac fatal complications. Cardiac resynchronization therapy (CRT) provides synchronization of the dyssynchronous left ventricular (LV) contraction in heart failure patients with conduction abnormalities and severely reduced left ventricular function, resulting in an immediate improvement of the LV intra- and interventricular dyssynchrony, mitral regurgitation and also in an acute increase of LV intraventricular endiastolic pressure. During long term follow-up, patients exhibit significant reduction of LV diastolic and LV systolic volume, and improvement in LVEF, and this process is described as LV reverse remodeling.

Cardiac resynchronization therapy, or a combination of CRT with an implantable cardioverter defibrillator(CRT-D), is proven to reduce heart failure symptoms, hospitalization and mortality of patients with New York Heart Association Class I-IV drug refractory heart failure, with reduced ejection fraction (LVEF ≤ 35% and QRS prolongation ≥ 120 ms), and has been accepted as a well-defined therapeutic option (1).

Despite the success of the cardiac resynchronization therapy (CRT) in the treatment of systolic heart failure with

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ejection fraction below 35%, there have remained unanswered questions of the proper patient selection for CRT, leading to a renewed interest in defining more appropriately the electrocardiologic expression (2, 3) of the left bundle branch block (LBBB).

Normal cardiac activation and QRS complex

Patients with LBBB have a significant dyssynchrony between activation of interventricular septum and left ventricular wall, and that is corrected in most of CRT patients. In contrast, in cases of increased QRS duration due to other, nonspecific, interventricular conduction disturbances like right bundle branch block, LV dilatation or hypertrophy, intramural or fascicular blocks, hyponatraemia, hyperkalemia, infiltrative diseases like sarcoidosis and amyloidosis, CRT does not result in functional improvement of LV systolic function. It is important to emphasize that in cases of diffuse slowing of intraventricular conduction without a considerable changing in LV activation sequences, the activation delay between the interventricular septum and left lateral LV wall is proportional only with the systemic activation slowing without significant LV dyssynchrony.

Normally, the interventricular septum is the first portion of the ventricle to be depolarized. It is activated from left to right by fibers originating from the proximal portion of the left bundle branch, and this is responsible for the electrophysiologic contribution of the initial part of the QRS complex. The initial depolarization wave most often results in a small, narrow Q wave in leads I, aVL V_5 and V_6 – commonly described as "septal Q wave" – , and often associated with small R waves in the V_1 and V_2 leads (4). Thereafter the impulse spreads down the main fascicles of the left bundle, and in the right bundle – which are divided also into two, rarely three, fascicles, – leading to the simultaneous activation of the Purkinje network, and depolarizing of the two ventricles terminating the electrical activation of the posterobasal parts of both ventricles (5).

When the impulse conduction in the left bundle branch is blocked, the initial activation of the interventricular septum, that goes from left to right, cannot occur, and only the right bundle branch is activated. After the right bundle branch activates the right ventricle, the electrical impulse – by a slow muscular conduction – spreads through the interventricular septum and reaches the septal endocardial surface of the LV. From the electrophysiological point of view it means that by loss of the initial left-to-right direction of electrical activation the normal septal Q waves in the I, aVL, V_5, V_6 are not generated, and the normally visible initial V_1 and V_2 R waves are missing. All of that is also expressed as the significant prolongation of the depolarization and deformation of the QRS complex.

QRS duration and effectiveness of cardiac resynchronization therapy

The results of the major multicentric randomized trials (6, 7) has led to the adoption of CRT approved as the ≥ 120 ms QRS duration as a minimal ECG requirement for the success of the biventricular pacemaker therapy, and does not select patients on the basis of QRS morphology. In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, patients without LBBB did not have significant benefit, and those with QRS duration ≤ 147 ms had absolutely no benefit (6). A pooled analysis of two smaller trials (8) found no significant improvement in LVEF or maximal oxygen consumption in patients with right bundle branch block (RBBB). A report on almost 14,946 patients receiving CRT showed that those without LBBB had increased early and late mortality compared to the patients with LBBB, and QRS duration of ≥ 150 ms predicted more favorable outcomes in LBBB, but not in RBBB (9). These studies involved patients only with severe (New York Heart association class III and IV) heart failure. The Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT) trial enrolled patients with New York Heart association class I and II heart failure and QRS duration ≥ 130 ms (10). In this study the final analysis considered thresholds of QRS duration separately for men and women. The benefit from CRT was significant in women beginning at QRS duration ≥ 130 ms (QRS duration 130 to 139 ms HR 0.19, $p < 0.05$), but there was no benefit in men with QRS durations < 140 ms (HR 1.12, $p > 0.05$) and nonsignificant benefit in the QRS duration from 140 to159 ms (HR 0.76, $p > 0.05$) (10).

Former data of the electrocardiologic investigations on left bundle branch block

The first reliable electrophysiologic description of LBBB originates from the human epicardial stimulations of the right and left bundle branch of Barker et al (11) in which they simulated the ECG pattern of RBBB and LBBB. After the introduction and more widespread application of the precordial 12-leads Wilson (12), using a dog model of surgically induced LBBB, described in details the ECG findings, and as characteristics of LBBB he described rS wave in the V_1 - V_2 leads, and a single broad notched R wave in the V_5 and V_6 leads. He also stated (11) that when precordial leads are not available, the key distinguishing feature of "complete LBBB" from "incomplete bundle branch block" is a QRS of ≤ 120 ms. Thus the threshold of 120 ms was established on the basis of experiments made on dogs, and not on objective measurements on women and men (12). It is important to mention that the concept of left anterior and posterior

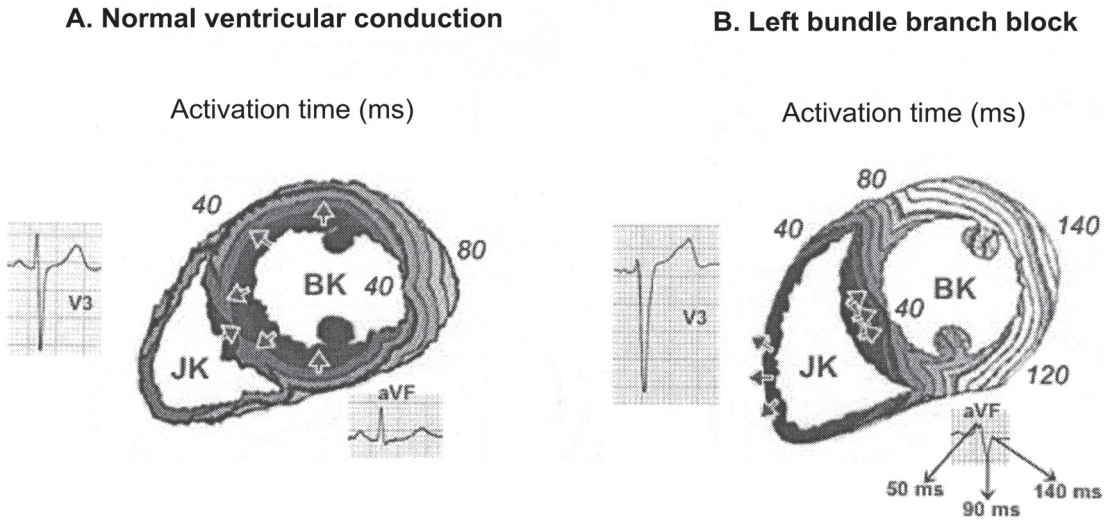

Figure 1 Ventricular activation sequences and time intervals in normal ventricular conduction (A) and in left bundle branch block (LBBB) (B). In normal conduction the interventricular septum activates from left to right. In LBBB the right ventricle activates normally (initial 30-40 ms), and the activation proceeds through the septum for 40 to 50 ms before reaching LV endocardium. It then requires another 50 ms for reentry into the LV Purkinje network and to propagate to the posterolateral wall of the left ventricle. The increase in septal or posterolateral wall thickness, or LV endocardial surface area, further increases QRS duration. The first notch occurs (about 50th ms) and represents the time when the electrical depolarization wave front, after proceeding through the septum, reaches the LV endocardium. The second notch occurs when the depolarization wave front begins to reach the epicardium of the posterolateral wall (modified according to 3)

hemiblock, and the effect of left ventricular hypertrophy which could also prolong QRS time beyond 120 ms, had not been distinguished at this time (3).

In 1956 Grant and Dodge (13) studied 128 patients with QRS durations ≥ 120 ms and LV conduction delays, who had an ECG of normal intraventricular conduction during the previous two years. They emphasized that LBBB can be justified only by the histologic examination of the bundle branch. In their own series of 128 patients who developed LBBB by conventional ECG criteria, 51 (40%) had no change in the direction of initial QRS forces (13). They concluded that the prolongation of the QRS in these LBBB patterns could be linked primarily by LVH or by earlier myocardial infarction and consequent myocardial scar. They concluded that in 1/3 of the cases according to the LBBB criteria established in earlier dog experiments (12) could not be applied to humans. Their basic ECG observations in "true" LBBB were the follows:

a. In LBBB, the width of QRS complex increases by ≥ 40 ms, but as a mean by 50-60 ms.
b. The direction of the initial QRS forces by the development of LBBB also changes, and the V_1 and V_2 (septal) inital R waves – which are the physiologic signs of left-to-right direction septal activation, mostly disappear.

After the retarded (muscular) right-to leftward activation of the interventricular septum, the activation of the left lateral wall takes also 50 ms, as is proved by the computer simulation model of Selvester and Solomon (14). The altered septal activation, which is the first 30-40 of the QRS interval, is dominated by the right ventricular activation. A recent investigation indicates (15) that if the V_1 R wave is ≥ 0.1 mV, this practically excludes LBBB, since it is an indication of the left-right septal activation wave front **(Figure 1)**.

Endocardial potential mapping in left bundle branch block

In 1984 Vassalo et al (16) performed endocardial catheter mapping with 10 mm interelectrode distance in 18 patients with LBBB. Four patients had no organic disease (group I), six had cardiomyopathy (group II) and eight had coronary artery disease and previous myocardial infarction (group III). Total left ventricular (LV) activation time was significantly longer in group III (119 ms) than group I (81 ms; $p < 0.05$) and group II (61 ms; $p < 0.01$). Duration of mean total right ventricular (RV) activation was 36 ms and the longest activated site of RV endocardial activation after the onset of the QRS complex was at 44 msec. The QRS durations were 156 ± 5 ms, 158 ± 15 and 191 ± 14 ms in groups I, II and III, respectively. After the right ventricular activation, the septal activation occured with a right to left direction,

with a highly variable LV breakthrough time. In 12 of out of the 18 patients they found only a single LV brakthrough site, which was located on the mid-septum, and in 6 cases multiple breakthrough sites occurred. The inferior basal or lateral free wall was the latest site of LV activation in 12 of the 18 patients. The authors also found that the surface QRS complexes in patients with LBBB and previous myocardial infarction were significantly longer than those in patients with no known heart disease or patients with no ischemic cardiomyopathy. In the terminal phase of endo-epicardiaal left lateral wall activation the isochrones has a wider spacing, suggesting a more rapid spread of activation, possibly due to participation of the Purkinje system (17, 18).

Auricchio et al. in 2004 (19) studied LV activation sequences in 24 patients with heart failure and LBBB QRS morphology, using simultaneous application of 3D contact and noncontact mapping during intrinsic rhythm and asynchronous pacing. Approximately one third of the patients with typical LBBB, QRS morphology had normal transseptal activation time, and slightly prolonged or near normal LV activation time. The time between the onset of earliest QRS deflection and the left ventricular endocardial breakthrough (transept activation time) was < 20 ms (19). Patients with coronary artery disease had a significantly longer total LV edocardial activation time (121 ±17 ms) versus the nonischemic patients (99 ± 17 ms), p < 0.02, but a similar transseptal activation time (39 ±34, versus 45 ± 33 ms, p= 0.724). In 68% of the patients the transseptal time was longer than 40 ms, and patients with longer than 40 ms transseptal time also had a longer QRS complex (170 ± 16 ms, versus 133 ± 28 ms) respectively. The same authors in a subsequent study included patients with either RBBB or LBBB (20). All patients with RBBB had a single RV septal breakthrough site, with a mean transeptal activation time of 59 ± 13 ms. This provided further evidence that patients with LBBB by conventional ECG criteria, but transseptal times < 20 ms, do not actually have complete LBBB.

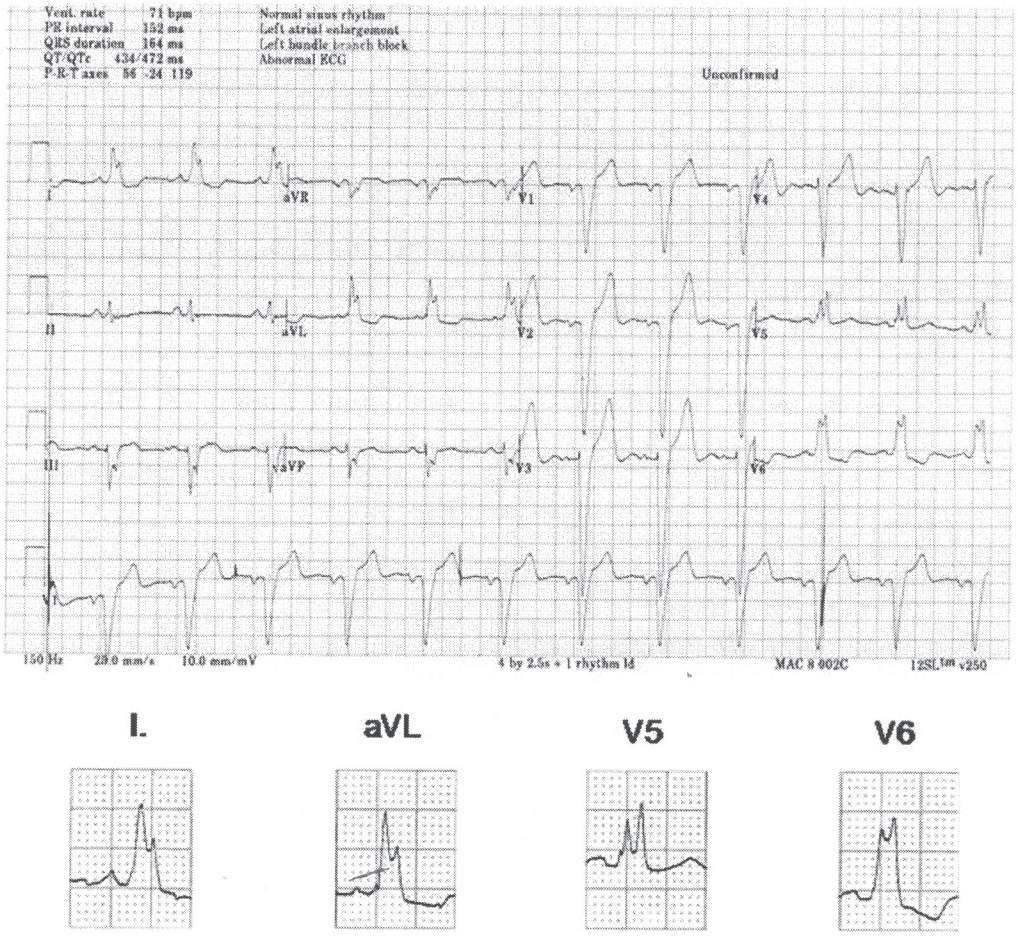

Figure 2 "True" left bundle branch block, total QRS duration is 160 ms. Notice the QRS morphology that includes distinctive mid-QRS notching in leads I and aVL, V_5 and V_6 along with mid-QRS slurring.

Definition of the complete left bundle branch block

Conventional criteria for LBBB that are used clinically include a QRS duration ≥ 120 ms, QS or S in lead V_1, and a monophasic R wave with no Q waves in lead V_6 and I (21). There is a more detailed definition in the AHA/ACCC/HRS recommendations (22) that also includes "broad notched or slurred R waves in leads I, aVL, V_5 and V_6 and an occasional RS pattern in V_5 and V_6 attributed to displaced transition of the QRS complex". The delayed (≥ 40 ms) septal activation time seems to be a determining point in the morphology of complete LBBB. The notched or slurred R waves that are present in a minimum two leads from I, aVL, V_1, V_2, V_5 and V_6 are also important as has been demonstrated by computer simululation of LBBB (23). The first notch (at the 50th ms of QRS) represents the time when electrical depolarization wave front gets through the septum and reaches the endocardium of the LV. The second notch indicates the point when the depolarization wave front begins to reach the epicardium of the lastly depolarizing posterolateral LV wall **(Figure 2)**. The slurring between the two notches is due to the moderate change in QRS amplitude, and to the persisting magnitude and direction of the mean electrical vector, whereas the endocardial depolarization wave front proceeds around the LV approaching the posterolateral free wall.

Knowing the prolonged septal activation time and retarded LV circular activation that gradually reaches the posterolateral wall, there is a minimum threshold to diagnose complete LBBB of ≥ 140 ms in men and ≥ 130 ms in women (3). The thresholds differ because men have larger hearts that take longer to depolarize. In normal conduction, the mean QRS duration is 92.7 ± 9.3 ms for men and 87.1 ± 8.7 ms for women (24). In cases of LBBB there is an addition intraventricular conduction delay of a minimum 60 ms, which consists of 40 ms conduction retard of activation to reach the LV endocardial surface and a further ≥ 20 ms to reenter the Purkinje network and proceed to the LV lateral wall (2, 12). It takes altogether 150 ms, which was the shortest QRS time duration, where the biventricular pacing modality gave a statistically favorable outcome on LBBB patients participating in the MADIT-CRT investigation (25).

In the endocardial mapping study by Auricchio et al. (19) of patients of LBBB by conventional ECG criteria, the QRS duration was also consistent with that, 170 ± 16 ms, whereas QRS duration was 133 ± 28 ms in other LBBB patients. A recent study by Mascioli et al. (26) investigated the *new strict LBBB criteria* (3) to predict benefit from CRT. In multivariate analysis, the presence of "false LBBB" (meeting conventional LBBB criteria but not the *new strict LBBB criteria*) predicted a close to four-fold (HR: 3.98) increase of heart failure hospitalization or death, compared with "true LBBB", and "true LBBB" was the only variable significantly related to a greater increase in LV ejection fraction (HR: 4.57). This was however a small, single center study and the results should be confirmed in a larger population. A recent publication indicates also a new perspective in data handling, since automated analysis of ECG records and QRS duration thresholds could also be normalized to a case specific LV size and morphology (27).

As a summation of the previous experimental data on LBBB, and the significance of QRS morphology provided by the evidence based CRT, studies evaluating the success and patient benefit of CRT intervention give solid evidence that the "conventional criteria of LBBB" cannot be applied for selecting appropriate CRT candidates. The retrospective analysis of MADIT-CRT (10, 25) and also data review of other CRT populations (3, 4, 8, 9, 26) indicate statistically proved benefit in the amelioration of HF symptomatology in patients who fulfill, as a minimum, points 1. and 2. of the n*ew strict LBBB criteria that follow:*

1. QRS duration ≥ 130 ms in women and ≥ 140 ms in men.
2. Double notching and slurring from the onset of QRS of depolarization 40 ms in minimum two of the I, aVL, V_1, V_2, V_5, and V_6 leads.
3. Abrupt prolongation of the QRS complex with normal conduction (if former ECG available) by a minimum 40 ms, but frequently by 50-70 ms.
4. Continuously documented prolongation of the QRS (without sudden increase) suggests left anterior hemiblock and LV hypertrophy or other (metabolic/infiltrative) origin.

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