Differentiation between left bundle branch block and left ventricular hypertrophy: Implications for cardiac resynchronization therapy

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Abstract

Recent clinical trials have demonstrated that cardiac resynchronization therapy (CRT) reduces heart failure hospitalizations and mortality in patients with complete left bundle branch block (LBBB), but potentially not those with right bundle branch block or nonspecific LV conduction delay, such as that due to LV hypertrophy (LVH). Furthermore, endocardial mapping and simulation studies have suggested that one-third of patients diagnosed with LBBB by conventional electrocardiographic criteria are misdiagnosed, and these patients likely have a combination of LVH, LV chamber dilatation and delayed initiation of LV activation (incomplete LBBB). Increase in LV size due to hypertrophy/dilatation and slowed intramyocardial conduction velocity prolong QRS duration in patients with LVH, which can frequently go above the QRS duration threshold of 120 ms conventionally used to diagnose LBBB. New strict criteria for diagnosing complete LBBB have been proposed that utilize longer QRS duration thresholds (130 ms in women and 140 ms in men) and require the presence of mid-QRS notching/slurring in at least 2 of the leads I, aVL, V1, V2, V5 or V6. The emergence of CRT has led to an increased need to differentiate complete LBBB from LVH and other types of intraventricular conduction delay, which should be further studied.
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Cardiac resynchronization therapy (CRT) improves left ventricular (LV) mechanical function, decreases heart failure hospitalization and prolongs survival in patients with heart failure and prolonged QRS duration by decreasing dyssynchrony between the interventricular septum and LV lateral wall.[1–4] However, as demonstrated in recent analysis, CRT results in large benefit in patients with complete left bundle branch block (LBBB),[5] but potentially not those with right bundle branch block or nonspecific LV conduction delay (intraventricular conduction delay), which could be due to left ventricular hypertrophy (LVH). This was especially evident in analysis of the Multicenter Automated Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT), which enrolled New York Heart Association Class I and II heart failure patients.[3,6] CRT led to a significant reduction in heart failure events or death in LBBB patients, however there was a trend (p = 0.10) toward more heart failure events and death in patients with intraventricular

conduction delay who received CRT-Defibrillators compared to implantable defibrillator only.[6] This highlights the importance of being able to differentiate conduction delay due to LVH from conduction delay due to complete LBBB.

QRS prolongation with LVH

While the most common electrocardiographic (ECG) criteria for LVH consider only QRS voltage changes, the Cornell time–voltage index or QRS area measurement improves the diagnosis of LVH.[7] Increasing thickness of the LV wall results in an increased QRS duration. With an average transmural conduction velocity of 30 to 40 cm/s, every 3 to 4 mm of increased LV wall thickness in computer simulations added 10 ms to activation and QRS duration (Fig. 1).[9] Accompanying LV dilatation or decreased conduction velocity, which often occurs with LVH, further increases activation time and QRS duration. This results in patients with LVH having QRS duration greater than 120 ms, which is traditionally used as the threshold to diagnose LBBB. Fig. 2 shows successive ECGs from a

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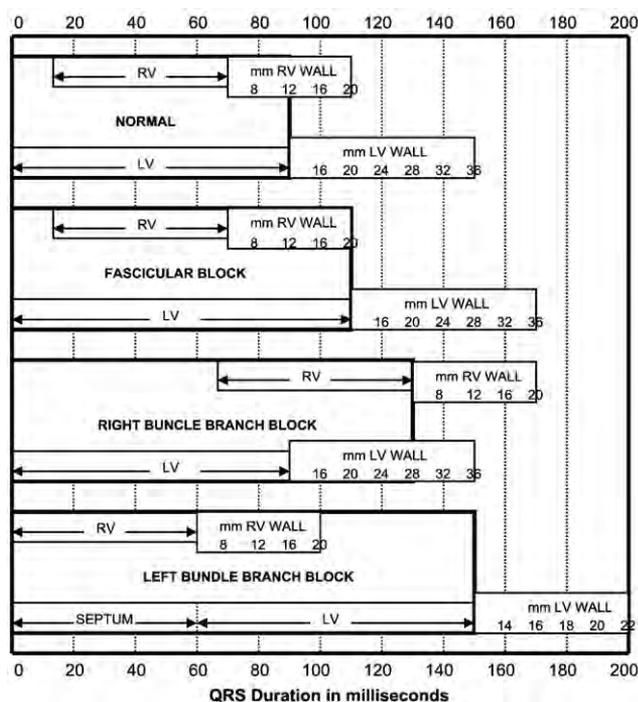 *E-mail address:* david.strauss@fda.hhs.gov

Fig. 1. Combined effects of conduction defects and hypertrophy on QRS duration. Top row shows normal conduction, second row shows fascicular block, third row shows RBBB, and fourth row shows LBBB. The effect of LVH (mm LV wall) on QRS duration is different in LBBB because the depolarization of the anteroseptal and posterolateral walls is completely uncoupled. Modified with permission from Selvester.[8]

patient who had a QRS duration of 92 ms at baseline and over 6.5 years developed progressive QRS prolongation to 142 ms documented by 42 ECGs. The gradual QRS prolongation of 6.2 ms/year is characteristic of QRS prolongation due to progressive LVH, not complete LBBB that results in a sudden QRS prolongation of greater than 60 ms (Fig. 3). The gradual QRS prolongation in this patient may be due to a combination of increased LV wall thickness and dilatation, along with slowed intramural conduction velocity that can occur with LVH.

False-positive diagnosis of LBBB

Separate evidence has accumulated that one-third of patients diagnosed with complete LBBB by conventional ECG criteria (QRS duration $\geq$ 120 ms and LV conduction delay) are misdiagnosed.[11] Specifically, two endocardial mapping studies found that one-third of patients with LBBB by ECG did not have activation consistent with complete LBBB,[12,13] and one study with ECGs before and after

supposed LBBB onset found that one-third of patients did not have a change in the electrical vectors of the first 40 ms of the QRS with LBBB, which should occur if septal activation is only occurring from right to left in true LBBB.[14] Instead, patients meeting conventional ECG criteria for LBBB, but not having endocardial activation consistent with complete LBBB, likely have a combination of LVH, LV dilatation, slowed intraventricular conduction, delayed initiation of LV activation (incomplete LBBB) and left anterior fascicular block.[9,10] Bacharova and colleagues demonstrated with simulations that delay in the onset of activation in the LV (incomplete LBBB) or slowed intramyocardial conduction velocity in the LV could lead to typical LBBB patterns on the ECG.[15] On the basis of additional insights from computer simulations, new criteria for complete LBBB have been proposed that include a terminal negative deflection in V1, QRS duration $\geq$ 140 ms for men and $\geq$ 130 ms for women, and also mid-QRS notching or slurring in at least 2 of the leads I, aVL, V1, V2, V5 or V6.[9,10] Different QRS duration thresholds for men and women are used because men have larger ventricles that take longer to depolarize.[16] Furthermore, the presence of notching is critical for the diagnosis of LBBB. The notch should begin after the first 40 ms of the QRS, but before 50% of QRS duration, when the activation wavefront reaches the endocardium of the LV (at 50 ms in Fig. 4). The notch should end at approximately 2/3rd through QRS duration when the activation wavefront reaches the LV lateral wall epicardium (at 90 ms in Fig. 4). Taking note of where the notch occurs is important because chronic infarction[9,17,18] or scar in nonischemic cardiomyopathies[19–21] can create QRS notching. This can occur in patients with LVH or non-specific LV conduction delay (potentially resulting in false positive LBBB diagnosis) and in patients with LBBB (potentially changing the amplitude of where the notch occurs). The reader is referred to prior reports that detail how to differentiate and quantify infarction in the presence of LBBB, LVH and other conduction abnormalities.[9,17,22]

Future directions

LVH is a complex disease that results in anatomical and electrophysiological changes.[23] Conventional criteria for LBBB likely diagnose many patients with LBBB that actually have QRS prolongation due to LVH. Patients with combinations of LVH / LV dilatation and LBBB should have very significantly prolonged QRS duration. As the diagnosis of LBBB is important for predicting benefit from CRT, the emergence of this new therapy has led to a need to revisit

Fig. 2. Electrocardiograms from a patient who developed an LV conduction delay with a QRS duration of 142 ms that can be classified as LBBB under conventional criteria but likely represents progressive LVH. The scatterplot (A) shows QRS duration measurements over time from 42 electrocardiograms from the same patient. The patient's QRS duration increased linearly at a rate of 6.2 ms/year. Electrocardiograms are shown at baseline (B) and after 6.5 years (C). Although later electrocardiograms met conventional ECG criteria for LBBB (QRS duration $\geq$ 120 ms with an LV conduction delay), review of the serial electrocardiograms demonstrated that QRS morphology did not change as the QRS prolonged. The onset of true complete LBBB should result in a sudden increase in QRS duration with a change in QRS morphology. The gradual increase in QRS duration over time strongly suggests the development of intraventricular conduction delay due to hypertrophy rather than the onset of bundle branch block. Although serial electrocardiograms are not always available, this patient did not have mid-QRS notching in front-to-back (V$_1$, V$_2$) or left-to-right leads (I, aVL, V$_5$, V$_6$), which should be present for the diagnosis of complete LBBB. Reproduced with permission from Strauss et al.[10]
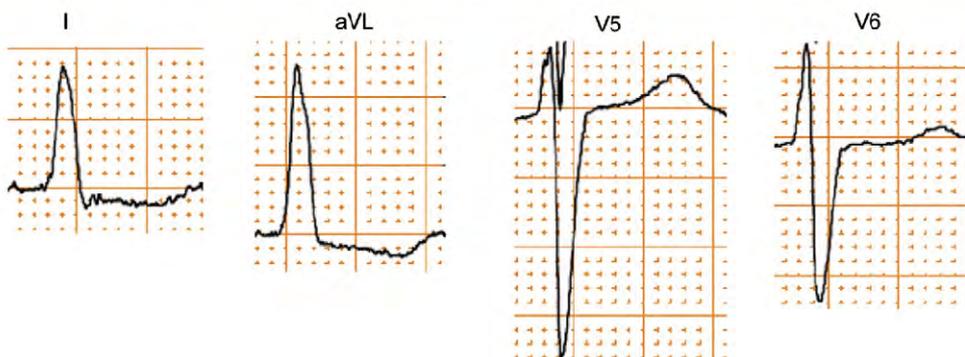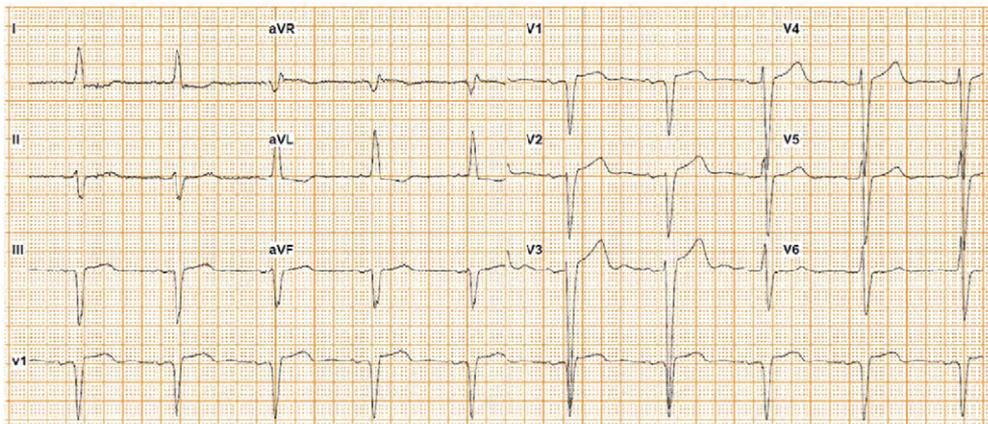
A. QRS duration over time

R=0.92 (*P* < .001)

Slope of line = 6.2 ms/year
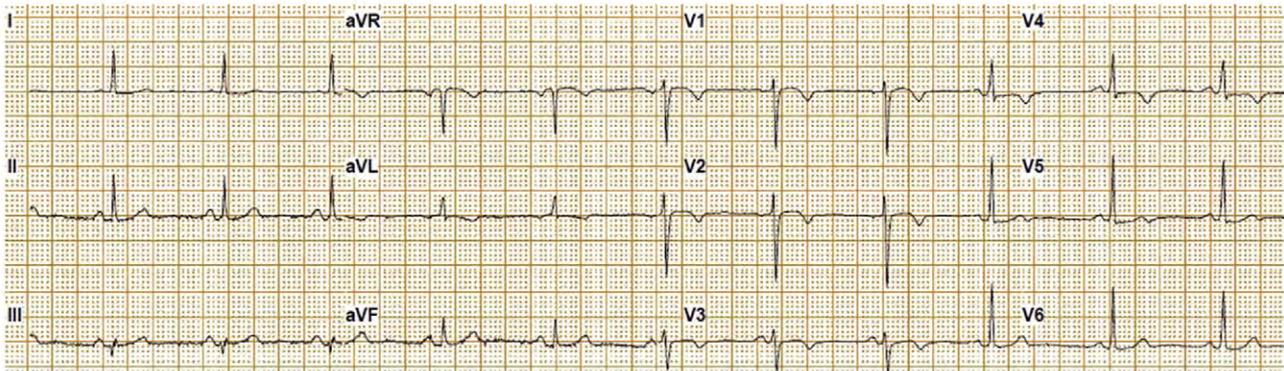increase in QRS duration
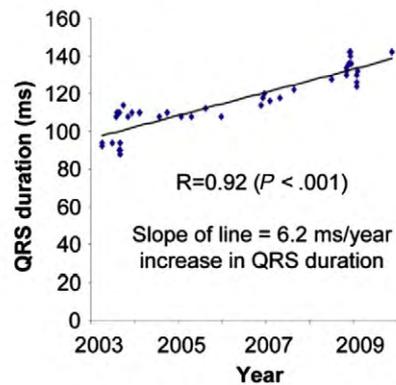
B. Initial ECG: QRS duration = 92 ms
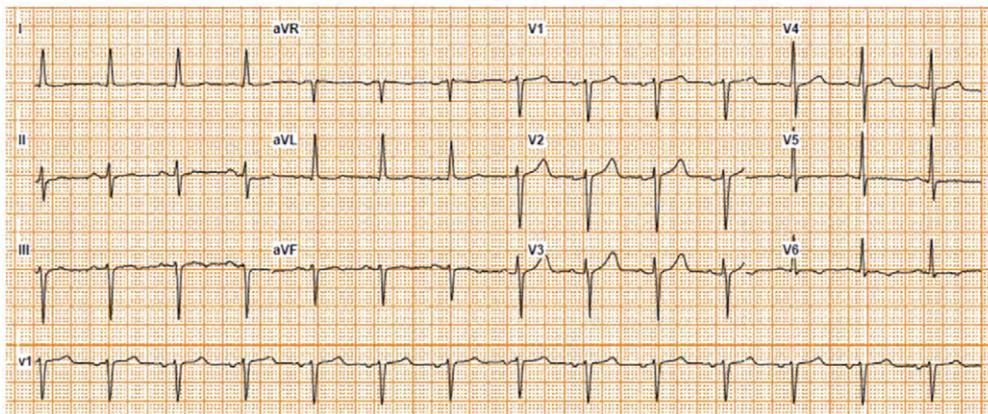
C. ECG after 6.5 years: QRS duration = 142 ms

A. Initial ECG: QRS duration = 76 ms

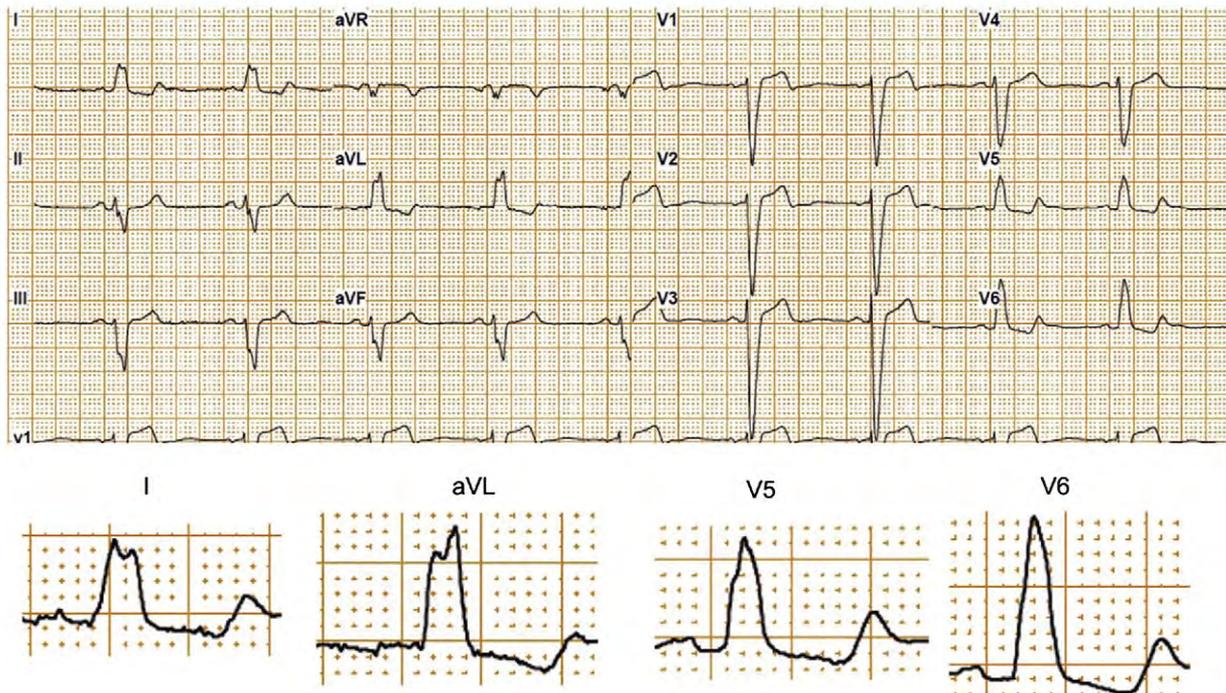## B. ECG 1 year later: QRS duration = 148 ms

Fig. 3. Electrocardiograms from an 82-year-old woman with a sudden increase in QRS duration from 76 ms (A) to 148 ms (B) 1 year later (a 95% increase) with the development of complete LBBB. In addition to the increase in QRS duration, notice the change in QRS morphology that includes distinctive mid-QRS notching in leads I and aVL, along with mid-QRS slurring in leads V_5 and V_6. Reproduced with permission from Strauss et al.[10]

ECG criteria for LBBB and LVH. In the future, it might be possible to normalize QRS duration thresholds to body surface area, or LV mass or LV anatomy[24]; thus, using anatomical measurement of LVH and LV dilatation to guide the diagnosis of LBBB.

Regarding the scope of this issue, the National ICD Registry, which is estimated to capture 90% of ICD implantations in the U.S., documented 58,953 CRT-D implants in 2009,[25] indicating there were approximately 65,500 total CRT-D implants in the U.S. that year. A prior study showed that 31% (20,000) of CRT-D patients were diagnosed with RBBB or nonspecific intraventricular conduction delay.[26] Of the remaining 45,000 CRT-D patients diagnosed with LBBB by conventional ECG criteria, 1/3rd (15,000) may not actually have complete LBBB. This does not include patients receiving CRT without defibrillation ("CRT-P"), and all patients outside the U.S.

Future studies should continue to characterize the ability of the ECG to predict which patients will benefit from CRT. Rickard et al. found that increased QRS duration in non-LBBB patients was associated with better response to CRT (defined by decrease in LV end-systolic volume).[27] However, that study did not involve a control group. In the Multicenter InSync Randomized Clinical Evaluation (MIR-ACLE) trial, 435 patients received CRT device implants, however half of the patients were randomized to have pacing turned off, which was blinded to the patients and treating physicians. That study revealed that 27% to 44% in the control group (pacer off) "responded" to CRT according to the three primary clinical end points.[28,29] This highlights that there can be an apparent significant benefit from CRT in studies that is a combination of the placebo effect and patients receiving better care when enrolled in a clinical study. Inclusion of adequate control groups is critical to take
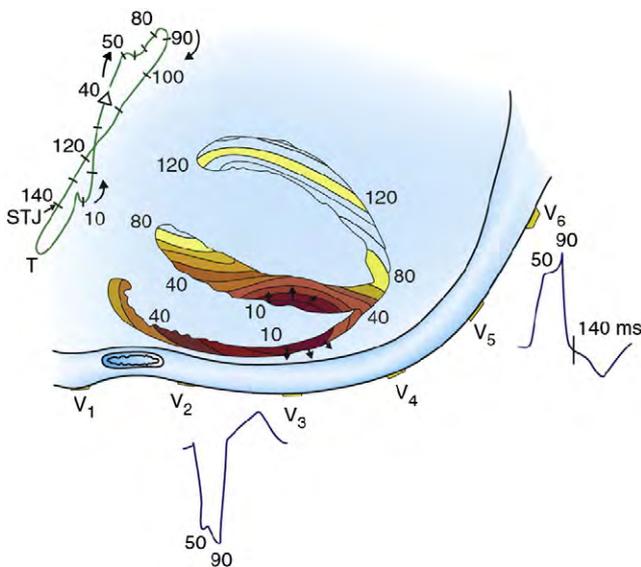
Fig. 4. Ventricular activation sequence, electrocardiogram waveforms, and transverse plane vector loop (vectorcardiogram) in LBBB. Colored lines represent areas of myocardium activated within the same 10-ms period (isochrones). Numbers represent milliseconds since beginning of activation. The characteristic mid QRS notching of LBBB begins when activation breaks through to the LV endocardium (50 ms) and ends when activation reaches the epicardium of the lateral wall (90 ms). Modified with permission from Strauss and Selvester.[9]

this into account and separate biomarkers (e.g. such as QRS duration or morphology) that predict prognosis from those that predict efficacy of therapy.

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