ECG Patterns In Cardiac Resynchronization Therapy

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Abstract
Cardiac resynchronization therapy is an established treatment modality in heart failure. Though non-response is a serious issue. To address this issue, a good understanding of the electrical activation during underlying intrinsic ventricular activation, biventricular as well as right- and left ventricular pacing is needed. By interpreting the 12-lead electrocardiogram, possible reasons for suboptimal treatment can be identified and addressed. This article reviews the literature on QRS morphology in cardiac resynchronization therapy and its role in optimization of therapy.

Introduction
Cardiac resynchronization therapy (CRT) is a useful treatment modality in patients with left ventricular (LV) dysfunction and ventricular conduction disturbances. The delayed ventricular electrical activation results in a dyssynchronous ventricular contraction. CRT aims to restore the dyssynchronous contraction and has shown to result in improved quality of life, exercise tolerance, cardiac function, and survival.1-5

As a significant amount of patients does not respond to CRT, a lot of research has deservedly focused on optimization, and better patient selection. Various techniques have been studied to identify the proper CRT candidate. Interestingly, of all the techniques studied, the most trustful method to identify the presence of ventricular dyssynchrony is the use of the “simple” 12 lead electrocardiogram (ECG).6-7 This is the reason why current guidelines only include ECG parameters as measurement of ventricular dyssynchrony, which are QRS duration and the presence of left bundle branch block (LBBB) QRS morphology.8

Although many studies focus on the ECG to select patients for CRT, only a limited number of studies focus on the ECG during CRT. This seems remarkable as the ECG during CRT can provide important information on LV lead location, presence of scar at LV pacing site, and fusion of intrinsic activation or RV pacing with LV pacing. In this manuscript we review literature on QRS patterns during CRT.

QRS Morphology Patterns
The QRS pattern in CRT is usually composed of two merging activation wave fronts, which makes interpretation more difficult. CRT is mostly achieved by a combination of RV and LV pacing (biventricular pacing) or LV pacing fused with intrinsic ventricular activation. Therefore, it is important to understand the timing and direction of the activation wave fronts during a) underlying intrinsic ventricular activation, b) RV only pacing, and c) LV only pacing, before the QRS patterns in d) biventricular pacing can be understood.

QRS Pattern Of Underlying Ventricular Activation
In several studies it has been shown that the ideal patient, who responds to CRT, is the patient with underlying LBBB. In patients with LBBB, conduction through the right bundle branch is not affected and the ventricular activation begins in the right ventricle, before it proceeds to the LV endocardium. The LV endocardium is reached through the septum, which takes 40 to 50 ms. This transseptal conduction time can however be prolonged in the presence of heart failure.9 It then requires another 50 ms to propagate to the endocardium of the posterolateral wall and takes an additional 50 ms to activate the myocardium at this side of the LV. Producing a total QRS duration of 140 to 150 ms (figure 1).

Conventional ECG criteria to describe LBBB include a QRS duration ≥120 ms, QS or rS in lead V1, and a monophasic R wave with no Q waves in leads V6 and I (figure 2). Strauss et al.10 strongly supported that notched or slurred R waves should also be present in lead I, aVL, V5, or V6, as demonstrated in figure 1. The first notch, which occurs approximately 50 ms after onset of the QRS, represents the electrical depolarization of the septal endocardium. The second notch occurs when the depolarization wave front begins to reach the epicardium of LV free wall and endocardium of the LV lateral wall. The reason there is slurring with little change in QRS amplitude
between the 2 notches is that the magnitude and direction of the mean electrical vector remains constant once depolarization reaches the endocardium of the LV because it has to proceed outward in the septum and around the LV to the lateral free wall. These notches are best seen in leads I, aVL, V1, V2, V5, and V6.

Eventhough studies show LBBB patients to have higher response-rates, the large randomized clinical trial such as REVERSE, MADIT-CRT and RAFT have used LBBB criteria that are non-specific. (QRS≥120ms, rS/QS in V1). Therefore, an important part of patients included in these large trials would have had a non-LBBB QRS morphology when more specific (ESC, AHA or Strauss) criteria would have been used. Studies of activation mapping in non-LBBB patients however, are less common. A recent study using epicardial activation mapping showed that intraventricular conduction delay (IVCD) was associated with a significantly more heterogeneous ventricular activation than in LBBB. Though mean total LV activation time was significantly shorter than in LBBB patients. Possibly because of lesser and more favorable ‘lines of block’ as visualized by ECG mapping. This results in significantly less ventricular electrical uncoupling (VUE) and interventricular dyssynchrony.11 As a consequence more studies are needed to (1) identify the LBBB criteria best correlated to outcomes in CRT, and
(2) to identify which patients with a non-LBBB QRS morphology could still benefit from CRT.

QRS Pattern During Rv Pacing
Different RV lead locations have been studied in CRT. RV apex, RV septal and RV outflow tract region are the locations used to target RV pacing. Studies up till now have not shown any differences in outcomes of CRT for the different RV pacing locations.12-14 In clinical practice the RV pacing site that is mostly used in CRT is the RV apex.

RV pacing results in a LBBB like QRS pattern in the precordial leads with a negative QRS complex in lead V1 recorded at the 4th intercostal space. RV apex pacing usually produces a left superior paced QRS axis in the frontal plane as the activation spreads from right to left and superiorly away from the apex. Occasionally a right superior QRS axis is found in RV apex pacing, especially with enlarged and leftward displaced hearts.

Pacing from a septal RV lead position results in a more horizontal to left inferior heart axis, as in normal intrinsic ventricular activation.15,16 Positioning of the RV pacing lead at the RV outflow tract shifts the paced QRS axis further to left inferior or even right inferior, as the pacing site shifts more superior, close to the pulmonary valve.

A dominant R wave in lead V1 is considered to be right bundle branch block (RBBB) pattern and associated with a pacing site on the LV free wall. Therefore, a positive QRS complex during RV pacing should prompt evaluation of a RV pacing lead. RV pacing lead can for example be accidently placed in the mid cardiac vein. Firstly however, the position of precordial leads V1 and V2 should be checked as a dominant R wave can sometimes be recorded with ‘misplacement’ at the third intercostal space.17 Nevertheless, an initial small ‘r” in lead V1 is also often seen in uncomplicated RV pacing. To our experience this initial “r” in lead V1 is most often seen with an infero-septal RV lead position resulting in a superior spread of activation with late activation of the RV outflow tract. As a consequence, an initial “r” wave in lead V1 during biventricular pacing does not necessarily indicates contribution from LV pacing.

Differences between RV Pacing and LBBB
RV apex pacing QRS pattern is often considered to be very similar to LBBB QRS pattern. Therefore in animal experimental studies RV apex pacing is often performed as surrogate for endogenous LBBB.18 Detailed analysis of the ventricular activation patterns of RV pacing

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![Figure 1: QRS morphology in complete left bundle branch block. The LBBB activation sequence and representative QRS-T wave forms are depicted in their anatomic locations for the sagittal, transverse, and frontal planes. Figure used from Strauss et al.10](image1)

![Figure 2: Conventional ECG criteria for left bundle branch block. (1) QRS duration >120 ms, (2) QS in lead V1, (3) monophasic R wave with no Q waves in leads V6 and I. Also included ‘notching’ as described by Strauss et al.10](image2)
and LBBB however, revealed some clear differences. In general, QRS duration is usually more prolonged in RV pacing as compared to LBBB. Left ventricle activation is affected in several ways. In RV pacing, transseptal activation time is decreased in most patients, but because of an increase in LV free wall activation time, a mild net increase in total LV activation time is the result. RV activation itself is prolonged in RV pacing, as compared to intrinsic activation by the his-purkinje system in LBBB. In LBBB the activation wavefront spreads in a circumferential direction whereas the activation wave front has a more apico-basal direction in RV apex pacing. As a consequence the area of latest activation is located more basally in the lateral wall as compared to LBBB (figure 3). Moreover, due to a delayed RV activation and LV activation in an apico-basal direction the interventricular dyssynchrony is often less pronounced as compared to LBBB. Whether less interventricular dyssynchrony during RV pacing as compared to LBBB is associated with decreased CRT response, still needs to be investigated.

QRS Pattern During LV Pacing

Since the beginning of CRT the target location of the LV lead is the LV free wall in a mid-lateral segment. There is increasing evidence that LV lead placement in the region of the latest activation, defined either electrically or mechanically, results in a better response to CRT. This region can be reached epicardially via a tributary of the coronary sinus, or surgical placement. Also, endocardial LV lead placement has been described by using an atrial transeptal, ventricular transeptal or transapical approach. However clinical implementation of these approaches awaits more experience and studies on long-term results. Therefore information on myocardial activation in pacing using these approaches remains scarce.

For analyzing the ECG during LV pacing it is important to program a very short AV delay or, even better, to stimulate in VVI mode to avoid fusion with intrinsic activation via the right bundle. Fusion produces electrical resynchronization of the two wave fronts coming from the paced LV and intrinsic activated RV (see below). Pacing from the coronary venous system usually results in stimulation of the LV free wall. Therefore resulting in a right bundle branch block QRS pattern with a dominant R wave in lead V1. Exceptions exist with LV lead positioned in the mid cardiac vein with preferential exit to the RV or a LV lead advanced deep in the great cardiac vein resulting in stimulation of the RV outflow tract rather than the LV anterior wall.

Therefore, as a first step in the evaluation of the LV pacing a RBBB QRS pattern should be present in lead V1 (figure 4, step 1). Next, the frontal plane axis during LV pacing should be used to identify the pacing site in the circumferential direction. A paced QRS with either a left or right superior axis is associated with an inferior or infero-lateral LV lead position. On the other hand, a left inferior or right inferior paced QRS is associated with anterior or antero-lateral LV lead position (Figure 4, step 2). It should be noted that LV pacing does not necessarily results in a negative QRS in lead I. When LV pacing is performed from the basis of the LV, especially in dilated and leftward displaced hearts, the activation spreads from basis to apex and from left to right, resulting a positive QRS in lead I (figure

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**LBBB**

**RV apex pacing**

**Coronary venogram**

**Figure 3**: Increased delay in LV electrical activation during RV apex pacing as compared to intrinsic LBBB. Local electrical activation time has been projected on the coronary venous electro-anatomic maps using the same color coding for both intrinsic LBBB and RV apex pacing. ALV = anterior inter-ventricular vein, ALV-1 = first antero-lateral vein, ALV-2 = second antero-lateral vein, CS = coronary sinus, LBBB = left bundle branch block, LEAT = local electrical activation time, LV = left ventricle/ventricular, RV = right ventricle/ventricular, RAO = right anterior oblique view. Figure adapted from Mafi Rad et al.

**Figure 4**: Protocol for determination of the LV lead position using the LV-paced QRS morphology, based on ECGs from LV originating ventricular tachycardia. Step 1: A positive QRS complex in V1 indicates an LV lead position at the LV free wall. Step 2: Lead aVF differentiates the LV lead position in the circumferential direction with a negative QRS complex indicating a more inferolateral position. Step 3: Trace the transition from positive to negative QRS complexes in the precordial leads to determine the apico-basal direction. Figure used from Van Deursen et al.
is much more frequent in epicardial LV pacing from the coronary veins.\textsuperscript{35,36} This difference in prevalence can be explained by the longer distance from the electrode to the subendocardial His-Purkinje system. Where the impulse has to travel through venous tissue and epicardial fat, the naturally slower epicardial propagation, especially in diseased myocardium, and additional antiarrhythmic drug effects on the myocardium. Prolonged LV pacing latency during simultaneous biventricular pacing can consequently produce an ECG pattern dominated by RV pacing, thus resulting in inadequate CRT.\textsuperscript{37}

Also important to realize is that the QRS morphology evaluation during LV pacing is of predictive value for response to CRT. A relatively narrow QRS complex during LV pacing is associated with a better response to CRT.\textsuperscript{22,38} Both avoidance of fractionation and large QRS width can be indirect tools to prevent LV pacing in a region of poor conduction due to scar or fibrosis.\textsuperscript{39,40}

ECG Pattern During Biventricular Pacing

The ECG during biventricular pacing is often not easy to analyze because of merging wave fronts. CRT is most commonly achieved by using biventricular pacing, resulting in merging wave fronts of RV and LV pacing. The CRT device allows programming of the atrioventricular and interventricular delay in order to optimize the positive effects of CRT. Echocardiography, ECG or hemodynamic measurements are often used to accomplish optimization of CRT programming. However, these forms of optimization are often resource-intensive and haven’t been shown to be beneficial in any large multi-center randomized clinical trial so far. As a consequence, only a minority of physicians routinely optimize AV- and VV-delays in their patients.

Various studies have shown that LV pacing alone can be as effective as biventricular pacing.\textsuperscript{41-43} Especially in patients with normal atrioventricular conduction, when LV only pacing is adequately timed with intrinsic activation, response in cardiac function improvement can be even superior to that in biventricular pacing.\textsuperscript{42,43} However, adequately timed fusion at rest can be lost as atrioventricular conduction changes during exercise. Algorithms which promote intrinsic activation-based LV pacing should automatically adapt the atrio-left-ventricular pacing delay by periodical evaluation of the intrinsic atrio-right-ventricular conduction time.\textsuperscript{44} Studies validating...
these algorithms are needed to be able to use this pacing mode in daily practice. The QRS axis in the frontal plane during biventricular pacing is most often directed towards the right superior quadrant resulting in a dominant R wave in lead aVR. Sometimes, with a more posterior LV lead position, the QRS axis is directed towards a left superior quadrant. However, a QRS axis in the other quadrants does not necessarily indicate inappropriate programming or LV lead position. Especially with fusion of LV pacing with intrinsic activation and/or a basal LV lead position a normal QRS axis can be found in CRT sometimes.

To assess whether there is contribution of LV pacing, QRS morphology has to be evaluated in the precordial leads. The QRS complex during biventricular pacing most often has a dominant R wave in lead V1-2, suggestive of contribution from LV pacing. However, a dominant R wave in lead V1 is not diagnostic of biventricular pacing as RV only pacing occasionally produces the same pattern, as described earlier. Therefore, adequate assessment of biventricular pacing should include evaluation of RV only and LV only pacing. A negative QRS complex in lead V1 should warrant further evaluation, although it does not necessarily indicate inadequate CRT, as this may occur in incorrect lead V1 placement, marked LV pacing latency or slow activation from the LV pacing site, LV lead dislodgement or inappropriate LV lead placement (middle or anterior cardiac vein) (figure 6).45

In a large group of patients response to CRT in relation to the biventricular paced ECG was studied. This analysis revealed expression of biventricular fusion on the ECG by new or increasing R wave in lead V1 and V2 to be significantly related to the probability of reverse remodeling after adjusting for the degree of myocardial scar.46 More recently, an additional, extensive QRS analysis was performed on the biventricular paced QRS morphology in lead V1-2.45 Three different V1-V2 QRS complex patterns during CRT were identified (figure 7):

1) fusion complex with increased or dominant R wave, independent of QRS duration,
2) QS pattern with QRS duration normalization, and
3) QS pattern with increased QRS duration. Although QRS type 2 was a relative small group of patients in this study, these patients had the largest benefit in reverse remodeling. Probably, in this group, RV and LV pacing wave fronts are opposite, generating QRS normalization by activation wave cancellation. On the other hand, another study did not find the presence of a dominant R wave in lead V1, but the activation reversal to dominant negativity in leads I and aVL, to correlate best with acute hemodynamic improvement after AV- and VV- optimisation.47 Though promising, these analyses should be confirmed in prospective trials.

Literature on the prognostic value of the QRS duration during CRT is controversial. This can partly be explained by the aforementioned studies, where the biventricular paced QRS duration is not of importance with a type 1 QRS pattern in lead V1 but is related to improved outcome in patients with a QS pattern in lead V1 with QRS duration normalization. On the other hand it seems that at least for patients who are upgraded from RV pacing to CRT, QRS narrowing is associated with improved outcome.48

Clinical Implications

The 12 lead ECG provides important information for clinical follow-up in CRT, but needs to be carefully evaluated. Understanding the electrophysiology of LBBB, RV, LV, and biventricular pacing with or without fusion helps to evaluate CRT in heart failure patients. However, as the QRS pattern is complex due to merging wave fronts careful analysis of the ECG during underlying rhythm as well as during RV only and LV only pacing should be performed for better understanding of the ECG during CRT. Especially in CRT non-responders a simple analysis of the QRS pattern in CRT can show whether biventricular pacing is adequately performed. When the QRS duration is not decreasing and no contribution from LV pacing is seen, further analysis of the ECG during intrinsic rhythm, RV only, and LV only pacing can reveal inadequate CRT programming and LV lead positioning.

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