WHEN TO CHOOSE CARDIAC RESYNCHRONIZATION THERAPY IN CHRONIC HEART FAILURE: TYPE AND DURATION OF THE CONDUCTION DELAY

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Abstract

Cardiac Resynchronization Therapy (CRT) is an established treatment for patients with Heart Failure (HF), impaired left ventricular function and wide QRS complex. The initial randomized clinical trials, which led to the widespread use of CRT, selected patients on the basis of QRS duration, not focusing on QRS morphology. However, recent evidences emphasized the role of LBBB morphology in patients that underwent CRT in order to predict better response to therapy. Moreover, conventional RV apical pacing might have long-term detrimental effects on cardiac structure and left ventricular function, possibly leading to the development of heart failure. Therefore current guidelines recommend upgrade from conventional PaceMaker (PM) or Implantable Cardioverter Defibrillator (ICD) to CRT or de novo CRT in patients with high (or expected high) percentage of ventricular pacing and reduced EF.

We reviewed current knowledge on candidates' selection for CRT based on conduction delays that lead to electrical and mechanical dyssynchrony of the left ventricle.

Cardiac Resynchronization Therapy (CRT) is an established treatment for patients with Heart Failure (HF), impaired left ventricular function and wide QRS complex. The abnormal activation sequence observed in patients with Left Bundle Brunch Block (LBBB) results in a dyssynchronous ventricular activation and contraction leading to cardiac remodeling, worsening systolic and diastolic function and progressive HF. The key concept of "biventricular pacing" was developed with the aim to restore the dyssynchronous contraction resulting in improved symptoms, quality of life, exercise tolerance, cardiac function and survival [1].

Candidates' selection: what guidelines tell us

Current guidelines recommend CRT in chronic HF patients with impaired cardiac function documented by Left Ventricular Ejection Fraction (LVEF) ≤35% who remain in NYHA function class II, III or ambulatory IV despite optimal medical therapy and typical LBBB with QRS duration ≥150 ms [2]. Lower strength of recommendations appears when QRS duration is between 120 to 150 ms. Non-LBBB morphology should be considered only in patients with QRS duration ≥150 ms [2]. Recently sub-analyses of randomized clinical trials emphasized the primary role of QRS morphology over and above the QRS width showing a greater efficacy of CRT in patients with typical LBBB compared to patients with Right Bundle Branch Block (RBBB) or non-specific intraventricular conduction delay [3,4].

Even with well-selected patients, there is a wide range of response to CRT with a subset of patients showing little or no improvement [2]. Since the early studies on the effects of conduction tissue disturbances on diastolic filling time and septal contribution to the Left Ventricular (LV) ejection, the link between electrical dyssynchrony and mechanical contraction and cardiac output was clear [5,6]. Therefore, echocardiography has been extensively tested to study mechanical dyssynchrony in order to identify the best parameters able to predict the efficacy of CRT, reducing the percentage of non-responders to the therapy. However, the recent PROSPECT (Predictors of Response to CRT) trial tested the efficacy of different echocardiographic measures of mechanical dyssynchrony but no one could reliably predict the response to CRT [7]. The poor contribution of echocardiographic assessment of dyssynchrony for the prediction of CRT response was also confirmed by the EchoCRT trial that failed to show a benefit from CRT in patients with QRS ≤130 ms and dyssynchrony assessed echocardiographycally [8].

Therefore, current guidelines recommend the use of QRS duration and morphology for the selection of HF patients as candidates for CRT. LV mechanical dyssynchrony assessed with imaging techniques is not currently considered a criterion for resynchronization therapy [2].

Candidates' selection: keep an eye on QRS duration and morphology

If the standard criteria used to identify HF patients with an LVEF ≤35% and a NYHA functional class between II and ambulatory IV is not under debate, the definition of complete LBBB has been extensively studied and discussed.

Under normal conditions, the myocardium is activated by a uniform, high-velocity electrical waveform that propagates through the His-Purkinje system and the bundle branches resulting in a synchronized depolarization of the ventricles. In patients with LBBB, ventricular activation starts in the right ventricle, because the right bundle branch is not affected, and then proceeds from the RV endocardium to the LV endocardium through the interventricular septum. Then it propagates to the endocardium of the posterolateral wall and it completely activates the ventricle without the use of the rapidly conducting Purkinje system. So, in the presence of complete LBBB, there is a significant

delay between the activation of the interventricular septum and the activation of the LV free wall, resulting in a QRS duration ≥140 ms (fig. 1) [9,10].

Conventional ECG criteria used clinically to describe LBBB morphology include: QRS duration ≥120 ms, QS or rS in lead V1 and a monophasic R wave with no Q waves in leads V6 and I. Defining complete LBBB, current guidelines recommend also to evaluate the presence of broad notched or slurred R wave in leads I aVL, V5 and V6 and an occasional RS pattern in V5 and V6 attributed to displaced transition of QRS complex [11]. Notches or slurred R wave represent the propagation delay of the depolarization wave front to reach the endocardium of the LV (first notch) and the epicardium of the posterolateral wall (second notch) through the ventricular working myocardium instead of the rapidly-conducting Purkinje system [9].

Several studies performed endocardial mapping in patients considered to have LBBB by conventional ECG criteria [12,13]. It was demonstrated that almost 1/3rd of the LBBB patients has 2 LV endocardial breakthrough sites instead of one, consistent with 2 of the 3 breakthrough sites described in normal hearts. In 1/3rd of the LBBB patients, there is no significant delay between the RV activation and the start of activation of LV endocardium with a transseptal time <20 ms suggesting that there is a subset of patients with an LBBB diagnosed by conventional criteria that do not actually have a complete LBBB but more likely a combination of left anterior fascicular block and left ventricular hypertrophy [12,13].

On the basis of additional insights from computer simulations, Strauss e al proposed stricter criteria for complete LBBB that include mid-QRS notching or slurring in ≥2 contiguous leads and a QRS duration ≥140 ms for men and ≥130 ms for women [9]. In a recent study, the presence of mid-QRS notching or slurring emerged as a strong predictor of better response to CRT [14].

The initial randomized clinical trials, which led to the widespread use of CRT, selected patients only on the basis of QRS duration (≥120 ms) not focusing on QRS morphology. However, recent evidences emphasized the role of LBBB morphology in patients that underwent CRT. A report of Medicare registry showed that non-LBBB patients that received CRT had poorer outcomes compared to those with LBBB [15].

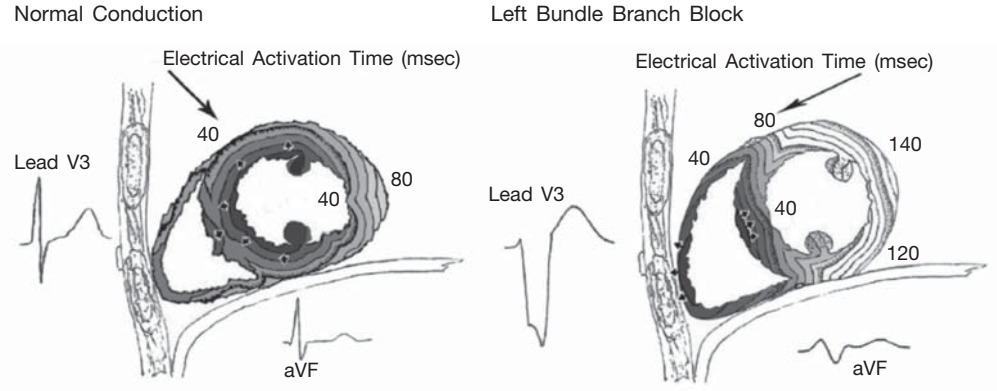

Fig. 1. Electrical activation times and QRS duration in normal and complete LBBB. Reprinted with permission (Strauss et al.) [9].

Recent subgroup analyses based on QRS morphology of the MADIT-CRT, RAFT and REVERSE trials suggested that patients with complete LBBB showed a greater benefit on the composite of morbility/mortality from CRT compared with patients with right bundle branch block (RBBB) or non-specific intra-ventricular conduction delay (IVCD) [4,16,17]. In particular, in the MADIT-CRT, the use of CRT- defibrillator (CRT-D) in LBBB patients was associated with a clinical benefit compared to ICD-only therapy in all the pre-specified subgroups based on age, QRS duration ≥150 ms, LV volumes and LVEF. No evidence of clinical benefit from CRT-D was identified in non-LBBB patients [4]. A meta-analysis of the major CRT-trials confirmed these data suggesting that CRT implantation should be discouraged in non-LBBB patients [18]. Therefore, based on this evidence, current class I recommendations for CRT were restricted to patients with complete LBBB.

Candidates' selection: RV apical pacing for bradycardia and heart failure

In the last decade, increasing evidences showed that conventional RV apical pacing might have detrimental effects on cardiac structure and left ventricular function, possibly leading to the development of heart failure [19].

The slow and heterogeneous propagation of the electrical wavefront from the pacing site through the myocardium rather than through the His/Purkinje conduction system results in an abnormal activation pattern of the ventricles comparable to the left bundle branch block. The mechanical activation pattern follows the changes in electrical activation showing an early systolic shortening of the regions near the pacing site with a resultant stretch of the late-activated regions. This abnormal contraction determines mechanical dyssynchrony, redistribution of myocardial strain, changes in cardiac metabolism and regional perfusion, decreased cardiac output, increased LV filling pressure, ventricular dilation and functional mitral regurgitation. Several studies with a crossover design evaluated the upgrade from conventional pacemaker to CRT in patients requiring permanent or frequent RV pacing for bradycardia who have symptomatic HF or low LVEF. In all of them, during CRT study phase, the patients consistently showed improved cardiac function, less hospitalization, symptoms' improvement compared to the RV study phase [20,21]. Therefore current guidelines strongly recommend the upgrade from conventional pacemaker (PM) or ICD to CRT in all HF patients with LVEF < 35%, high percentage of ventricular pacing who remain in NYHA class III or more despite optimal medical therapy [2].

In the PREventing VENTricular Dysfunction in Pacemaker Patients Without Advanced Heart Failure (PREVENT-HF) trial and in the Biventricular versus right ventricular pacing in patients with AtrioVentricular (AV) block (BLOCK-HF) trial, de novo cardiac resynchronization therapy pacing was tested in patients with conventional indication for anti-bradycardia pacing. The PREVENT-HF showed no advantage to CRT compared to conventional RV pacing in terms of LV remodeling in patients with AV block and expected ventricular pacing >80% after 12 months [7]. In the BLOCK-HF trial, patients with AV block, LVEF ≤50% and NYHA functional class I to III were randomly assigned to biventricular or RV pacing and followed for 37 months. The trial showed a significant reduction in the primary composite endpoint of

death, heart failure-related urgent care or adverse left ventricular remodeling in CRT patients compared to patients with RV pacing only [22].

Considering the observed detrimental effects of RV pacing on LV function in patients with preexisting LV dysfunction and high ventricular pacing rate, it was hypothesized that also patients with baseline normal cardiac function may be affected by pacing-induced mechanical dyssynchrony. However, in a large cohort of pacemaker recipients, patients with AV block requiring frequent or permanent RV pacing had similar survival with no difference in development of LV dysfunction or deterioration of preexisting mild LV dysfunction after PM implantation compared to patients with sinus node dysfunction that required minimal RV pacing [23]. Preliminary results from the Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization BIOPACE trial showed no significant difference in the incidence of death and heart failure hospitalization after >5 years between biventricular pacing and RV pacing in patients with conventional pacemaker indication and preserved LV systolic function. Therefore, current guidelines recommend de novo CRT in HF patients with conventional pacemaker indication, expected high percentage of ventricular pacing and reduced EF. At present, de novo CRT is not indicated in patients with baseline normal EF.

Candidates' selection: keep an eye on PR interval

PR prolongation alters normal AtrioVentricular (AV) mechanical coupling reducing left ventricular filling, stroke volume and resulting in diastolic mitral regurgitation. Dual-chamber pacing acutely improves hemodynamics restoring AV coupling but it failed to demonstrate improved long-term outcomes probably due to the detrimental effects of ventricular desynchronization. Therefore patients with longer AV delay would be more likely to respond positively to CRT as it was described by a post-hoc analysis of the COMPANION study [24].

However, other studies have found that a prolonged PR interval seems to be a marker of atrial and structural remodeling and it is associated with more severe HF disease [25,26]. The CARE-HF trial described worse outcomes in patients with prolonged PR interval regardless of the treatment arm (CRT or optimal medical therapy) [27]. In a recent study comparing patients with CRT, a baseline PR prolongation is an independent predictor of worse prognosis and lower probability of reverse remodeling, expecially for patients with non-LBBB morphology [26].

Conclusions

There is strong evidence that CRT reduces mortality and hospitalization and improves cardiac function in symptomatic HF patients despite optimal medical therapy with a depressed LVEF and complete LBBB. Recent evidences suggested that complete LBBB predicts better response to CRT therapy. Therefore stricter criteria for LBBB that include wide QRS duration and mid-QRS notching or slurring in ≥2 contiguous leads should be used in order to identify the true LBBB configuration (fig. 2).

RV apical pacing might have long-term deleterious effects on cardiac

structure and function. Therefore, current guidelines recommend upgrade from conventional PM or ICD to CRT or de novo CRT in patients with high (or expected high) percentage of ventricular pacing and reduced EF (fig. 2).

A prolonged PR interval seems to be a marker of atrial and structural remodeling and it is an independent predictor of worse prognosis and lower probability of reverse remodeling after CRT (fig. 2).

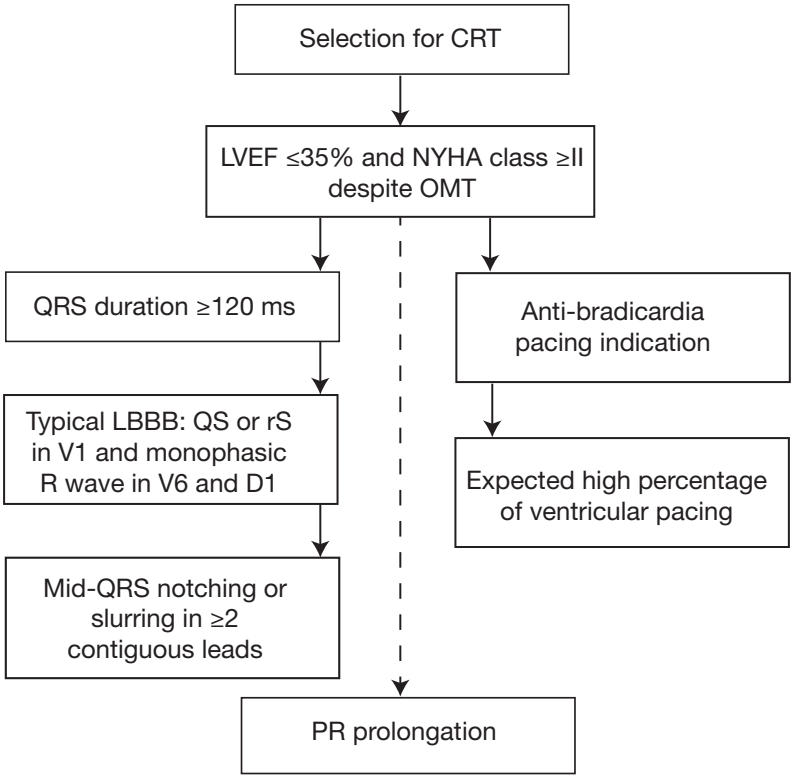

Fig. 2. Schematic representation of clinical and electrocardiographic characteristics of patients before CRT. CRT= Cardiac Resynchronization Therapy; LVEF= Left Ventricular Ejection Fraction; NYHA= New York Heart Association; OMT= Optimal Medical Therapy; LBBB= Left Bundle Branch Block.

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