Review

Update in LV Only Fusion CRT Pacing: Annals and Future Perspectives

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ABSTRACT: Triple-chamber cardiac devices are utilized for cardiac resynchronization therapy (CRT) and is the standard-of-care therapy for heart failure (HF) patients in the current guidelines. In the setting of biventricular (BIV) pacing it involves a mandatory implantation of right ventricular (RV) lead that allows simultaneous BIV pacing with 0 ms VV (ventricular to ventricular) interval. Nevertheless, it seems that response to CRT is not related to RV lead position. RV pacing is known for deleterious effects on RV/Left Ventricle (LV) function and should not be used in persons with normal atrioventricular conduction (AV) and sinus rhythm. As it compensates for the additional asynchrony induced by unnecessary stimulation of RV pacing, only pacing the left ventricle (LV) may result in improved cardiac resynchronization therapy (CRT) outcomes and a decrease in the number of individuals who do not respond to the procedure. Furthermore, leadless LV fusion CRT pacing without RV lead could be a potential CRT therapy alternative to BIV pacing in nonischemic heart failure patients with preserved AV conduction. The aim of our study is to made an update in cardiac resynchronization therapy with LV only fusion pacing.

KEYWORDS: *Heart failure, cardiac resynchronization therapy, LV only pacing, cardiac resynchronization therapy.*

Introduction

Cardiac resynchronization therapy via BIV pacing combined with optimal medical therapy, promotes left ventricular (LV) reverse remodeling, improves LV function, clinical outcomes and leads to an important decrease in HF hospitalizations and all-cause mortality [1-4].

Despite the well-demonstrated benefits, by activating ventricular myocardium and not the specialized conduction system, the CRT via BIV pacing provides a non-physiological resynchronization and approximately 30% of patients are classified as nonresponses.

In the case of LV only pacing the pulses from the right bundle branch (RBB) come from several places of the Purkinje network, determining its multisite activation, maintaining the RV activation synchronism, while in biventricular pacing the RV pacing creates asynchrony with prolonged electrical activation.

Despite non-inferiority to BIV pacing [5,6], LV only pacing is not widely used in clinical practice.

Moreover, there is a lack of data regarding the use of LV fusion CRT pacing without an RV lead in real-world scenarios.

In patients with normal atrioventricular conduction and CRT indication, LV fusion pacing can be attained by utilizing bicameral pacemakers that are placed in the right atrium (RA) and left ventricle (LV) of carefully chosen individuals from the nonischemic cardiac resynchronization therapy with pacemaker (CRT-P) population and systematic follow-up [7,8].

Furthermore, for this category of patients, the number of "technique-dependent" nonresponses could be reduced using a future new CRT approach bicameral DDD RA/leadless LV system.

Anatophysiology of the Cardiac Conduct System

At the dawn of the 20th century a Japanese pathologist, Dr. Sunao Tawara, in his monumental monograph "Das Reizleitungssystem des Säugetierherzens" [9], outlined the organization of the elements comprising the cardiac conduction system, going from the atrioventricular node to the terminal Purkinje fibers.

The conduction system of the heart is an intricate structure of specific cardiac muscle cells

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that produce and transmit the electrical signals necessary for the synchronized contractions of the cardiac chambers.

It is constituted by the sinoatrial (SA) node, atrioventricular (AV) node, bundle of His, right and left bundle branches and Purkinje fibers [10].

The typical duration for transseptal transmission in the human heart is thought to range from 0.06 to 0.07 seconds in the two directions [11].

The initiation of left ventricle (LV) stimulation occurs within the endocardium and involves three specific regions: the anterior para-septal, central left interventricular septal, and backward para-septal regions.

This activation process takes place within the first 10 milliseconds.

The posterobasal or posterolateral regions, on the other hand, are the last to undergo activation [12].

Conduction defects can cause ventricular asynchrony at different levels: interventricular, intraventricular, and atrioventricular.

Consequently, this leads to regionally delayed electrical activation followed by disordered myocardial shortening and pump inefficiency. LBBB is the most prevalent type of conduction disturbance, which is followed by non-specific intraventricular conduction latencies and RBBB [13].

In cases of left bundle branch block (LBBB), the normal rapid conduction of electrical signals in the left ventricle is disrupted.

Instead, the electrical activation begins in the right anterior septal area through an unaffected right bundle, and then spreads progressively through the myocardium to the left basal posterolateral area [13].

Traditional BIV CRT even if it brings non-physiological ventricular activation patterns due to stimulation of LV epicardial site and RV endocardial site, ensures ventricular electrical connection and mechanical synchronization in patients diagnosed with left bundle branch block (LBBB) (Figure 1) [13-15].

In the case of LV only pacing the impulses in the right branch originate from several places of the Purkinje network, causing its activation in several locations and maintaining the RV activation synchronism, thereby achieving fusion of the wavefront of intrinsic activation with the wavefront of LV stimulation.

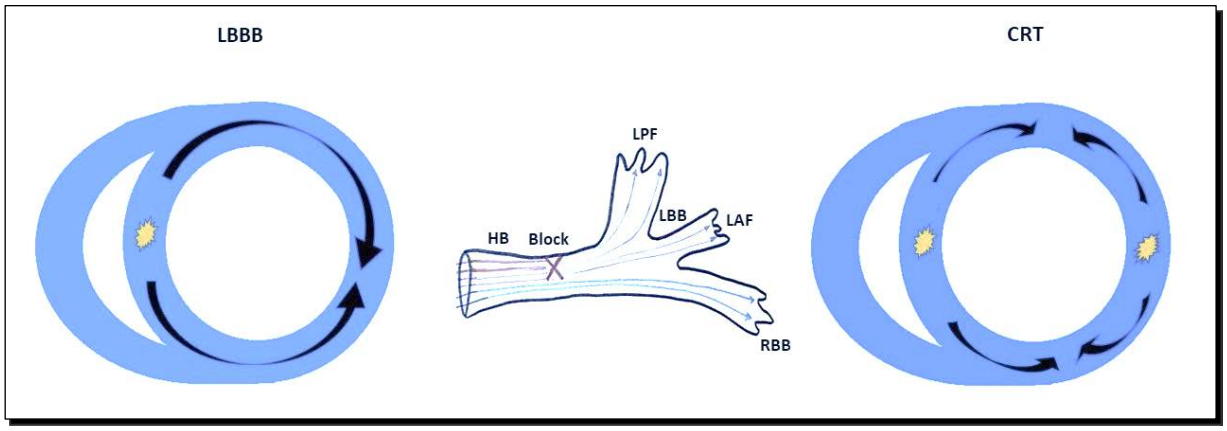

Figure 1. Effective fusion due to CRT by generating two depolarization wavefronts that move forward each other, synchronizing the LV walls, thereby reversing the adverse effects of LBBB.

Previously LV only pacing CRT

Left ventricle (LV) only pacing, which was suggested several years ago and examined in both acute and chronic studies, has promising results. [4,8,16].

BELIEVE was the first randomized, single-blind, parallel-controlled study wich included 74 patients diagnosed with NYHA class II-IV HF and left bundle branch block (LBBB) in a two-arm study: LV only and BIV pacing.

The LV only pacing resulted in a comparable response rate at 12 months (characterized as a definitive rise in the left ventricular ejection fraction (LVEF) exceeding 5%, or an increase in the value of the 6-Minute Walk Test by at least 10%.) relative to BIV pacing rate (75% vs. 70%). LVEF improvement was similar (+5.2 and+4.2%, p=0.70) with a comparable safety profile versus BIV stimulation [17].

The multicenter study DECREASE-HF randomized 306 patients with NYHA class III-IV, LVEF ≤35% and QRS ≥150ms to simultaneous BIV pacing, sequential BIV pacing and LV only pacing.

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The end-diastolic volume (LVEDV) and end-systolic volume (LVESV) of the left ventricle as well as LV function were analyzed by echocardiography at inclusion in the study, then at 3 and 6 months.

In all groups it was found that the end-diastolic volume (LVEDV) and end-systolic volume (LVESV) of the left ventricle showed a decrease, while the ejection fraction of the left ventricle (LVEF) demonstrated improvement ($p<0.001$) [18].

Non inferiority of LV only pacing to BIV pacing was also demonstrated in a series of 176 CRT-D candidates with NYHA class III-IV, LVEF ≤35% and QRS ≥130 msec.

The double-blind study (B-LEFT HF) showed favorable criteria for LV only CRT response (NYHA functional class, reduction of LVESV ≥10%) [5].

The most comprehensive study consisting only of patients with true left ventricle only was written in 2004 by Blanc JJ et al [19].

The researchers provided a twelve-month follow-up on this cohort, revealing that 10 out of 22 patients have been classified as NYHA class IV, with 7 of them having an ischemic etiology.

The study found that the left ventricular ejection fraction (LVEF) was 21.8±7.7%, the left ventricular end-diastolic diameter (LVEDD) was 76.5±9.4mm, and the QRS duration was 182±22ms.

However, there are also studies that favor BIV stimulation effects.

Sedlacek and colleagues reported, in a uncenter study that randomized 40 patients with idiopathic dilated cardiomyopathy, weaker results in LV stimulation at 1 year follow-up in the reversal process-remodeling [20].

LOLA-ROSE a pilot, cross-over study showed greater improvement in the NYHA class in the BIV versus single LV pacing group [21]. Still the small size of these research limits the conclusions we can draw.

Withal, it should be highlighted that the studies mentioned above did not aim to obtain a fusion rhythm.

AV intervals were optimized using echocardiography (BELIEVE, LOLA-ROSE, Sedlacek), automated algorithms based on intracavitary electrograms (DECREASE-HF) or no specific method (B-LEFT HF).

To maintain a constant fusion rhythm and improve CRT response medication optimization, exercise tests (ET), and device programming need to be performed systematically.

In 2021 ESC Guidelines on Cardiac Pacing and CRT exercise testing is recommended only in patients who experience symptoms suspicious of bradycardia during or after exertion, patients with suspected chronotropic incompetence and those with intraventricular conduction disease or AVB of unknown level [22].

Unfortunately, there are no mentions regarding the performance of exercise tests in the follow-up period of CRT populations.

Regarding device programming, two medical device companies analysed and implemented algorithms for fusion pacing in CRT: Smart Delay ™ (Boston Scientific) and AdaptivCRT ™ (Medtronic) [23,24].

The Smart Delay ™ system, developed by Boston Scientific, utilizes acute hemodynamic data collected from PATH CHF II studies [25].

The method autonomously calculates the inherent atrioventricular conduction durations at the RV/LV level, for both atrial detection and atrial stimulation, and suggests either LV-only pacing or BIV stimulation. LV fusion pacing is advised when the ventriculo-ventricular (VV) interval is equal to or greater than 20 milliseconds and the average value of atrio-ventricular (AV) intervals detected on the right ventricular (RV) lead is less than or equal to 271 milliseconds.

Furthermore, the algorithm suggests the most efficient AV intervals (both AV paced, and AV sensed) based on the positioning of the CS lead in the anterior region.

The algorithm is not applicable in the presence of a second-or third-degree AV block or when the intrinsic AV conduction exceeds 400-450ms.

The setting values do not undergo automatic updates, which means they may not align with the ideal values in various scenarios or at different times during follow-up visits [3].

AdaptivCRT ™ (Medtronic) dynamically optimizes the resynchronization mode (LV only vs. BIV pacing) and AV/VV intervals.

The algorithm measures the intrinsic AV conduction every minute for one beat (VVT mode supports resynchronization during this beat) and also the P wave and the duration of the QRS complex determined on the far-field electrogram values, collected using from the SVC coil or the RA probe ring, are refreshed every 16 hours for a duration of 5 heartbeats, without any underlying VVT stimulation.

If the physiological conduction of the atrioventricular (AV) system is functioning normally and the heart rate (HR) does not go above 100 beats per minute, the algorithm encourages left ventricular (LV) fusion

stimulation by setting the AV interval to approximately 70% of the intrinsic AV conduction.

Under these conditions, LV stimulation occurs with fusion and is preferable from a hemodynamic point of view.

Otherwise, the algorithm provides biventricular stimulation, and the AV interval is adjusted so that the electrical stimulus occurs 30 milliseconds after the ending of the P wave, but no less than 50 milliseconds before the initiation of the intrinsic QRS complex.

This method is corroborated by research that have shown that the optimal AV intervals can be approximated considering the duration of the P wave on the surface ECG and the intracavitary electrograms [26,27].

The algorithm is accessible in DDD (R) mode and is able to be configured to alternate between LV-only pacing and BiV pacing, or it can be configured to consistently operate in BiV stimulation.

So, the AV/VV intervals and LV only or BiV stimulation modes are updated every minute and will automatically adapt to changes in intrinsic AV conduction (during sleep).

The CRT trial investigators described this algorithm for LV-only stimulation as a safe and effective method that promotes intrinsic conduction and reduces RV pacing in 428 patients with a heart rate below 100/min, but not above this heart rate [28].

This value was selected without any evidence-based rationale, relying entirely on intuition and empirical observation.

Moreover, it is imperative to develop a novel algorithm for DDD pacemakers that can automatically adapt SAV/PAV intervals based on the correlation with AS-VS variability (including the spontaneous variability of the PR interval), with the goal of achieving consistent LV pacing (dynamic LV stimulation).

The Boriani group conducted a study published in Europace that tested the auto capture algorithm in patients with DDD LV without an RV lead [5].

This was the only algorithm tested in this specific patient population.

Current and future perspectives

Published literature has consistently demonstrated that CRT has his limitations with 30% „failed" population.

For this group of high-risk heart failure patients who either cannot receive (e.g. unsuccessful CS lead position/placement due to anatomical variations, high pacing threshold or diaphragmatic stimulation) or who have not responded to conventional cardiac resynchronisation therapy, WISE CRT could be an option [29].

This novel pacing system was first proposed by Aurrichio [30] in 2013 and received European CE mark approval in 2015.

LV endocardial stimulation is performed with a small wireless pacing electrode by converting sound energy from an ultrasound pulse generator positioned in an intercostal region [30].

Compared to traditionally LV endocardial stimulation via pacing leads placed transeptally there is no need for permanent oral anticoagulation.

The WICS-LV After Market Surveillance Registry [31] is the most extensive assessment of the operational fulfillment, security, and long-term effectiveness of leadless left ventricular endocardial pacing.

A study conducted in 14 European centers gathered prospectively collected data to determine the efficacy of this method.

The study found that procedural success occurred with biventricular endocardial pacing confirmed in over 94% of patients [31].

The SELECT-LV study and the SOLVE-CRT study reported comparable rates of clinical response [32,33].

Nevertheless, a constraint of these studies is the limited patient sample size and the absence of a control group as per the study design.

However, when compared to biventricular endocardial pacing systems that use lead-based technology, the present registry shows a lower death rate during follow-up compared to the ALSYNC study (Alternate Site Cardiac Resynchronization) [34].

Additionally, there is a significantly decreased risk of cerebrovascular events [31].

Therefore, in carefully selected CRT-P population, a new trend for LV fusion could be a bicameral DDD RA/LV system.

The primary critique of not utilizing an RV lead could derive from the potential variability of AV conduction.

However, this variability would impact the percentage of LV depolarization through the LV lead in a similar way, regardless of the presence of an RV lead.

Regarding the incidence of AV block, the annual risk per 10,000 cases of LBBB was found to be 80, which translates to 0.8% per year. In comparison, the incidence of AV block in the

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absence of BBB was 5 cases per 10,000, or 0.05% [29].

In the study conducted by Cozma et al., a cohort of 55 patients who underwent cardiac resynchronization therapy with a pacemaker that utilized only right atrial and left ventricular pacing demonstrated a favorable result, as shown in Figure 2 [7].

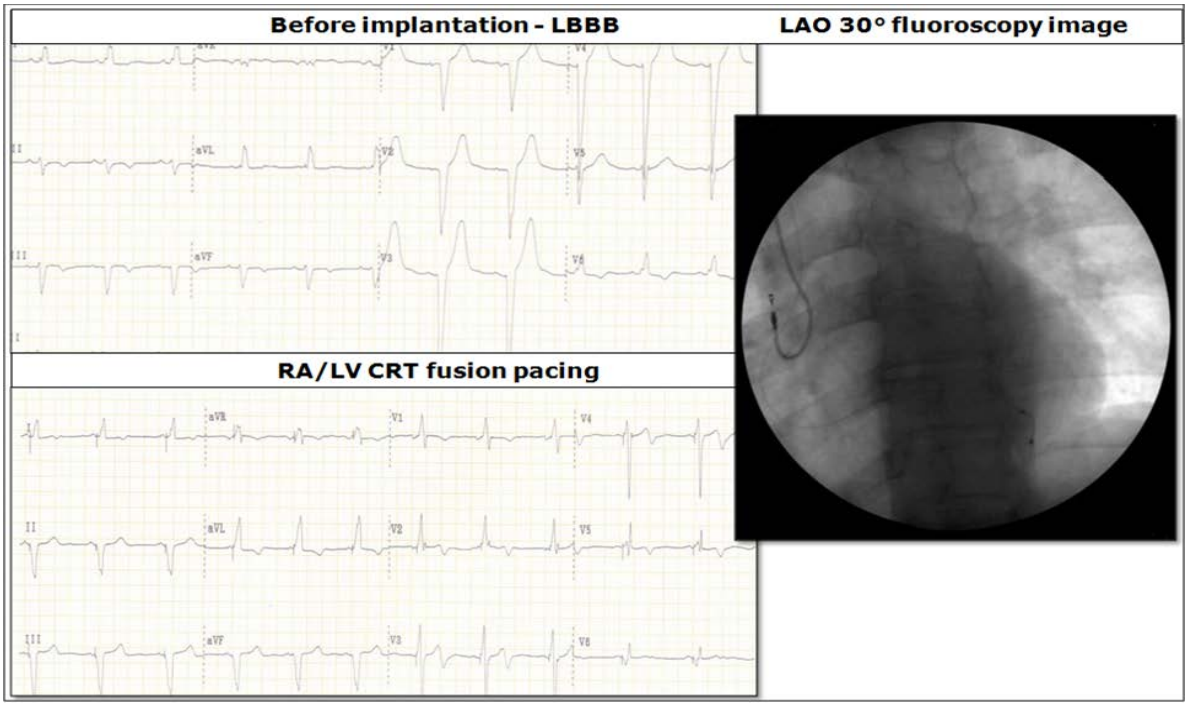

Figure 2. Right atrium/Left ventricle DDD CRT in a 6-year follow-up patient. ECG before and after CRT: left bundle branch block (LBBB) pattern before procedure; narrow QRS after procedure of implant with negative patterns QRS in DI, aVL, negative patterns QRS in V6, and rS pattern in V1; left anterior oblique fluoroscopy image. Reproduced with the permission of Dragos Cozma MD, PhD.

All patients without ischemic heart disease and with preserved AV conduction showed positive responses, including significant reverse remodeling of the left ventricle (LV) (LV end-diastolic volume decreased from 193.7±81mL to 243.2±82mL at baseline, $p < 0.002$) and increased LV ejection fraction (38±7.9% compared to 27±5.2% at baseline, $p < 0.001$).

The utility of Holter monitoring in reprogramming devices to achieve improved fusion pacing was found to be inferior when compared to exercise testing.

Holter monitoring, which involves repetitive and time-consuming procedures, was less effective in providing immediate results compared to exercise testing [8].

Withal RA/LV CRT configuration cannot be used when the patient has a concomitant indication for ICD.

According to Danish trial publication [35] the only requirement is to implant a right ventricular lead for cardiac resynchronization therapy (CRT). may be that of CRT-D, which is required in primary or secondary prevention of sudden cardiac death, and when AV block occurs in patients with permanent atrial fibrillation (PAF) who are unable to undergo left ventricular pacing triggered by the right atrium (RA).

The 2013 ESC Guidelines on Cardiac Pacing and CRT state that there is agreement that LV pacing alone, in patients who do not rely on pacemakers, appears to be just as effective as biventricular pacing in improving soft endpoints such as quality of life, exercise capacity, and reverse remodeling of the left ventricle.

This alternative may be considered to reduce costs and procedural complexity and to prolong the lifespan of the device [36].

In addition, the 2021 ESC Guidelines on Cardiac Pacing and CRT suggest that CRT should be preferred over RV pacing for patients with HFrEF, regardless of their NYHA class, if they require ventricular pacing and have high degree-AVB.

This recommendation also applies to patients with atrial fibrillation, and its purpose is to decrease morbidity [22].

The guide does not provide any specific information about LV fusion pacing using bicameral pacemakers (RA/LV).

Instead, it suggests the use of leadless pacemakers as an alternative to transvenous pacemakers in cases where upper extremity venous access is not available or when there is a high risk of device pocket infection (IIaB).

Leadless pacemakers may also be considered as an alternative to standard single lead ventricular pacing (IIbC) [22].

One of the advantages of this modern technique is its high implant success rate, which exceeds 99%, along with a low rate of major complications at 12 months, which stands at 4% [37,38].

Additionally, this technique results in low pacing thresholds after implantation and eliminates complications related to leads and pockets.

One drawback is that only single-chamber ventricular pacing is available.

Potential advancements for this technology involve the creation of dual chamber leadless pacemakers, enabling the simultaneous placement of communicating devices in separate chambers of the heart.

Therefore, with continued improvement to the technology, a DDD RA/LV leadless system could be a future CRT-P technique in non-ischemic heart failure with preserved AV conduction that could reduce the "failed" CRT population.

Conclusions

LV only pacing without RV lead it may be an elegant alternative to classical triple CRT, that allows less complication and save costs.

Furthermore, for the "failed CRT population" from technical implantation issues a DDD RA/LV leadless system may lead to a decreased number of nonresponders.

The mean presence of RV lead does not ensure effective LV pacing and capture either.

The necessity of a major randomized trial to compare in a much larger group Left ventricular pacing without right ventricular lead/Left ventricular pacing with right ventricular lead/true biventricular pacing is needed to confirm the feasibility, long-term safety, and effectiveness of this novel CRT-P approach.

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Conflicts of Interest

The authors declare no conflict of interest.

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