Editorial

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What Is the Cause of Non-responders in CRT and How to Identify It?

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Introduction

Almost more than a decade, Cardiac Resynchronization Therapy (CRT) has been accepted as an effective therapy for heart failure (HF) patients with reduced left ventricle ejection fraction (LVEF) and wide QRS complex.[1] There is a plethora of evidences which show the benefits of CRT in reduction of morbidity and mortality and improvement of quality of life.[2,3] The CRT indication has also been extended to Implantable Cardioverter Defibrillator (ICD)-indicated patients and some landmark trials have notified the superiority of CRT with defibrillator (CRT-D) over ICD alone.[4-6] As the device development becomes more complicated, it definitely raises a cost issue, especially when incorporated with ICD (CRT-D).

Unfortunately, there is a significant number of patients who do not response sufficiently (non-responders, NR) with average incidence of 30%[7] and only 50% this group will survive at four years after implant.[8] The terminology of responder and non-responder is confused over outcome after CRT implant since the ability to predict which patient will benefit by how much is still limited.[9] This problem needs to be addressed holistically so that the patients will gain the outmost benefit of this costly therapy. However, there are dissimilar opinions with regards to definition and criteria used for this terminology. Response and outcome are not similar. What is very clear that non-responders are linear to pre-, peri-, and post-implant factors.[10] The ability of timely identification of these components are essential for both implanting and referring physicians so that early corrections could be carried out appropriately.

Which patients are considered non-responders?

HF is a complex and dynamic process along its natural course and so is its response towards a therapy. Thus, the criteria of NR is not easy to define as it involves multifactorial components. Even, most of major CRT trials adopted different criteria for NR.[11] From the patient's and clinician's perspective, alleviation of symptom (dyspnea) and reduction of re-hospitalization are essential especially for patients with New York Heart Association (NYHA) functional class III and IV. In summary, the parameters considered clinically practical are functional capacity and quality of life, mortality, and remodeling indicators (increment of ejection fraction, reduction in left ventricular dimension and LV end-systolic volume index).[7,10,11]

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Pre-implant: Appropriate patient selection

The strongest predictor for satisfactory outcome in CRT is ECG pattern of left bundle branch block (LBBB) with prolonged QRS duration (≥150 millisecond) as proven by Auricchio, et al.[12] In Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, those without LBBB does not have significant clinical benefit and those with QRS duration ≤147 ms does not have any benefit at all.[13] When multiple QRS cut- points were considered, male patients who received CRT-D benefited only when the QRS duration was at least 160 ms, although female patients benefited from CRT therapy across all QRS durations <180 ms.[14]

Although QRS duration recruited in trials ranged between 120 ms to 200 ms, the median is around 150 ms. Thus, all recent international guidelines recommend to apply this simple criteria for patient selection and classified as Class Ia indication (strong recommendation).[1,15] Strauss, et al[16] proposed a better criteria for LBBB which includes QRS duration ≥140 ms (men) or 130 ms (women), QS or rS in leads V_1 and V_2, and mid-QRS notching or slurring in ≥2 of leads V_1, V_2, V_5, V_6, I, and aVL. **Figure 1** represents a classical pattern of ECG for CRT and the patient responded very well three months after implant.

Other clinical variables (male gender, ischemic etiology, NYHA functional class IV) and echocardiographic parameters (severe mitral regurgitation, prominent LA dilatation, and short interventricular mechanical delay) are strongly related to poor outcome.[17] Presence of concomitant diseases, such as renal dysfunction and ischemia, will blunt the positive effect of CRT.[10]

Atrial Fibrillation (AF), dominantly permanent AF, is not uncommon in HF patients and it counts around 25% of CRT population.[18] The negative consequence of AF in CRT patient, especially if the intrinsic rate is very fast, is the sub-optimal percentage of captured biventricular pacing. Therefore, the indication of CRT in patients with AF, ejection fraction ≤35%, QRS duration ≥130 ms is set under class IIa.[1] Interventional approach (AV nodal junction ablation) is reserved only when drugs fail to achieve sufficient ventricular rate.

Peri-implant: Targeting the most delayed area (LV lead placement)

Appropriate LV lead placement remains challenging in CRT implant as the coronary sinus (CS) tributaries anatomy varies among individuals. However, in general, lateral or posterolateral position, and basal location is preferred as it linearly associates with positive response.[19] These locations are considered the most delayed portions of LV; so that if being

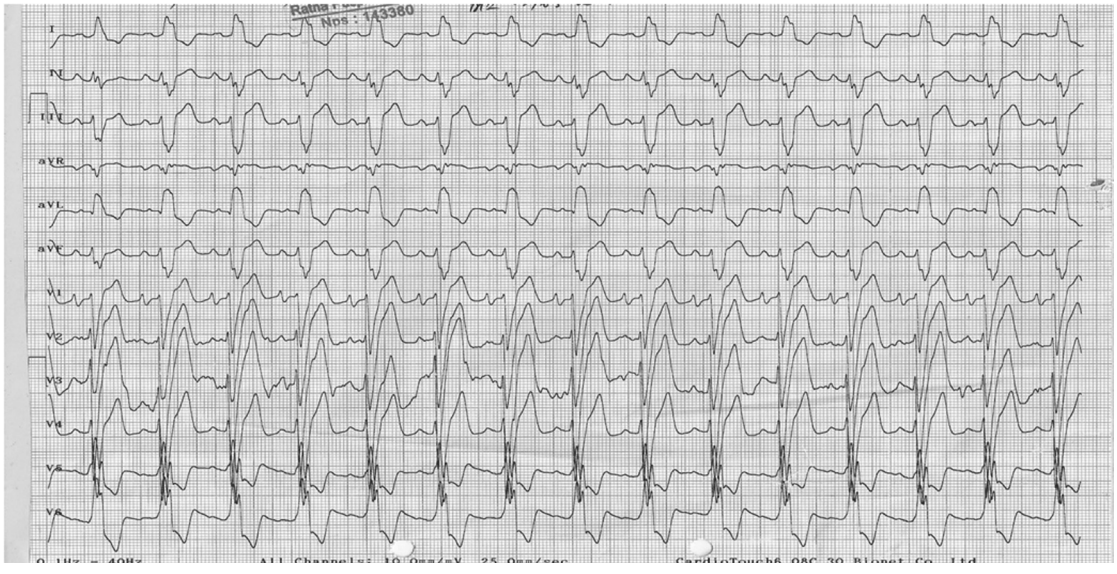

Figure 1. Pre-implant EKG of a patient who is considered super-responder. Note the LBBB pattern with QRS duration of 160 ms. rS pattern in V1, and QRS notching or slurring in V5-V6 and I-AVL.

paced in a synchronized passion, will increase cardiac output. Several non-invasive modalities (spectral echocardiography, electromechanical mapping) are being utilized to identify the most delayed part of LV as the target for pacing site. However, its adoption in routine clinical arena is time consuming and not practical. Moreover, spectral echocardiography was unable to differentiate outcome among patients with QRS duration ≥150 ms, but it was able to predict event in patients with QRS duration between 120 ms and 150 ms.[20]

During implant, distance between surface EKG and LV electrogram (>90ms) could be applied to recognize the presence of most delayed part of LV which correlates with reverse remodeling.[21] **Figure 2** demonstrates example method of determining the most delayed part of LV from surface EKG and LV electrogram.

The commonest handicaps during LV lead implant are uncaptured site and the phrenic nerve stimulation. Multi-point pacing algorithm is currently available with beneficial evidence to overcome those problems.[22] Quadri-polar lead is also another option as it is able to span a larger area of myocardium and give us the ability to pace more hemodynamically and electrically beneficial sites.[23]

Post-implant: Optimal heart failure management and device follow-up

The complexity of HF pathogenesis requires a multidisciplinary approach which involves cardiac rehabilitation, education, and nutritionist. Drug therapy should be optimized as recommended by guidelines (guideline directed medical therapy, GDMT) which include ACE-inhibitor, Angiotensin-Receptor blocker (ARB), diuretics, beta-blocker, aldosterone-antagonist, and digitalis.[1]

Thus, GDMT is mandatory in HF management to help obtain the criteria of 'responder' for those who received CRT. Optimization of neuro-hormonal blockers is more important than diuretics as proven by Schmidt, et al.[24]

Post-implant programming is essential to prevent NR especially with regards to pacing mode, capture output, lower and upper rate, and AV-VV intervals and an observational study has proved that sub-optimal AV-VV delay as a meaningful factor of poor response.[2] The ESC guidelines recommend to first programmed a fixed 100 – 120 ms AV delay without VV interval.[25]

Several potentially correctable causes (atrial fibrillation, premature ventricular contraction (PVC), secondary valvular heart disease, and ischemia) may co-exist in HF patients. The co-existence of AF (see **Figure 3**) and PVC may reduce resynchronization pacing which worsen the outcome.

Antiarrhythmic drugs (AAD) are indicated and

Figure 2. LV lead is placed at posterolateral branch of coronary sinus. The delay between onset of surface EKG and LV electrogram was noted around 170 ms (lower panel). It indicates that LV lead position is delayed enough and this patient gave significant response after three months.

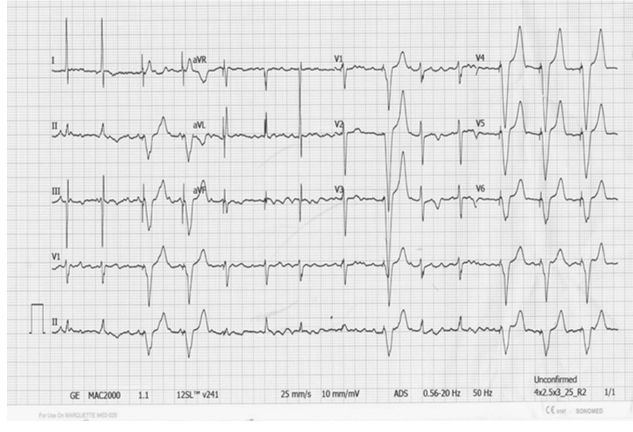

Figure 3. Intermittent biventricular pacing (wide QRS complex) is induced by the presence of atrial fibrillation. This patient only got 86% of resynchronized pacing which was noted from the programmer counter (ideal percentage of pacing should be closed to 100%).

should be individualized to abolish the rhythm disorder. To some extent, catheter ablation may be a good treatment of option.

The presence of secondary valvular heart disease, especially mitral regurgitation (MR), is prevalent in HF patients. A study on interventional mitral-clip for severely symptomatic CRT non-responders, has noted that 70% of patients improved and showed reverse remodeling after 12 months.[26] Another important issue that needs careful attention is the presence of ischemia in HF patients. Imaging modality such as MRI or perfusion test could predict the significance of ischemic area and viability assessment of left ventricle. If necessary, revascularization—either by percutaneous intervention or CABG—is advised to improve clinical response and reverse remodeling.

Conclusion

Non-responders remains a challenging issue in CRT population and requires a comprehensive understanding and multi-disciplinary approach to overcome. The preventive strategy should be applied from the patient selection phase with very meticulous criteria to achieve responders (wide QRS duration with LBBB morphology and non-ischemic etiology). To obtain maximum resynchronization, LV lead should be placed at the latest portion of LV (either by selection of posterolateral or lateral CS branch or by measuring the delay between surface ECG and LV EGM of more than 90 ms). Quadripolar or multi-site pacing may be utilized to optimize LV pacing sites. Post-implant follow-up is of outmost importance to solve some issues contributing to non-responders such as medical therapy escalation, arrhythmia abolition, and ischemia treatment. This holistic strategy should be exercised from time to time during follow-up to achieve most benefit from this costly therapy.

Abbreviations

AAD: antiarrhythmic drugs
AF: atrial fibrillation
ARB: angiotensin-receptor blocker
COMPANION: comparison of medical therapy, pacing, and defibrillation in heart failure
CRT: cardiac resynchronization therapy
CRT-D: CRT with defibrillator
CS: coronary sinus
GDMT: guideline directed medical therapy
HF: heart failure
ICD: implantable cardioverter defibrillator
LBBB: bundle branch block
LVEF: left ventricle ejection fraction
NR: non-responders
NYHA: New York Heart Association
PVC: premature ventricular contraction

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