REVIEWS

Cardiac resynchronization therapy – current status and perspectives

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Abstract: This update is not intended to be an exhaustive review about this topic. Its purpose is to illustrate the complexity of the CRT issue, to summarize today applications, limits and a few trends toward therapy improvement. CRT is the step forward from cardiac rhythm therapy, started more than 50 years ago, when the firs pacemakers were invented, to cardiac contractility optimization. The later is done by controlling the timing of atrial and ventricular contraction and the place of the initial (bi)ventricular electrical depolarization. The foundation of CRT lies in electrical and mechanical heart dyssynchronization which occurs in over a quarter of all the heart failure patient population. The latest recommendations based on the newest trials are available from 2013 (2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy). These guidelines simplified the management of HF patients, when speaking about CRT, and discouraged the use of the device in class I NYHA and non-LBBB pattern with QRS <150 ms patients. Unfortunately, about one third of the implanted patients prove to be non-responders to therapy. There are two major directions when seeking improvement in CRT: better patient selection and technique improvement.
Keywords: heart failure, cardiac resynchronization therapy, response to therapy

Rezumat: Prezenta actualizare a statusului terapiei de resincronizare cardiacă (CRT) nu se dorește a fi un exercițiu exhaustiv al subiectului, ci doar o încercare de a ilustra complexitate problematicii acestui tip de tratament, indicațiile actuale, limitările ei, precum și de a prezenta câteva tendințe ce vizează îmbunătățirea rezultatelor postprocedurale. CRT reprezintă trecerea de la terapia ritmului cardiac, începută acum mai bine de 50 de ani cu primele stimulatoare cardiace, la terapia de optimizare a contractilității miocardice în insuficiența cardiacă. Aceasta se realizează prin controlul și alegerea momentului contracției atriale și ventriculare și a locului inițial al depolarizării electrice (bi)ventriculare. Se estimează că aproximativ un sfert din populația pacienților cu insuficiență cardiacă prezintă criterii electrice și mecanice de asincronism cardiac. Aceștia reprezintă ținta terapiei de resincronizare. Indicațiile actuale ale terapiei de resincronizare folosesc criterii bazale de selectie, fără putere predictivă mare în ceea ce privește răspunsul la tratament. Aproximativ o treime dintre pacienții supuși procedurii de resincronizare se dovedesc a fi nonresponderi la terapie. Formulăm două direcții majore în încercarea de a crește numărul beneficiarilor post-resincronizare; prima se referă la o mai buna selecție a pacienților candidați pentru implant și a doua vizează îmbunătățirea aspectelor tehnice legate de implant.
Cuvinte cheie: insuficiență cardiacă, terapia de resincronizare cardiacă, răspuns la terapie

INTRODUCTION

It's been over 50 years since the first pacemakers were invented. Since then, important changes have been introduced concerning bradycardias, but also anti-tachycardia therapies such as anti-tachycardia pacing, internal defibrillation and devices aimed to improve synchronization in the failing heart. There is a dynamic regarding the indications for these therapies, which was imposed by the technical development of these incredible "mini"-computers, a process that still goes on today. Historically, there were experiments regarding cardiac resynchronization (CRT) starting with 1986 (Burkhoff et al) and also in 1990 (Latucca et al), by using animal models. Eight years later (1994) the first CRT was surgically implanted in a human being – Serge Cazeau. In 1998 Daubert (et al) presented the technique using the coronary sinus and later in 2001

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FDA approved the use of this new therapy in humans (US). Very important, in the same year (2001) we had the first CRT-P device implanted in our country and in 2003 the first CRT-D implanted in Bucharest and Timisoara. Interesting is that the theoretical foundation for CRT was understood years after the first implants, only when the modern imaging of the depolarization fronts, which occur in a dyssynchronized heart, was available. The principle of CRT consists in left and right ventricular pacing (bi-ventricular pacing) synchronized with the atrial (spontaneous or paced) activity. The pulse generator can be a three chamber pacemaker with or without defibrillator function. Thus, by optimizing cardiac electrical intervals, one can hope in the end to improve the cardiac output[1,3,14].

SUBSTRATE OF HEART FAILURE – CARDIAC DYSSYNCHRONIZATION

The foundation of CRT lies in electrical and mechanical heart dyssynchronization which occurs in over a quarter of all the heart failure patient population. This form of heart failure is now regarded as a separate entity of chronic cardiac insufficiency. The presence of electrical heart dyssynchrony is responsible of immediate and important contraction impairment, as it is known from studies regarding right ventricular (RV) pacing (induced left bundle branch block (LBBB)). The electrical activating sequence in LBBB describes a U-shape pattern, "turning around the apex": septum – apex – inferior wall – lateral wall, because of a functional blocking line which is orientated from LV base to the apex. Local contraction becomes time-variable, which leads to local strain impairment. Furthermore, these abnormalities cause regional myocardial differences in terms of work load. The last regions to depolarize have to deal with the highest work load. Globally, the entire heart suffers from pump deficiency[4]. There are three levels of mechanical asynchrony: the first level is atrial-ventricular – it is responsible for reducing the diastolic filling time and the initiation of diastolic mitral regurgitation; the second one is the inter-ventricular asynchrony - it represents early activation of the RV with direct consequences over the interventricular septum contraction, which causes a decrease in LV performance; the third and most important is the intra-ventricular asynchrony – it is the result of early activation of the septum and late activation of the lateral wall as presented before (some authors consider the interventricular form as part of the intra-ventricular asynchrony)[2,4,14].

INDICATIONS FOR CRT

CRT represents one of the most modern and useful treatment techniques aimed to alleviate heart sufferance. The early conducted studies, at the beginning of the CRT era (about two decades ago), were small-size medical investigations which rapidly showed improvement in systolic LV function and cardiac output. From that point on, as the experience regarding implants grew and the number of CRT treated patients expanded considerably, large scale studies were possible and our understanding of this phenomenon gradually increased.

The first important changes concerning indication for CRT came with the 2012 ACCF/AHA/HRS Focused Update for CRT, where clear specifications in respect of NYHA Class severity, QRS morphology and duration, presence of sinus rhythm or atrial fibrillation, were made[30]. The early CRT studies focused only on QRS duration and the severity of heart failure[5]. Later, the high understanding of the relationship between symptom improvement and the decrease in cardiac dyssynchronism lead to further investigation of the potential effects of multisite biventricular pacing and intraventricular conduction delay (MUSTIC trial). This trial proved important symptomatic benefits in CRT patients, especially among class III NYHA, EF <35% and QRS duration over 150 ms[6]. QRS duration was also largely debated in the 2008 guidelines, but even though the best results had been noticed among patients with QRS >150 ms, these guidelines failed to make specific recommendations based on QRS morphology and duration. Very important, though, is that no large scale trial mentioned at that time managed to demonstrate any benefit in resynchronizing patients with normal or near normal (120-130 ms) QRS duration, even when echocardiographic elements of dyssynchrony were noticed[1,14]. Recent papers reinforce this statement adding that CRT may actually have deleterious effects in this group of HF patients (EchoCRT study)[7]. Other major trials like Resynchronization for Ambulatory Heart Failure Trial (RAFT)[8], Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT)[9], Cardiac Resynchronization in Heart Failure Study (CAREHF)[10], Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION)[11] were able to demonstrate greater benefits when CRT was performed in wide QRS population. A meta-analysis of these trials, which included also the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study, proved important benefits in terms of morality and

hospitalization for heart failure, in the QRS >150 ms patient population, regardless of HF severity[12].

Current information reveals there is no benefit, or even there is a harmful effect when implanting a three chamber pace-maker when QRS duration is lower than 120-130 ms[1]. Regarding NYHA classification of HF, the REVERSE trial was the first one to notice that CRT has a reverse-remodeling effect in mildly or asymptomatic HF patients (when assessing left ventricular end systolic volume – LVESV in the CRT-ON group vs CRT-OF)[12]. Importantly, the reverse-remodeling effect was significantly lower in the non-LBBB pattern. Also, the study revealed that the longer the QRS duration, the greater the decrease in the LVESV. Another important aspect was the comparison between CRT-D and ICD alone, which was studied in the RAFT trial[8]. Overall, there was a better protection in terms of all-cause mortality, cardiovascular death and hospitalization (primary end point) offered by CRT-D implant (the differences were noticed only in the wide QRS complex (>150 ms), LBBB morphology and sinus rhythm). Similar conclusions were obtained in the MADIT-CRT trial, when comparing CRT-D vs ICD in patients with HF class I-II NYHA, QRS >130 ms[9]. A subanalysis of this study proved that only patients with LBBB morphology benefit more from CRT-D vs ICD, whereas in the group presenting right bundle branch block (RBBB) or intraventricular conduction delay (ICVD) patterns there was no difference in terms of better protection between CRT-D and ICD[9].

The latest recommendations based on the newest trials are available from 2013 (2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy). These guidelines simplified the management of HF patients, when speaking about CRT, and discouraged the use of the device in class I NYHA and non-LBBB pattern with QRS <150 ms patients[1].

The summarization of CRT indications is listed in Table 1.

THERAPY LIMITATIONS

It is estimated that 5-10% of all the HF population has indication for CRT. This represents a large number of patients, about 400/1.000.000 inhabitants/year in Europe[14]. Unfortunately, about one third of the implanted patients prove to be non-responders to therapy. We believe that this is mainly due to a lack of clear criteria able to predict response to therapy; next stands the technical impairment[15]. There is heterogeneity of mechanisms determining resynchronization success. As seen above, the present indications for CRT widely uses basic criteria in terms of LVEF, NYHA class and QRS duration, which apparently are insufficient when predicting the responders to therapy[16].

What is a responder?

To answer this question, we must first establish the timing of evaluation. There is no consensus regarding this aspect, but there is a general opinion that at least 6 months must pass from the implant before we make an assumption[17]. There are at least three sets of parameters to have in mind. Firstly, of course, there are the morality-morbidity indicators[21]. Secondly, but maybe the most important, there are the clinical parameters: NYHA class (at least 1 class decease), 6 mwt (>50 m improvement), QOL, VO2 (>10 %). On the third position comes the echocardiographic evaluation (LVEF >5% and LVESV >10-15%)[18]. Interestingly, there is no direct correlation between QRS duration (narrowing) and the clinical/hemo-dynamical benefit after CRT, according to literature[19]. According to these parameters, the responders to therapy are classified in super-responders (EF improvement >20%, reduction of LVTSV > 30%), responders (EF improvement 5-20%, reduction of LVTSV 15-29%) and non-responders (EF improvement <4 %, reduction of LVTSV 0-14%)[20].

Causes of non-response[1,9,14,21-,25]

1. Indication related causes
   - inappropriate patient selection
   - narrow QRS, non-LBBB pattern, NYHA class I
   - the absence of mechanical dissynchrony
   - absence of contractile reserve
   - presence of scar tissue at the place of the LV lead positioning
2. Patient related causes
   - individual factors
   - male gender
   - ischaemic etiology
   - RV dysfunction
   - mitral regurgitation
   - atrial fibrillation
   - absence of complete myocardial revascularization before CRT implant
   - other comorbidities
3. Device related/ Implant difficulties
   - anatomical factors
   - suboptimal lead positioning
   - loss of LV capture (exit block, lead fracture)
   - insufficient Bi-Ventricular pacing
   - high cardiac rate / Atrial Fibrillation
   - failure of device optimization (A-V, VV intervals)

Table 1. The summarization of CRT indications

Class IA:	Sinus rhythm, NYHA class II-IV, LBBB, QRS >150 ms, LVEF <35% Patients with conventional pacemaker indications, NYHA III-IV, LVEF <35%
Class IB:	Sinus rhythm, NYHA II-IV, LBBB, QRS 120-150 ms, LVEF <35%
Class IIa:	Sinus rhythm, NYHA II-IV, non-LBBB, QRS >150 ms, LVEF <35% Atrial Fibrillation, NYHA III-IV, QRS >120 ms, LVEF <35% Atrial Fibrillation, candidates for AV junction ablation and reduced LVEF Patients with conventional pacemaker indications, HF and reduced EF
Class IIb:	NYHA II-IV, non-LBBB, QRS 120-150 ms, LVEF <35%

FUTURE PERSPECTIVES

There are two major directions when seeking improvement in CRT: better patient selection and technique improvement. The first direction refers to a superior selection strategy capable of predicting greatest benefit from three-chamber pacing. Summarizing today's understanding of this topic, LBBB remains the strongest substrate for resynchronization and patients with this pathology enjoy the best benefit[24]. The MADIT-CRT study was able to identify, among the 191 super-responders to therapy, a number of six clinical characteristics significantly related to procedural success: female gender, non-ischaemic etiology, QRS duration >150 ms, LBBB pattern, body mass index <30 kg/m^2 and small left atrial volume[9,26,27]. But one can say that patients are more complex than these six aspects, so future assessments should take into consideration more detailed clinical issues like patient co-morbidities, LBBB pattern (typical, atypical, non-specific), mechanical dyssynchrony or the presence of myocardial scars (imaging methods)[1,25,29]. Biological testing can be added to the ones mentioned above, including the old natriuretic peptides or newer biomarkers like myocardial oxidative stress testing[9,28].

The second major direction refers the technical aspects regarding the implant procedure and device optimization during follow-up. It is known that no single ideal LV site for lead placement deserves the entire patient population[1,9]. Latest activated LV segment should be the first option, but in practice it is often very challenging to find and use the appropriate coronary sinus affluent[30,33]. One study demonstrated that sub-optimal lead placement (e.g. anterior wall) was responsible for 21% of causes leading to non-response[31]. General considerations regarding the ideal site include lateral wall in non-ischaemic etiology and imaging derived selection of the appropriate LV wall (cardiac MRI, echo) in iscahaemic cardiomyopathies[32]. There are new implant techniques under surveillance, including LV endocardial implantation[34], multisite left ventricular pacing[35] or surgical epicardial lead implant[36]. Endocardial approach has long been an appealing perspective restricted by technical difficulties (trans-septal approach using puncture needle or radio-frequency punction) and cardio-embolic complications (the need for chronic anticoagulation)[37]. Experience in this direction is enlarging; there are at least 4 trials underway with promising perspectives. The idea of multisite pacing is extremely appealing especially in extremely dilated left ventricle[38]. Two small-size studies demonstrated the superiority of dual-site pacing vs single-site and there are at least two ongoing randomized studies with encouraging perspectives (DIVA and TRUSTCRT)[39,40]. There are also new emerging technical possibilities using ultrasound/wireless leads that will indeed modify the fundamentals of cardiac pacing[41]. When other techniques fail, there is always the option of an open chest approach using surgical epicardial LV lead implantation. This approach has the disadvantage of an invasive thoracic surgery, but the advantage of selecting the desired place for LV lead placement[42,43]. Techniques using the heart apex approach are also used by some medical centers. The optimization of atrial-ventricular (AV) and ventricular-ventricular (VV) intervals is also a corner stone when defining procedural success in CRT. Many trials were conducted by using echocardiography guided AV and VV optimization with little or no long-term effect[54]. Besides achieving >99% biventricular pacing, experts recommendations, nowadays, refer to echo-guided AV optimization early after implant using E and A waves and the use of synchronous biventricular pacing (0 ms VV interval) (2013 ESC Pacing and CRT Guideline)[1]. If no benefit is observed, then echo-optimized VV interval should be tried out. Noninvasive ventricular mapping techniques are developed, like the multichannel mapping vest combined with CT imaging in the hope of better device programming[13]. New encouragement comes from using the newly developed automatic device optimization of AV and VV intervals by using complex algorithms. One such example, where this method is tested in comparison with standard approach, is the RESPOND CRT trial (*Automatic Opti-*

mization of Cardiac Resynchronization Therapy Using SonR — Rationale and Design of the Clinical Trial of the SonRtip Lead and Automatic AV-VV Optimization Algorithm in the Paradym RF SonR CRT-D)[44]. The SonR algorithm is based on weekly optimization of AV and VV intervals using an accelerometer able to measure changes in SonR signals (myocardial vibrations during isovolumetric contraction – which are proven to be correlated with the intensity of the first sound and with cardiac contractility – related with dP/dT value)[45,46]. The method seems to be of great value as it has already shown superiority to conventional optimization techniques. Finally, we should mention that a special place is held by the remote monitoring device management, a method that is already in use in the USA and many European countries. Regarding ICD's and CRT, remote monitoring proves to be of substantial aid when speaking in terms of long term survival and total hospitalization as shown in CONNECT and LATITUDE trials[1,9,14].

CONCLUSIONS

One can say that the last decade brought resynchronization therapy from the state of timid trials to a reliable therapeutic method. Even though subject to many imperfections, it has proven to be a distinct healing direction and not a closed road. There are a lot of ongoing trials meant to improve both patients' selection and implantation techniques that will surely alleviate the burden of HF disease. New ideas derived from better understanding of cardiac electrophysiology, supported by an incredible technical progress, form the background that could fundamentally shape the way we see CRT implant today.

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