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Change in indication for cardiac resynchronization therapy?

Dennis Lawin and Christoph Stellbrink*

Klinik für Kardiologie und Internistische Intensivmedizin, Klinikum Bielefeld, Bielefeld, Germany

* Corresponding author. Klinik für Kardiologie und Internistische Intensivmedizin, Klinikum Bielefeld, Lehrkrankenhaus der Westfälischen Wilhelms-Universität Münster, Teutoburger Strasse 50, 33604 Bielefeld, Germany. Tel: +49-521-5813401; fax: +49-521-5813498; e-mail: christoph.stellbrink@klinikumbielefeld.de (C. Stellbrink).

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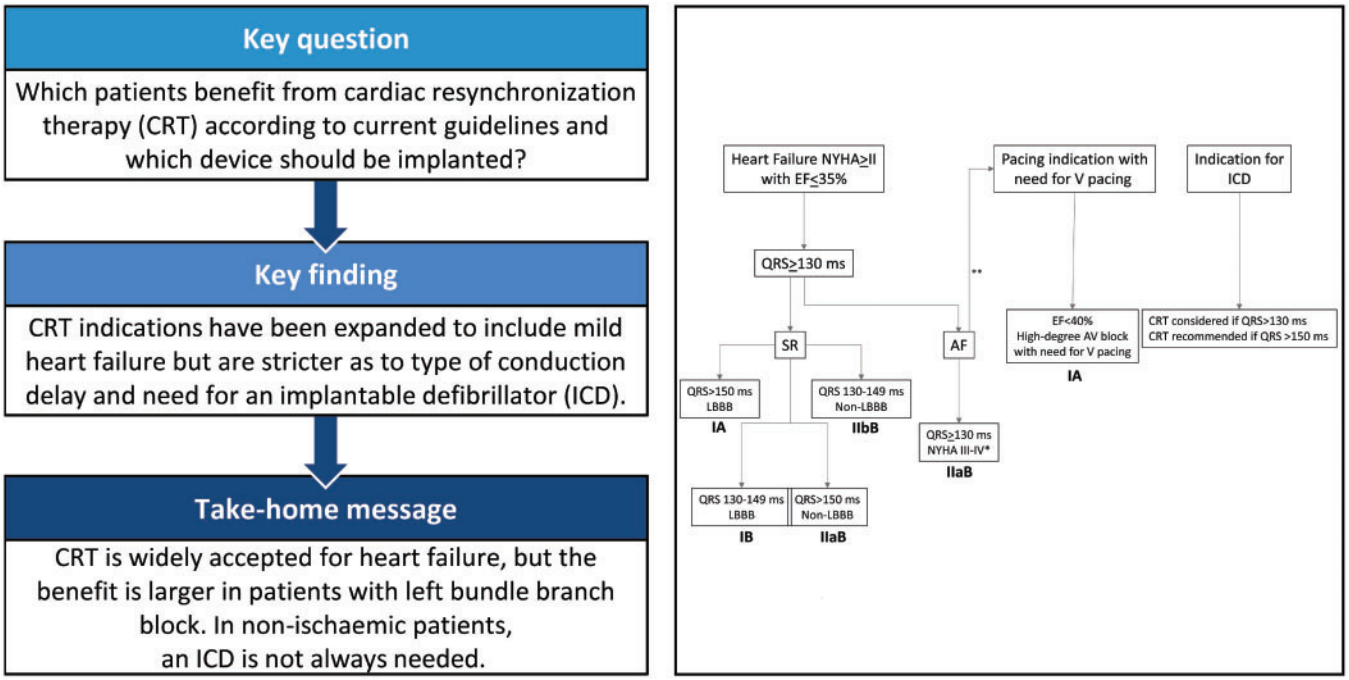

Summary

Cardiac resynchronization therapy (CRT) has rapidly evolved as a standard therapy for heart failure (HF) patients with ventricular conduction delay. Although in early trials, only patients with sinus rhythm and advanced stages of HF have been candidates for CRT, more recent data have expanded the indications to patients with mild-to-moderate HF and atrial fibrillation and patients in need of antibradycardia pacing with reduced left ventricular function. On the other hand, it is now well recognized that patients with a wide QRS (>150 ms) and left bundle branch block morphology benefit most from CRT, whereas in patients with a more narrow QRS complex (<130 ms) CRT may actually be harmful despite the evidence of ventricular dyssynchrony by echocardiography. There is no prospective randomized study showing mortality benefit from a combined CRT defibrillating device over a CRT pacer alone. This is especially important because recent data indicate that older patients with non-ischaemic cardiomyopathy may not benefit from the implantable cardioverter-defibrillator as much as previously thought. Thus, the decision for a CRT pacer versus CRT defibrillating should be tailored to the therapeutic goal (improvement in prognosis versus symptomatic relief), patient age, underlying cardiac disease and comorbidities. This article gives an overview over the current indications for CRT according to published literature and the European guidelines for pacing and HF.

Keywords: Cardiac resynchronization therapy • Implantable defibrillator • Left bundle branch block • Heart failure

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INTRODUCTION

The fundamental knowledge that intraventricular conduction delay can contribute to worsening of the left ventricular (LV) systolic function [1] and has prognostic implications in systolic heart failure (HF) [2], which has led to the concept of treating dyssynchrony by biventricular pacing [3–5]. Prospective randomized studies have shown that the cardiac resynchronization therapy (CRT) improves the LV ejection fraction (EF), New York Heart Association (NYHA) functional HF class and reduces HF hospitalization and mortality in suitable patients [6, 7]. Therefore, CRT has rapidly evolved into a standard therapy for patients with HF and ventricular conduction delay in the current guidelines [8–10]. Although CRT was initially confined to patients with sinus rhythm and advanced HF, more recent trials have expanded the concept to patients with mild HF [11–14]. In addition, current implantation practice also includes patients with atrial fibrillation (AF), in need for antibradycardia pacing or with a primary indication for an implantable cardioverter-defibrillator (ICD) and additional conduction delay. On the other hand, delayed LV contraction is the main therapeutic target in CRT. Therefore, the type of conduction delay, i.e. right versus left bundle branch block (LBBB), matters for the response to CRT. This article summarizes the current knowledge on CRT and the change in indications caused by more recent study data. Figure 1 provides a decision flowchart based on the most important recommendations in the current guidelines.

'THE CLASSICAL INDICATION': CARDIAC RESYNCHRONIZATION THERAPY IN THE HEART FAILURE PATIENT WITH SINUS RHYTHM

The above-mentioned prospective randomized trials [3–7] provided the basis for the CRT recommendations in the current guidelines for pacing and HF [8–10]. The most recent guideline on HF gives a class I indication with a level of evidence (LoE) A for patients with symptomatic HF, an EF $\leq$35% (despite optimized medical treatment), LBBB and a QRS duration $\geq$150 ms, and a class I indication (LoE B) in patients with LBBB and a QRS width of 130–149 ms. The QRS cut-off of 130 ms differs from the recommendations in the European Society of Cardiology (ESC) guideline for pacing and CRT set at 120 ms. This change was based on results of the Echo CRT trial published between the 2 guidelines, which demonstrated unfavourable effects in patients with a QRS <130 ms despite echocardiographic evidence of LV dyssynchrony [15].

ADVANCED VERSUS MILD HEART FAILURE

Early CRT trials enrolled only patients with advanced HF, i.e. NYHA class III–IV [3–7]. Later, this concept was broadened to patients with mild HF in 3 trials [11–14]. The largest of these trials, Multicentre Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT), also included patients in NYHA class I HF if they had ischaemic HF. However, the number of NYHA class I patients included was too low to provide enough evidence to demonstrate the benefit of CRT in this subgroup. Thus, the CRT indication is limited to patients with symptomatic HF [9]. An unresolved question is whether an asymptomatic patient with ischaemic cardiomyopathy and LBBB requiring an ICD should receive a combined CRT device obviating the need for a later upgrade should the patient become symptomatic. Data from the European CRT survey suggest that physicians in Europe implant CRT devices in this scenario as 3% of CRT recipients are in NYHA class I [16]. Current guidelines state that for ICD candidates with sinus rhythm and a QRS $\geq$130 ms, CRT defibrillating (CRT-D) may be considered and is recommended when QRS duration exceeds 150 ms [9]. This recommendation is based on the existing evidence showing the benefit of CRT-D compared with ICD alone [11, 12]. At the other end of the HF spectrum are patients with end-stage HF. Cardiac transplantation remains the gold standard for these patients but death on the waiting list has become an increasing problem due to shortage of donor organs. Although randomized data are lacking for this population, a recent meta-analysis suggests that rescue CRT in inotrope-dependent patients may allow the weaning of the majority of patients from intravenous inotropic support, reduce mortality and thus be used as a bridge-to-transplant or to a ventricular assist device in suitable patients [17]. Usually, a CRT-D system should be used in this situation as a similar benefit has been shown in the US in a large retrospective analysis of the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) registry for the ICD [18].

QRS WIDTH AND MORPHOLOGY VERSUS MECHANICAL DYSSYNCHRONY

Theoretically, not QRS widening *per se* but the resulting mechanical dyssynchrony leads to a negative effect on LV contraction and deterioration of HF symptoms [19]. Moreover, in patients with a narrow QRS complex mechanical dyssynchrony may be detected [20]. Therefore, CRT has been investigated in patients with a narrow QRS and an echocardiographic evidence of mechanical dyssynchrony. Despite encouraging results in smaller trials [21, 22], the first large, prospective randomized trial was terminated early because of a negative impact of CRT in patients with a QRS width <130 ms and a mechanical dyssynchrony demonstrated by tissue Doppler imaging and speckle tracking [15]. Thus, QRS duration remains the main entry criterion for CRT.

Although early CRT trials made no upfront distinction of LBBB versus non-LBBB, the MADIT-CRT trial defined the type of conduction delay at study entry and thus its influence could be prospectively studied. It was demonstrated that patients with a non-LBBB pattern derive less clinical and prognostic benefit from CRT [23]. This is in accordance with the concept that delayed contraction of the LV free wall in LBBB deteriorates LV function, which may be corrected by advancing LV free wall contraction through pacing. Thus, CRT received a lower class of recommendation for patients with a non-LBBB QRS morphology, i.e. a class IIa recommendation at a QRS $\geq$150 ms and a class IIb recommendation for patients with a non-LBBB pattern and a QRS of 130–149 ms [9].

LEAD POSITION AND CARDIAC RESYNCHRONIZATION THERAPY OPTIMIZATION

Despite the accepted criteria for CRT indication, the number of non-responders to CRT still remains at about 30%. This rate can be further reduced by optimizing CRT delivery. First, biventricular pacing should be delivered continuously; at least 92% of biventricular capture should be aimed for to obtain an optimal functional

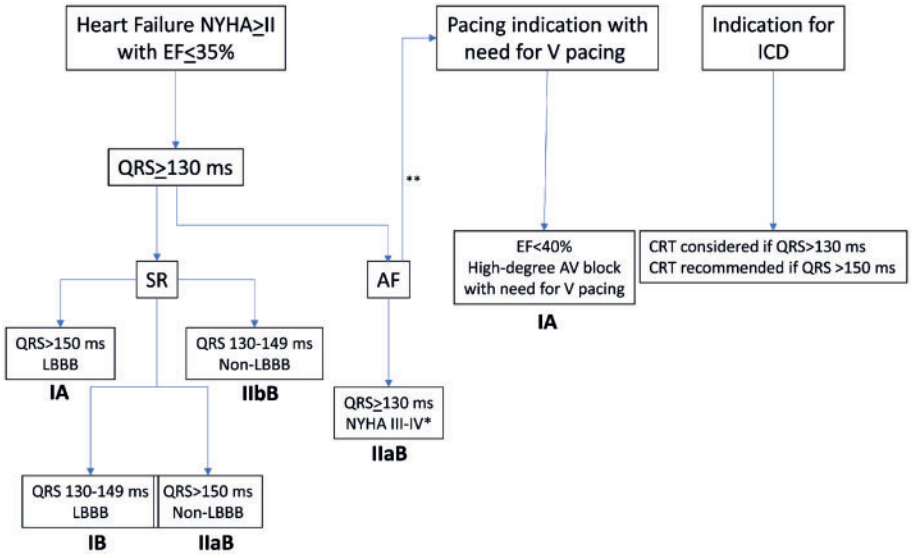

Figure 1: A flowchart of the most important (not all) recommendations for CRT based on the current European Society of Cardiology (ESC) heart failure guidelines [9]. The class of indication according to the ESC classification are in boldface. For patients with a primary ICD indication, no indication class for CRT is provided in the guideline. The choice for CRT pacer versus CRT defibrillating should be individualized to patient age, underlying cardiac disease (ischaemic versus non-ischaemic) and comorbidities (see also text). AF: atrial fibrillation; AV: atrioventricular; CRT: cardiac resynchronization therapy; EF: ejection fraction; ICD: implantable cardioverter-defibrillator; LBBB: left bundle branch block; NYHA: New York Heart Association; SR: sinus rhythm; V: ventricular. *Near 100% biventricular pacing capture should be ensured (e.g. by AV node ablation); **Includes patients scheduled for AV node ablation for AF with rapid ventricular response.

response [24], even higher percentages may be advantageous for mortality reduction [25]. AF, premature ventricular beats, fusion beats and inappropriately programmed long atrioventricular (AV) delay decrease the percentage of biventricular pacing [25–27]. Therefore, efforts to achieve biventricular pacing close to 100% in these circumstances are necessary, e.g. AV nodal ablation in AF or antiarrhythmic drugs to suppress premature ventricular beats. Secondly, the position of the LV pacing electrode should be optimized. A posterolateral LV lead position (Fig. 2) is frequently associated with a superior haemodynamic response [28] because in the majority of cases it is the site of the most delayed LV activation in HF patients with LBBB [29]. However, in some patients other LV regions may show more delayed activation. Therefore, placing the LV lead at the site of the most delayed LV activation or contraction may improve haemodynamic and clinical response to CRT [30, 31]. Moreover, positioning of the LV lead in an apical position may yield inferior long-term results [32]. Finally, transvenous implantation of LV leads may fail in up to 8% of implants [33] because of a missing target vein or inaccessibility of the coronary sinus. In these cases, an open surgical, epicardial approach using fixated or screw-in leads can be used as an alternative.

Third, modern CRT devices allow great variations in the pacing configuration, e.g. the AV and interventricular delay. Haemodynamic studies indicate that the haemodynamic response to CRT remains rather constant over a broad range of AV delays [34] and a short interventricular delay with preactivation of the left ventricle may provide a superior haemodynamic response. Several non-invasive optimization methods such as echocardiography or device-based algorithms have been used [35–38]; the gold standard remains echocardiography [35] but measurements are prone to large intraindividual and interindividual variations [39] and echocardiographic optimization is time-consuming. Therefore, AV/interventricular delay optimization is usually confined to poor responders with no other obvious reasons for non-response.

Finally, multisite pacing at more than 1 left or right ventricular (RV) site has shown promising results in small studies [40, 41]. As the number of lead-related complications increases with more leads, these approaches are limited to patients not responding to conventional CRT [42].

CARDIAC RESYNCHRONIZATION THERAPY WITH OR WITHOUT IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR BACKUP

There is a large overlap in indications for CRT and ICD therapy and thus most CRT patients are treated with a combined CRT-D device, although there are some regional variations in the use of CRT pacer (CRT-P) versus CRT-D [43]. The only trial randomizing CRT-P versus CRT-D was the COMPANION trial [7], which showed no significant survival benefit of CRT-D. However, the trial was not powered to detect a difference between the 2 CRT arms. Thus, the question whether CRT-D is superior to CRT-P for mortality reduction remains open. The ESC HF guidelines state that CRT-D should be used in patients in whom the primary reason for implant is improvement in prognosis, e.g. patients after an aborted sudden cardiac death or with recurrent, sustained, haemodynamically compromising ventricular tachycardia because of the proven survival benefit with the ICD [44]. However, the situation is less clear in patients with HF and a prophylactic ICD indication. The SCD-HeFT trial demonstrated a survival benefit with the ICD in patients with NYHA class II–III HF of ischaemic or non-ischaemic origin and a left ventricular ejection fraction ≤35% compared to amiodarone or placebo [45]. Although this study confirmed previous data in patients with ischaemic HF [46], there was only a non-significant trend toward mortality reduction with the ICD in non-ischaemic patients, in accordance with the previous data [47]. The DANISH trial readdressed this question by randomizing patients with

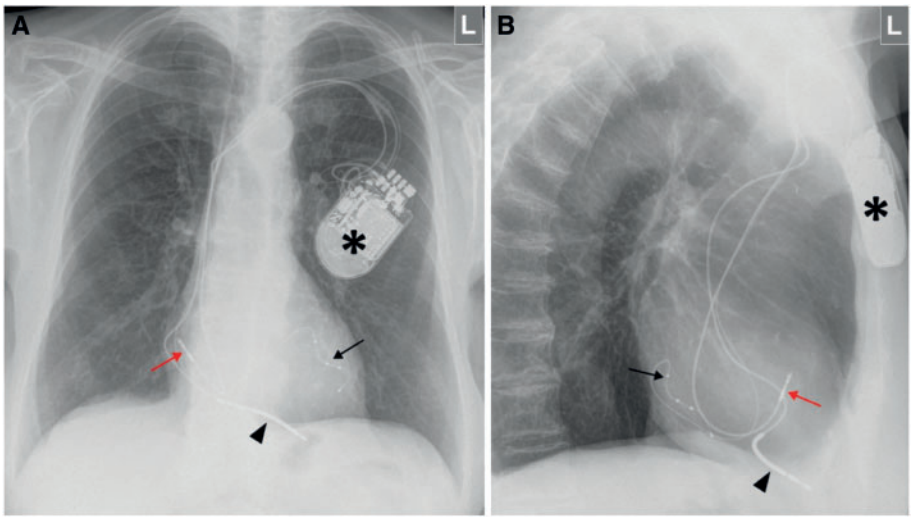

Figure 2: Posterior/anterior (**A**) and lateral (**B**) chest radiograph of a cardiac resynchronization therapy defibrillating system in a 61-year-old patient with symptomatic heart failure (ejection fraction 30%) due to ischaemic cardiomyopathy and left bundle branch block with a QRS of 160 ms. The pulse generator (asterisk) is implanted in the left infraclavicular region. A quadripolar stimulation lead is placed into a posterolateral branch of the coronary sinus for left ventricular stimulation (black arrow), a bipolar pace/sense lead in the right atrium (red arrow) and a single-coil lead in the right apex for stimulation and defibrillation (black arrowhead). L: left.

symptomatic non-ischaemic HF and left ventricular ejection fraction ≤35% to prophylactic ICD implantation or medical treatment alone [48]; 58% of the patients were treated by additional CRT. Prophylactic ICD implantation did not reduce mortality, irrespective of additional CRT therapy. A survival benefit with the ICD was observed only in younger patients. These results were confirmed in a recent, large observational study that showed a survival benefit from CRT-D versus CRT-P only in patients with ischaemic HF [49]. Thus, sudden cardiac death prevention in HF depends on the underlying cardiac substrate and the decision to implant a CRT-P or CRT-D device is more delicate in non-ischaemic than in ischaemic patients. As the benefit from CRT is larger in non-ischaemic compared to ischaemic patients, the risk of ventricular arrhythmias may be further reduced by HF improvement. In fact, CRT alone has been shown to reduce not only overall mortality but also the sudden death rate [50]. CRT-D may be preferred in mild HF because the proportion of sudden death in early HF stages is higher than death from pump failure. Comorbidities play a major role as an increase in comorbidities reduces the mortality benefit with ICD treatment [51]. Therefore, in older patients with more comorbidities, more advanced HF and non-ischaemic cardiomyopathy, the therapeutic goal may be symptom relief rather than improvement in prognosis and thus, implantation of a CRT-P rather than a CRT-D system may be justified. Moreover, although the perioperative risk is similar for CRT-P and CRT-D implantation, a higher incidence of long-term complications (mainly infections) with CRT-D devices should be taken into consideration [52].

CARDIAC RESYNCHRONIZATION THERAPY TO PREVENT CARDIAC DYSSYNCHRONY IN PATIENTS NEEDING ANTIBRADYCARDIA PACING

RV pacing may cause delayed LV activation similar to the pattern observed in LBBB [53] and may thus lead to deterioration in HF symptoms [54]. Current pacing guidelines advocate the use of algorithms to reduce RV pacing in patients without high-degree AV block [8]. But in patients requiring constant ventricular pacing, CRT may be used to prevent LV desynchronization. The BLOCK-HF trial [55], randomizing patients with high-degree AV block, a left ventricular ejection fraction <50% and HF NYHA class I–III to conventional RV dual-chamber pacing and CRT, demonstrated a significant reduction of the combined primary end point of death, HF events or increase in LV end-systolic volume by CRT. On the basis of these data, CRT is recommended in patients with reduced EF and an indication for ventricular pacing due to high-degree AV block [9]. HF patients who develop worsening of LV function due to high percentage of conventional RV pacing may be considered for an upgrade to CRT (class IIb, level B) [9]. However, this does not apply to all patients requiring ventricular pacing. The BIOPACE study [56], comparing conventional dual-chamber pacing to CRT in patients with high-degree AV block and near-normal LV function, failed to show any significant improvement in mortality and hospitalizations by CRT. Thus, CRT should be reserved to patients with some degree of LV dysfunction.

CARDIAC RESYNCHRONIZATION THERAPY IN ATRIAL FIBRILLATION

Owing to the high prevalence of AF in HF, the question whether CRT is also effective in AF patients is of high clinical relevance. Unfortunately, no prospective randomized trial investigating the effect of CRT on hard end points (e.g. mortality and hospitalizations) and only including AF patients has been performed; only one of the major CRT trials included AF patients [11]. Therefore, current recommendations rely on small, randomized studies with functional end points, observational trials and meta-analyses. In contrast to sinus rhythm patients, AF patients have more comorbidities, often higher and irregular heart rates and the lack of an atrial rhythm triggering biventricular stimulation makes effective delivery of CRT often difficult. Adequate rate control is extremely important, which can often only be ascertained by AV nodal ablation. In patients with reduced LV function requiring AV node ablation for rapid AF CRT is superior to

conventional RV pacing with regard to functional capacity, hospitalizations and even HF death [57, 58]. Meta-analytic evidence suggests that AF patients derive a similar benefit from CRT as sinus rhythm patients with regard to EF reduction but have a less functional response and remain at a higher risk of non-response and death [59]. Thus, CRT is indicated in AF patients with reduced LV function if they have an indication for ventricular pacing (including patients undergoing AV node ablation) regardless of functional NYHA class (class I, LoE A) and should be considered in patients with NYHA class III–IV HF, an EF ≤35%, a QRS ≥130 ms (class IIa, LoE B), provided a strategy to ensure biventricular capture is in place or the patient is expected to return to sinus rhythm [9].

FUTURE DIRECTIONS

Although CRT has been firmly established in the management of HF patients some open questions remain that need to be addressed in future studies. The fact that patients with AF are frequently implanted with a CRT device although data in this patient group are mostly retrospective or non-randomized highlights the need for a prospective randomized trial in this population. Another major open question is whether implantation of a CRT-D system offers mortality benefit compared to a CRT-P device. This is currently being investigated in a prospective-randomized trial (RESET-CRT: Re-evaluation of Optimal Re-synchronisation Therapy in Patients with Chronic Heart Failure, ClinicalTrials.gov Identifier: NCT03494933).

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