A Critical Reappraisal of the Current Clinical Indications to Cardiac Resynchronisation Therapy

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Abstract

Cardiac resynchronisation therapy (CRT) is a well-established non-pharmacological treatment option for patients with refractory symptomatic heart failure (HF) already under optimal medical therapy. CRT is founded on the principle that interventricular conduction disturbances and more in particular left bundle branch block (LBBB) are deleterious to cardiac performance, and may contribute to the systolic and diastolic incompetency typical of patients with HF. Although CRT is associated with a not negligible percentage of non-response, all the international guidelines on chronic HF have extended their indications to CRT, also to patients with less symptomatic HF who are already showing signs of systolic dysfunction and interventricular dyssynchrony, without giving any substantial advice to reduce the number of failures of this therapy. This review seeks to point out the potential issues linked to CRT, with the aim of making a reappraisal of the clinical evidences supporting the current indications to CRT, and to figure out which type of research should be warranted in the field for the future to reduce the percentage of non-responders to this therapy.

Keywords

Cardiac resynchronisation therapy, heart failure, left bundle branch block, NYHA class II

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Cardiac resynchronisation therapy (CRT) is a well-established non-pharmacological treatment option for patients with refractory symptomatic heart failure (HF) already under optimal medical therapy.¹ CRT is founded on the principle that interventricular conduction disturbances and especially left bundle branch block (LBBB) are deleterious to cardiac performance and may contribute to the systolic and diastolic incompetency typical of patients with HF.² Restoring the original synchrony of contraction with biventricular pacing has demonstrated to improve cardiac function and to reduce morbidity and mortality in this population.³

Recently, all the international guidelines on chronic HF have extended their indications to CRT, also to patients with less symptomatic HF who are already showing signs of systolic dysfunction and interventricular dyssynchrony.⁴ This change in the indications to CRT will surely increase the number of devices that will be implanted in the near future, potentially increasing the number of those patients known as 'non-responders'. At present, the general understanding is that 20–30 % of patients do not benefit from CRT.³ Lack of response to CRT is a complicated enigma, which raises a lot of attempts at a solution. Indeed, response to CRT, in particular when identified with left ventricular reverse remodeling, has demonstrated to be predictive for long-term outcome in CRT patients.⁵ This means that the scientific community should address its future efforts in understanding the reasons, which hide behind lack of response, because increase of response to CRT will eventually result in a better and longer survival of this group of patients.

Bearing this in mind, our main concern is whether this extension of current indications to CRT affects the incidence of non-responders. Will this number be estimated to increase or decrease? As often happens, to give an answer to the future, it is advisable to look at the past. Indeed, this review seeks to point out the potential issues linked to CRT, with the aim of making a reappraisal of the clinical evidences supporting the current indications to CRT, and to figure out which type of research should be warranted in the field for the future to reduce the percentage of non-responders to this therapy.

What is the Definition of Response to Cardiac Resynchronisation Therapy?

There is no universal agreement on what should be considered a positive response to CRT. It is well-known that the definition of response varies greatly among the studies, and that there is a myriad of criteria used to define it. Briefly, there are echocardiographic criteria, clinical criteria and composite criteria – obtained with a combination of the first two. The lack of a universal definition of response to CRT is contributing to the general uncertainty on its real effects, and is a clear obstacle to any significant advancement in the field. Searching PubMed for the words 'response' and 'CRT' evokes in the majority of cases studies aiming to understand the predictors of response to CRT; whereas articles trying to deepen the understanding of what has to be considered the response to CRT can be counted on the fingers of one hand. Bearing this in mind, it is worthwhile to report the findings of the study by Fornwalt et al.⁶ that sought to investigate agreement between the various published response criteria to CRT. From a wide literary search performed on Web of Science®

'Science Citation Index Expanded™' database using the topics 'cardiac resynchronization' and 'response', the authors extrapolated 17 different response criteria from the 26 most relevant publications on the topic. Agreement between response criteria was assessed with information from the baseline and six-month follow-up visits for the 426 patients in the Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) study. Response criteria were classified as echocardiographic if they include echocardiographic measurements, such as left ventricular ejection fraction or left ventricular volumes; and clinical if they include clinical parameters such as New York Heart Association (NYHA) class, six-minute walking test or maximal oxygen consumption (VO₂ max). They also found a study in which the criteria used to define the response to CRT were combined (echocardiographic and clinical). Not surprisingly, the agreement calculated with the Cohen kappa (κ) coefficient between all the identified response criteria was poor in 75 % of comparisons and strong only in 4 %. Even more significantly, the authors found a very poor concordance between echocardiographic and clinical response criteria and stated that "the agreement between echocardiographic and clinical criteria for defining a positive response to CRT is only slightly better than that expected by chance alone".

The findings of Fornwalt et al. are not surprising since both echocardiographic and clinical parameters are not completely reliable or interchangeable.

Echocardiographic Parameters

Even if monodimensional mode (M-mode) and two-dimensional echocardiography have been routinely used for the inclusion of the patients in the major clinical trials on CRT, and provide excellent diagnostic and prognostic information, it is well-known that these techniques are operator-dependent and that they are based on the geometrical assumption that three-dimensional left ventricular structures can be derived from mono- or two-dimensional slices. The recent advances in computer processing and transducer technology that have made three-dimensional echocardiography (3DE) a reality will perhaps help in overcoming this limitation.⁷ Indeed, the incremental value of 3DE in assessing left ventricular volume and function is already a reality, and has recently been accredited in the American Society of Echocardiography position paper.⁸ The use of 3DE should be encouraged during the process of identification of responders to CRT in clinical trials to reduce operator-dependent bias. On the other hand, not all the new echocardiographic technologies have brought real innovation. The results of the PROSPECT trial⁹ are well-known and unfortunately have demonstrated the unusefulness of echocardiographic measures of mechanical synchrony in this field.

Clinical Parameters

The most used clinical parameter in the assessment of the functional status of a patient with HF is NYHA class. Developed in 1928 for use as a clinical tool for a comprehensive cardiac diagnosis,¹⁰ NYHA classification has been promoted progressively to an entry criterion or an efficacy outcome measure in several clinical trials, not having the features of objectivity and reliability usually required to this type of measures. Even if uniformity in the definition of a NYHA class is of primary importance to achieve consistency in research settings, poor reproducibility of symptom assessment by physician is unfortunately well-known. A survey of 100 cardiologists¹¹ revealed significant variability in the questions and criteria used to determine NYHA class, and even when same criteria were used to distinguish between different NYHA classes, different physicians often did not agree on

their assessments. For example, 67 % of the interviewed cardiologists classified a patient who is able to climb a flight of stairs, stopping only one time as NYHA class II and 33 % as NYHA class III. Interestingly, in some studies,^{12,13} it has shown the difference in patients' self-assessed functional classification compared with clinician reported NYHA classification. Furthermore, a poor correlation has also been found between NYHA class and some objective measures of cardiac function such as peak oxygen consumption and six-minute walk distances.¹⁴

The definition of response to CRT is affected by other not negligible inconsistencies. One inconsistency is related to the definition of the minimum amount of follow-up required to assess the response to CRT – some studies focused on a very short-term timeframe (1–2 days from the implantation), others reported on three or six months. Nevertheless, it has to be stated that, in the clinical setting, evaluation of response to CRT can be done up until one year after the implant, but in most cases occurs in the first six months. A standardisation of the minimum follow-up is warranted for the future. Furthermore, no clear information is available on the inclusion of death in the definition of response to CRT. To reduce these contradictions it will be useful in future to link the response to CRT to the most objectivable parameters, such as left ventricular end-systolic volume reduction, which has showed to predict long-term survival better than improvement in the clinical status.¹⁵

What is the Minimum Value of QRS Duration Amenable for Cardiac Resynchronisation Therapy?

All international guidelines recommend the implantation of a biventricular pacing device alone or in combination with a defibrillator back-up in patients with symptomatic HF and a duration of the QRS ≥ 120 milliseconds (ms). The cut-off of 120 ms has been obtained from the most important clinical trials, such as Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and Cardiac REsynchronisation in Heart Failure (CARE-HF) for patients in NYHA class III and IV, and REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) for patients in NYHA class II (in Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy [MADIT-CRT] trial the cut-off was ≥ 130 ms). However, how strict should the adherence to this QRS cut-off be? As brilliantly noted by Kramer et al.¹⁶ there is a huge discrepancy between the entry and exit criteria in these trials. The 120 ms cut-off used in CARE-HF, COMPANION and REVERSE is significantly different from the mean QRS of the patients really enrolled in these trials, which was between 150 and 160 ms. Furthermore, all subgroup analysis on patients with narrower QRS have failed to demonstrate a clear benefit from CRT. Against this backdrop, all the international guidelines on the topic have given the strongest recommendation to CRT to patients with a QRS duration ≥ 120 ms, leaving very little space for further investigation in subgroups with narrower QRS intervals. Indeed, any institutional review board or investigator would consider it unethical to exclude in future studies a subgroup of patients who have already received a strong recommendation to receive a CRT device and who potentially can benefit from CRT.

A short mention should be made on the importance of QRS morphology. The electrocardiographic criteria of LBBB, which include a QRS duration ≥ 130 ms, QS or rS in lead V₁, broad R waves in leads I, aVL, V₅ or V₆ and absent q waves in leads V₅ and V₆¹⁷ should always be taken into consideration in the process of selection of a candidate for CRT. Indeed in the MADIT-CRT trial¹⁸ and in the National Cardiovascular Data

Registry's Implantable Cardioverter Defibrillator (ICD) registry,¹⁹ patients with a non-LBBB QRS pattern have no benefit from CRT as compared with patients showing a typical LBBB QRS pattern.

What Has to be Included in the Primary Endpoints of Cardiac Resynchronisation Therapy Trials? Are There Specific Admission Criteria to be Fulfilled to Define the Appropriateness of Hospitalisation?

No uniform criteria for hospitalisations in the major CRT trials were adopted, nor was there uniformity in the definition of the primary endpoints in the different trials. For example, in the COMPANION trial²⁰ "hospitalization events were defined as an admission to a hospital for any reason that was associated with a date change or the outpatient use of intravenous inotrope and/or vasoactive drugs for HF and for a duration >4 hours". In the CARE-HF trial,²¹ "All hospitalizations were adjudicated in a blinded fashion by the end-points committee... Hospitalization with worsening heart failure was defined by the occurrence of increasing symptoms and the need for treatment with intravenous diuretics or a substantial increase in oral diuretics (an increase of at least 40 mg of furosemide per day, 1 mg of bumetanide per day, or 10 mg of torsemide per day) or the initiation of a combination of a thiazide and a loop diuretic". In the MADIT-CRT trial,²² "the primary end point was death from any cause or nonfatal heart-failure events, whichever came first. The diagnosis of heart failure, which was made by physicians who were aware of study-group assignments, required signs and symptoms consistent with congestive heart failure that was responsive to intravenous decongestive therapy on an outpatient basis or an augmented decongestive regimen with oral or parenteral medications during an in-hospital stay". In the REVERSE trial,²³ "The primary end point of the study was the HF clinical composite response... Using this end point, we classified patients into into 1 of 3 response groups at 12 months after randomization: worsened, unchanged, or improved". It is difficult for the average clinician to make a reasonable resumptive statement on the results of these high-profile trials, and to understand which patients could benefit mostly from CRT without being affected by a fastidious headache. Lack of agreement in the definition of primary endpoints is not an exclusive of CRT trials. HF trials have been struggling continuously in the past years in looking for objective measures of clinical status, with the conclusion that endpoints critical for one HF study have demonstrated to poorly predict the outcome in another trial, or to be confined to the list of adverse events or exclusion criteria in other publications. For example, rehospitalisations for HF, which are mainly used in the prediction of the outcome in CRT trials, have been relegated to subgroup analysis in ventricular assist device trials. It is time that the HF community standardises the outcomes, which have to be assessed in the randomised clinical trials, considering the huge difference between a patient enrolled in an outpatient source and a patient enrolled during an active hospitalisation.

What is the Definition of 'Optimal wMedical Therapy'?

All the current indications on CRT advise implantation of biventricular devices in patients with HF with electrocardiogram (ECG) evidence

of interventricular dyssynchrony and treatment with optimal medical therapy. Just looking at the newest clinical trials on CRT that have induced the extension of the actual indications in patients with less symptomatic HF (REVERSE and Resynchronization-Defibrillation for Ambulatory Heart Failure Trial [RAFT]),²⁴ we encountered a lack in uniformity concerning the definition of optimal medical therapy and how it should be pursued. The REVERSE and RAFT studies suggested target doses of optimal therapy prior to enrolment per discretion of the physician, in accordance with the American College of Cardiology/European Society of Cardiology/Canadian Cardiovascular Society (ACC/ESC/CCS) guidelines definition of optimal pharmacological therapy including optimal dosing. Unfortunately, while the RAFT trial encouraged up-titration of medications throughout the study, the REVERSE protocol did not require subjects to be on the target dose prior to enrolment, and discouraged up-titration. The consequence is a difficulty in making a real comparison of the two studies and in judging the real benefit given by CRT. It is not surprising then that in the REVERSE trial there was not a true optimisation of drug therapy and doses of HF drug therapy prior to enrolment were significantly below what reasonably could be considered optimal. Indeed, only a reduced percentage of the patients enrolled were under beta-blocker or angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) (23.0 % on target beta-blocker dose and only 10.6 % on target ACEI/ARB at baseline). Furthermore, the patients in the CRT-ON arm consistently had a higher mean dose of ACEI/ARB and more subjects were on target doses of ACEI/ARB. There was also a differential dosing at baseline and up to 12 months with the CRT-ON having higher doses of ACEI/ARB. Even though in the RAFT trial up-titration was encouraged throughout the study, only 15.7 % were on target beta-blocker dose and 9.6 % were on target ACEI or ARB at baseline. Furthermore, although medication doses remained fairly stable during the study, in the CRT-defibrillator (D) arm there was a percentage of subjects on target dose superior to that on target dose in the implantable cardioverter defibrillator (ICD) arm. This difference was probably related to the up-titration of dosages during the study and could partially be responsible for the perceived benefit of CRT in this trial.

In conclusion, absence of uniformity in the definition of response to CRT, in the minimum QRS required for CRT, in the definition of endpoints and in what should be considered for optimal medical therapy impedes a clear understanding of the results of the major clinical trials and hinders progress in the field. Therefore, we endorse any attempt the scientific community would do in the future to standardise all these complicated matters. For example, future research should concentrate its efforts on the identification of the so-called super-responder patients who might optimise the cost-effectiveness relationship related to CRT. Perhaps a significant help in this context will be given by linking the aetiology and the extent of left ventricular fibrosis to response, as recently demonstrated in different studies using cardiac magnetic resonance as a guide to selection of CRT candidates, and to the deployment of left ventricular leads.²⁵⁻²⁷ ■

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