

Ventricular Resynchronization: an Emergent Therapy

Roberto Muñoz Aguilera, José A. Serrano Sánchez, David Pascual Hernández, and José A. García Robles

Programa de Insuficiencia Cardíaca, Servicio de Cardiología, Hospital General Universitario Gregorio Marañón, Madrid, Spain.

Cardiac resynchronization therapy (CRT) is a new invasive technique. The devices used are expensive, the implantation procedure is usually lengthy, sometimes complex, and the technique is not exempt from complications. Despite these limitations, however, CRT has experienced great progress over recent years, both clinically and experimentally.

To what, then, do we owe this interest and expectation?

- CRT is based on sound pathophysiological arguments.

- CRT has experienced rapid technological development.

- CRT is synergistic with other proven treatments which have demonstrated their efficacy in the control of both heart failure and sudden death.

- CRT is very suitable for an increasing group of highly symptomatic, chronic patients with functional limitations in whom other therapeutic measures have failed. The social and economic costs associated with these patients are enormous, and any treatment capable of improving the quality of life and controlling symptoms has great repercussions.

- Economic evaluations of CRT are favorable, even before the technique has become fully developed and incorporated (before definitively proving it reduces mortality).

- Clinical results to date are consistently encouraging.

- Remaining gaps in knowledge, technical limitations and controversial aspects all represent a scientific challenge. Research in this field involves the interesting collaboration of several subspecialties.

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Correspondence: Dr. R. Muñoz Aguilera.
Programa de Insuficiencia Cardíaca. Servicio de Cardiología. Hospital General Universitario Gregorio Marañón.
Dr. Esquerdo, 46. 28007 Madrid. España.
E-mail: romunoz@mundofree.com

Full English text available at: www.revespcardiol.org

The publication in this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA of 3 original studies of CRT¹⁻³ provides an opportunity to present the current status of the technique and review certain aspects involved in the identification of susceptible patients and in the failure of this technique for the implantation of a device.

CURRENT STATUS

Cardiac resynchronization therapy has not only aroused the interest of cardiologists, it has also become recognized by scientific societies, who have included the technique in their clinical practice guidelines. The technique has found a niche in the therapeutic scheme for patients with left ventricular systolic dysfunction or advanced chronic heart failure (CHF) who remain symptomatic despite optimal medical treatment (New York Heart Association [NYHA] functional class III and IV) and patients with intraventricular conduction defects.⁴

Results of studies suggest that in the long term CRT produces an inverse remodeling effect with improvement of multiple parameters relating to systolic and diastolic ventricular function,^{5,6} sinus rhythm, and chronic atrial fibrillation.⁷ This has consistently resulted in significant clinical improvement in the scores obtained with quality of life questionnaires, in the NYHA subjective functional class, or in objective measures, such as the 6-minute walk test or the measurement of oxygen uptake. The technique has also been associated with a reduction of almost 40% in the combined end points of death and hospitalization for CHF and of 50% in hospitalizations for CHF.⁸ The combination of CRT with anti-arrhythmic therapy from an implantable cardioverter-defibrillator (ICD) has proved to have additional benefits in terms of the quality of life, functional status and exercise response, with no apparent pro-arrhythmic effect and without affecting the correct functioning of the ICD in patients with resynchronization criteria and an indication for ICD.⁹ The COMPANION study, which compared the effects of treatment with CRT and CRT-ICD with medical treatment alone, has recently reported the results. Treatment with CRT-

ICD was associated with reduced mortality. The group treated with CRT alone also experienced a reduction in the primary end point of death and hospitalization for CHF. The specific effect of CRT on mortality is currently being studied in the CARE-HF trial. To date, the only relevant data are those from the meta-analysis undertaken by Bradley et al, who found a significant reduction of 51% in the relative risk of death due to progression of CHF and a trend towards a reduction in overall mortality in patients treated with CRT.¹⁰

LIMITATIONS. CONTROVERSIAL ASPECTS

Asynchrony. Electrocardiographic and Echocardiographic Predictors of Response

Up to 30% of patients included in studies have consistently failed to show the expected response of symptomatic and functional improvement after implantation of the device. The causes for this have not yet been identified, since most research has been focused on the identification of those patients who respond to the therapy.

The information thus far collected has transformed the traditional concept of asynchrony. From its initial “purely electrical” concept it has moved on to a “mechanical and structural” concept, in which the measurements of electrical dispersion, such as the electrocardiographic pattern and the width of the QRS complex, are insufficient instruments.^{6,11} The relationship between these electrical patterns and ventricular activation and contraction is complex. Many patterns of contractile asynchrony with a prolonged QRS interval exist, and stimulation at different sites and with varying atrio-ventricular delays has been shown to produce different effects in “contractile cooperation¹²”. Neither the width of the baseline QRS complex nor narrowing of the biventricular stimulation consistently predict clinical, echocardiographic or hemodynamic improvement. The mere narrowing of the QRS complex is not an acceptable outcome of CRT. The technique implicitly involves not only a change in the way of identifying and defining asynchrony, but possibly also modifications in accordance with the mechanism of stimulation. The different activation patterns of asynchrony might be subsidiaries of different stimulation techniques.

Asynchrony in systolic and diastolic function is common in patients with systolic dysfunction and a narrow QRS interval, although the prevalence is lower than in patients with a wide QRS interval.¹³ The degree of intraventricular contractile asynchrony, as assessed by tissue Doppler, is a better predictor of the effectiveness of CRT than the baseline width of the QRS complex.¹⁴ Traditional electrocardiographic criteria used in trials and incorporated into clinical practice

guidelines exclude patients with systolic dysfunction and a narrow QRS interval. The benefit of CRT in this subgroup of patients with CHF has recently been shown after measuring contractile asynchrony using echocardiographic criteria.¹⁵

The need now exists for quantifying mechanical asynchrony with imaging techniques in order to improve the identification process of patients who might respond well to CRT. Large scale studies, such as CARE-HF, PROSPECT, or RAVE, currently under way might confirm these findings and define new criteria for patient selection and optimization of CRT.

CLINICAL ASPECTS OF THE IDENTIFICATION OF RESPONDING PATIENTS

Identification of the clinical predictors of response is difficult. This may explain the marked paucity of articles relating to clinical variables predicting response to CRT, in contrast with the profusion of echocardiographic studies. Two of the reports published in this issue address this problem.^{1,2}

The original study by Hernández Madrid et al¹ was undertaken to determine the evolution of brain natriuretic peptide (BNP) and its correlation with the clinical course in a sample of 28 patients with the usual criteria for CRT who underwent biventricular stimulation. The different methods generally used to evaluate the response are mainly subjective. A simple, objective tool to identify the potential responder, provide an early assessment of response, and control the follow-up would facilitate the decision-taking process. Sinha et al¹⁶ highlighted the ability of BNP to identify patients with reverse remodeling or absence of response after long-term CRT. They also showed the sensitivity of BNP to demonstrate sharp hemodynamic changes secondary to the initiation or termination of stimulation and its relation with the long-term response of the patient. A rise in BNP levels anticipated the onset of symptoms of CHF. However, the authors did not measure baseline levels of BNP and it was not possible to establish a predictive value of their concentrations. Hernández Madrid et al saw the concordance between BNP levels and patient course in response to CRT and describe the temporal evolution of BNP levels with a plateau 6 months after implantation. The BNP proved to be an independent predictor of response and, with the limitation inherent to the sample size involved, the authors suggest a cut-off value to predict the response to CRT. In order to establish the predictive values of BNP levels adequately, it would be convenient to design studies of sufficient size and with a control group. In agreement with previous reports, and based on the relation between BNP and different clinical variables, no relation was found between CRT response and left ventricular ejection fraction or the QRS width.

Díaz-Infante et al² present a study in which they

analyzed 63 patients who underwent biventricular stimulation. The patients were followed for 6 months to assess their response to CRT according to a composite clinical variable, which included absence of cardiac death or transplant and improvement on the 6-minute walk test. The authors conclude that lack of clinical improvement was associated with ischemic heart disease, clinical evidence of sustained monomorphic ventricular tachycardia prior to implantation and at least moderate mitral insufficiency (\geq II/IV). The interpretation of these results and their application to the general population of patients with CHF should be undertaken with caution, as the results were obtained in a reduced sample which was not representative of this group of patients. Up to 23% of the patients studied had no approved indication for CRT and the series included 20.6% of patients with an indication for the definitive implantation of a pacemaker. Although the prophylactic indication for CRT may be clinically reasonable in patients with CHF, marked ventricular dysfunction, and a conventional indication for a definitive pacemaker,^{17,18} the inclusion of these patients in the study represents a bias to be taken into account. Furthermore, the presence of a high number of patients with ventricular arrhythmia, 77% with a history of sustained monomorphic ventricular tachycardia, ventricular fibrillation and syncope with inducible ventricular tachycardia-ventricular fibrillation, may represent another selection bias. The conclusions are based on a different variable to the composite variable mentioned as the main outcome measure of the study, as patients who died or who received a transplant were included. When these are excluded from the analysis, mitral insufficiency is no longer a predictive factor for lack of response. This agrees with the pathophysiological basis of resynchronizing therapy and evidence from multiple mechanistic and clinical studies. Current evidence is that a reduction in the degree of mitral insufficiency constitutes an important factor for improvement with CRT.¹⁹

FAILURE IN THE IMPLANTATION OF THE DEVICE

The limitations of CRT include a documented failure rate of implantation of the biventricular device ranging from 8%-12.5%.^{2,8,20} The most usual reasons for this failure, once the initial learning curve has been overcome and bearing in mind the important technological advances now available, are an unfavorable venous anatomy in the patient's heart, dissection of the coronary sinus during the procedure, early displacement of the electrode, and the presence of high stimulation thresholds. Research therefore needs to be undertaken on alternative methods of implantation of the left ventricular electrode to guarantee a CRT with a low rate of mortality and morbidity in cases of failure

of the percutaneous technique. Indeed, it is due to its high rate of mortality and morbidity that the thoracotomy approach has been discarded. In this issue of the *REVISTA ESPAÑOLA DE CARDIOLOGÍA*, Fernández et al³ describe their initial experience with the implantation of epicardial electrodes in the left ventricle using minimally invasive video-assisted thorascopic surgery in 14 patients with the usual criteria for resynchronization. Their results are encouraging. Implantation was achieved in all the patients with no associated hospital mortality or morbidity and with maintenance of acceptable stimulation parameters. One theoretical advantage of this technique is the easy accessibility of the lateral and posterolateral segments of the left ventricle. Implantation in this area using the normal percutaneous technique can be undertaken in a relatively low percentage of patients for reasons such as the presence of high stimulation thresholds, phrenic nerve stimulation, unfavorable coronary anatomy or electrode instability. Several studies suggest that resynchronization is more effective with stimulation of these segments.^{21,22} As has been described previously,^{11,12} the authors report a similar improvement in the function and the left ventricular ejection fraction to that expected with biventricular stimulation. Whether there were any non-responders is not reported. The assumed contraindications for the procedure, mainly cardiac surgery and ischemic heart disease with previous transmural infarction, could limit the application of this technique in a large part of the target population. Indeed, the low number of patients with heart disease who were treated in this series is notable.

CONCLUSIONS

Cardiac resynchronization therapy in combination with the optimal medical treatment has shown its ability to improve symptoms and the perceived quality of life in a select population of patients with advanced CHF. This is an extremely important advance for this type of patient. Although the data are encouraging, they do not yet show conclusively that CRT is an effective tool for slowing disease progression and reducing mortality. The most pressing problem concerns the need to determine the criteria to improve the selection of patients who are candidates for CRT.

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