HOSPITAL CHRONICLES 2008, SUPPLEMENT: 185–188

Classical and Non-Classical Indications for Cardiac Resynchronization Therapy

George Andrikopoulos, MD, Stylianos Tzeis, MD, Ector Anninos, MD, Antonis S. Manolis, MD

First Department of Cardiology, Evagelismos General Hospital of Athens, Athens, Greece

ABBREVIATIONS:
ACC = American College of Cardiology
AHA = American Heart Association
CRT = cardiac resynchronization therapy
ECG = electrocardiogram
EHRA = European Heart Rhythm Association
ESC = European Society of Cardiology
HF= heart failure
ICD = implantable cardioverter defibrillator
LV= left ventricle
LVEF= left ventricular ejection fraction
NYHA = New York Heart Association

KEY WORDS: *cardiac resynchronization therapy; biventricular pacing; heart failure*

Address for correspondence:
George K. Andrikopoulos, MD
Evagelismos Hospital
First Department of Cardiology
45-47 Ypsilantou Street
Athens, Greece
E-mail: andrikop@hotmail.com

Heart failure (HF) is a medical problem of huge socioeconomic importance, mainly due to the increasing life expectancy in our societies and the strides in the treatment of ischemic heart disease which resulted in improved prognosis of our patients. These medical and socioeconomic issues may explain why HF poses a significant financial burden on our health care systems. It is estimated that acute decompensated HF accounts for 2.9% of all emergency room visits, its prevalence is steadily increasing in epidemic proportions and in age-dependent manner, reaching an incidence of almost 10% in patients aged >65 years.[1]

There has been considerable improvement in our therapeutic armamentarium over the years with significant benefit obtained with use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers and β-blockers. However, there is still a large population of HF patients who remain refractory to current therapeutic approaches and this therapeutic gap has recently been bridged by the newer mode of electrical therapy known as cardiac resynchronization therapy (CRT), effected by biventricular pacing.[2,3] CRT has been shown to improve symptoms and prognosis of patients with HF. The pathophysiological rationale for the development of CRT was the observation that some patients with advanced HF presented asynchronous contraction of the left ventricle (LV) on echocardiography. Asynchronous contraction due to cardiac conduction abnormalities, often described as cardiac dyssynchrony, reflected by the presence of left bundle branch block (LBBB) on the electrocardiogram (ECG), occurring in 20-30% of patients afflicted by HF, has been documented to adversely affect the function of the failing heart.[4] Furthermore, it has been shown that cardiac dyssynchrony has an unfavorable influence on prognosis in patients with HF.[5,6]

CRT aims to improve the mechanical function of the failing heart. Biventricular pacing is an effective way to achieve CRT and restore electromechanical synchrony by simultaneously pacing at different sites of the heart, classically at the right ventricular apex and the lateral wall of the LV. This is accomplished by inserting the LV pacing lead via the coronary sinus and placing it into a lateral cardiac vein tributary. In a large number of studies, it is a consistent finding that biventricular pacing increases LV ejection fraction (LVEF) and cardiac output and most importantly, improves quality of life, functional class and exercise capacity in the majority of the treated patients.[7-10] In terms of pathophysiology, CRT has a unique characteristic among other therapies for HF. Its favorable influence on cardiac performance has not been associated with increased oxygen consumption, an issue of profound importance especially in patients with ischemic cardiomyopathy.[11] These striking beneficial effects of CRT, had not been accompanied by any detectable survival benefit in the large number of small randomized trials that were published during the initial period of biventricular pacing.[7-10] Of course, these studies were not designed to detect a survival benefit and thus,

they were underpowered to study the effects of biventricular pacing on overall mortality. However, the lack of statistical significance should not be considered synonymous to the lack of clinical significance. In the case of CRT, this fact was firstly supported by a meta-analysis of four large randomized trials, which showed that CRT therapy significantly reduced all-cause mortality (relative risk=0.77).[12] Thereafter, the results of the two randomized studies having as primary end-point total mortality, the COMPANION[13] and the CARE-HF[14] trials, verified the aforementioned findings and provided the necessary evidence for the recommendations and guidelines on CRT use for patients with symptomatic HF, which were published three years ago by the American Heart Association (AHA)/American College of Cardiology (ACC)[15] and by the European Society of Cardiology (ESC).[16]

The accumulating evidence from the recently published studies resulted in the revised recommendations by the ESC and the European Heart Rhythm Association.[17] According to these recommendations, CRT is considered class I (level of evidence A) therapy for the HF patients who remain symptomatic in NYHA classes III–IV despite optimal treatment, with LVEF ≤35%, LV dilatation, normal sinus rhythm and wide QRS complex (≥120 ms). Although this general classical indication includes the majority of patients studied in everyday clinical practice, the authors of these guidelines tried to provide practical answers to a number of problematic unresolved clinical issues that raised questions regarding appropriate use of CRT.[17] Indeed, the authors of the 2007 ESC/EHRS guidelines devoted a great effort to analyze these unresolved issues which are expected to be enlightened by some large ongoing randomized trials (Table 1).

Thus, trying to provide a reasonable clinical approach to these unsolved issues despite the lack of solid evidence, they suggested that CRT can be a reasonable therapeutic option in HF patients with NYHA classes III–IV symptoms, low LVEF ≥35%, LV dilatation and a concomitant indication for permanent pacing (first implant or upgrading of conventional pacemaker) (Class IIa: level of evidence C). In addition CRT is considered appropriate for HF patients with a Class I indication for an ICD (first implant or upgrading at device change) who are symptomatic in NYHA classes III–IV despite optimal treatment, with low LVEF ≤35%, LV dilatation and wide QRS complex (≥120 ms)(Class I: level of evidence). Finally, heart failure patients with permanent atrial fibrillation who remain symptomatic in NYHA classes III–IV despite optimal treatment, with low LVEF ≤35%, LV dilatation and indication for AV junction ablation are considered candidates for CRT according to the latest guidelines (Class IIa: level of evidence C). A synopsis of the 2008 ESC/EHRA guidelines on CRT in comparison to the previous (published at 2005) ACC and ESC guidelines is presented at Table 2.

TABLE 1. Unresolved issues in CRT indications

1. Lack of electromechanical dyssynchrony
2. Narrow QRS on surface ECG
3. Atrial fibrillation
4. Right bundle branch block
5. Indication for permanent pacing in patients with mild heart failure or asymptomatic left ventricular systolic dysfunction
6. Patients with a previously implanted conventional pacing device and severe left ventricular dysfunction
7. Co-existing right heart failure
8. Heart failure and pacing in the pediatric population
9. Planned cardiac surgery and classical CRT indication.

COMMENTS ON UNSOLVED ISSUES AND POTENTIAL NEW INDICATIONS

CRT is a rapidly evolving therapeutic strategy which is expected to be influenced by the accumulation of evidence derived by ongoing studies, by the accumulation of increasing operator and centers' experience and by the development of new tools and modalities that can be used to achieve biventricular pacing. In this context, the current situation regarding indications and patients' selection criteria is expected to change. Many of the unsolved issues, which are presented in Table 1 are now considered as "non-classical indications". Some of them will possibly be included in future widely accepted indications, while others will be rejected in the light of new evidence. Although preliminary data may support the so called "non-classical indications" any comments on their applicability in everyday clinical practice will inevitably be, at least partly, subjective.

Although currently existing evidence from large scale studies is based on selection criteria solely related to the duration of QRS complex, it is well-known that electrical dyssynchrony does not always accompany mechanical dyssynchrony.[18] Taking into consideration that CRT through biventricular pacing aims to restore mechanical dyssynchrony, we believe that it should be directed only to these patients who present both electrical and mechanical dyssynchrony, simply because there are no data or even convincing assumptions that have associated the beneficial effects afforded by biventricular pacing with any other characteristic of patients with advanced HF apart from the mechanical dyssynchrony. Although preliminary results from the PROSPECT study[19] showed that no echocardiographic measure of mechanical dyssynchrony was found to be useful for identifying patients more likely to respond to CRT, we should not apply CRT in

TABLE 2. CRT guidelines in chronic heart failure patients according to the recently published ESC/EHRA recommendations in comparison to the guidelines published in 2005 by the ACC/AHA and by the ESC.

	Patients' characteristics	Clinical end-point	Class and level of evidence	Ref.
ACC/AHA Guideline Update for Chronic Heart Failure (2005 update)	NYHA class III-IV LVEF ≤35% Sinus rhythm Symptoms despite optimal medical therapy Cardiac dyssynchrony (currently defined as QRS >0.12 ms)	Symptoms, Hospitalizations, Mortality	I (A)	15
ESC guidelines for Chronic Heart Failure (2005 update)	NYHA class III-IV Reduced LVEF Symptoms despite optimal medical therapy	Symptoms, Hospitalizations	I (A)	16
	Cardiac dyssynchrony (QRS>0.12 ms)	Mortality	I (B)	16
ESC/EHRA guidelines for pacing and CRT (2007)	NYHA class III-IV LVEF ≤35% Symptoms despite optimal medical therapy Wide QRS complex (QRS>0.12 ms)	Morbidity and Mortality	I (A)	17

patients who lack electromechanical dyssynchrony given the lack of a relevant pathophysiological mechanism that could support the notion that improvement of LV function can be achieved by biventricular pacing independently of preexisting mechanical dyssynchrony.

On the other hand, another "non-classical" indication for CRT would be the application of biventricular therapy in patients with advanced refractory HF in the absence of prolonged QRS duration (<120 ms) but in the presence of echocardiographically documented inter- or/and intraventricular dyssynchrony. Again our enthusiasm should be tempered by the lack of convincing evidence. Notably, recently, Beshai et al evaluated this issue in a prospective, double-blind, randomized, controlled clinical trial (RethinQ study).[21] A total of 172 HF patients with a SCD-HeFT indication for ICD, NYHA class III functional class, QRS duration <130 ms and evidence of mechanical dyssynchrony as measured by echocardiography, were randomized to either CRT or no CRT. The presence of mechanical dyssynchrony was identified by using echocardiographic imaging methods. In 96% of cases the tissue Doppler-defined presence of an opposing wall delay ≥65 ms was used as a qualifying criterion, while the rest 4% of patients exhibited a significant mechanical delay in the septal-to-posterior wall, obtained by M-mode in the parasternal long-axis view. After 6 months, among 156 patients assessed (76 in the CRT and 80 in the control group), CRT was not shown to confer any benefit in patients with QRS duration < 120 ms, as evidenced by lack of improvement in peak oxygen consumption. However, we should keep in mind that the results of the RethinQ study are not conclusive and mostly, underline the need for further large-scale prospective, adequately powered, double-blind trials that could delineate the potential beneficial effect of CRT on the subpopulation of HF patients with narrow QRS as well as the optimal echocardiographic imaging method which enables the most accurate definition of cardiac dyssynchrony and the selection of responders. Amongst others, we have suggested[20] that until results from these studies are available, we should follow the recently published guidelines of the ESC/EHRA routinely precluding patients with narrow QRS from CRT, even in the case of echocardiographically determined cardiac dyssynchrony.

For the first time, the authors of the 2007 ESC/EHRA guidelines addressed the dilemma of providing CRT versus conventional pacing in patients with indication for permanent pacing, with mild heart failure or asymptomatic LV systolic dysfunction and the dilemma of CRT in patients with a previously implanted conventional pacing device and severe LV dysfunction. In both cases accumulating data[22] suggest that the detrimental role of pacing-induced dyssynchrony may justify the use of biventricular pacing in these patients. Regrettably, the authors of the recent guidelines included advanced NYHA class (III-IV) as a perquisite for this indication. However, it would be logical to hypothesize that a large proportion of NYHA II patients who will be implanted a conventional pacemaker or ICD, will deteriorate due to pacing-induced dyssynchrony and will need to upgrade to biventricular systems with profound consequences on efficacy, safety and cost-effectiveness of the management of the patient.

In conclusion, the classical indications for CRT have evolved considerably, while the non-classical should not be

routinely included in everyday clinical practice, despite the fact that they may represent reasonable therapeutic options in selected cases.

REFERENCES

1. Hugli O, Braun JE, Kim S, Pelletier AJ, Camargo CA. United States emergency department visits for acute decompensated heart failure, 1992 to 2001. *Am J Cardiol* 2005; 96:1537-1542.
2. Manolis AS. Cardiac resynchronization therapy in congestive heart failure: ready for prime time? *Heart Rhythm* 2004; 1:355-363.
3. Gould PA, Mariani JA, Kaye DM. Biventricular pacing in heart failure: a review. *Expert Rev Cardiovasc Ther* 2006; 4:97-109.
4. McAnulty HJ, Rahimtoola HS, Murphy E, et al. Natural history of "high-risk" bundle-branch block. *N Engl J Med* 1982;307:137-43.
5. Baldasseroni S, Opasich C, Gorini M, et al. Left bundle-branch block is associated with increased1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: A report from the Italian Network on Congestive Heart Failure. *Am Heart J* 2002;143:398-405.
6. Yu C-M, Chau E, Sanderson JE, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved chronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;105:438-45.
7. Auricchio A, Ding J, Spinelli JC, et al. Cardiac resynchronization therapy restores optimal atrioventricular mechanical timing in heart failure patients with ventricular conduction delay. *J Am Coll Cardiol* 2002;39(7):1163-9.
8. Cazeau S, Leclercq C, Lavergne T, et al. The Multisite Stimulation In Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344:873-80.
9. Abraham WT, Fisher WG, Smith AL, et al. For the MIRACLE Study Group. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346(24):1845-53.
10. Linde C, Leclerq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from Multisite Stimulation In Cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol* 2002;40(1):111-8.
11. Kass DA, Chen CH, Curry C, et al. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation* 1999;99:1567-1573.
12. Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 2003; 289(6);730-40.
13. Bristow MR, Saxon LA, Boehmer J, et al., for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-2150.
14. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-49.
15. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). ACC Web Site. Available at: http://www.acc.org/clinical/guidelines /failure//index.pdf.
16. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the ESC. *Eur Heart J* 2005;26:1115-1140.
17. Vardas PE, Auricchio A, Blanc JJ, et al. Guidelines for cardiac pacing and cardiac resynchronization therapy: the task force for cardiac pacing and cardiac resynchronization therapy of the ESC. Developed in collaboration with the European Heart Rhythm Association. *Eur Heart J* 2007;28(18):2256-95.
18. Hawkins NM, Petrie MC, MacDonald MR, et al. Selecting patients for cardiac resynchronisation therapy: electrical or mechanical dyssynchrony? *Eur Heart J* 2006;27:1270–1281.
19. Cleland JG, Abdellah AT, Khaleva O, et al. Clinical trials update from the European Society of Cardiology Congress 2007: 3CPO, ALOFT, PROSPECT and statins for heart failure. *Eur J Heart Fail* 2007 Oct;9(10):1070-3. Epub 2007 Sep 24.
20. Andrikopoulos GK, Tzeis S, Manolis AS. Cardiac resynchronisation therapy in heart failure patients with narrow QRS complex: quo vadis? *Hellenic J Cardiol* 2007;48(6):315-8.
21. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-Resynchronization Therapy in Heart Failure with Narrow QRS Complexes. *N Eng J Med* 2007 Nov 6;Epub ahead of print.
22. Leclercq C, Cazeau S, Lellouche D, et al. Upgrading from single chamber right ventricular to biventricular pacing in permanently paced patients with worsening heart failure: the RD-CHF study. *Pacing Clin Electrophysiol* 2007;30(Suppl. 1): S23–S30.