Europace (2006) **8**, 499–501
doi:10.1093/europace/eul047

Cardiac resynchronization pacing without defibrillator capability: is this a viable option?

Cengiz Ermis[1] and David G. Benditt[2]*

[1] *The Akdeniz University Medical School, Antalya, Turkey and* [2] *The Cardiac Arrhythmia Center, Department of Medicine, University of Minnesota Medical School, MMC 508 FUMC, 420 Delaware Street SE, Minneapolis, MN 55455, USA*

Received 17 August 2005; accepted after revision 19 March 2006

KEYWORDS
Implantable defibrillators;
Cardiac resynchronization;
Heart failure;
Quality-of-life

Improved cardiac resynchronization by pacemakers (CRT-P) and implantable defibrillators (CRT-D) benefits cardiac function, reduces heart failure (HF) admissions, and diminishes mortality in patients with severe left ventricular (LV) dysfunction. In terms of mortality benefit, current evidence suggests that CRT-D may be better than CRT-P alone when a broad range of HF patients is considered. However, the differential benefit may be small in certain patients. In individuals with severe and worsening HF due to systolic LV dysfunction, HF complications other than ventricular tachyarrhythmias contribute importantly to both quality-of-life (QoL) and duration of survival; these patients may be served cost-effectively by CRT-P enhancing QoL. A clinical trial evaluating CRT-D vs. CRT-P in terms of QoL and survival in such patients would assist physicians and payers to understand better the relative roles of CRT-P and CRT-D in the care of the sickest HF patients.

Biventricular pacemakers and pacemaker–defibrillator systems have been shown to improve cardiac function, diminish frequency of heart failure (HF) hospitalizations, enhance quality-of-life (QoL), and reduce mortality rates in patients with severe left ventricular (LV) dysfunction and intraventricular conduction disease who are already being administered maximally tolerated appropriate pharmacological treatment. The basis for these beneficial effects is multifactorial.[1–15] For biventricular pacemakers, the benefit is presumed to be primarily due to improved (albeit incomplete) synchronization of ventricular contraction in the diseased heart—thus the term 'cardiac resynchronization therapy' (CRT). In the case of biventricular implantable cardioverter-defibrillators (CRT-D devices) an additional anti-arrhythmic benefit is presumed, but its magnitude in this setting remains unclear.

Given the possibility of an increased mortality benefit associated with the presence of defibrillator capability in CRT-D vs. CRT pacemakers alone (CRT-P), physicians feel increasingly compelled to use CRT-D devices in LV dysfunction patients, despite the substantially greater cost. However, if convinced that CRT-P alone provided predictable anti-arrhythmic benefit (even if only in an identifiable subset of LV dysfunction patients) as suggested by both the COMPANION[12] and CARE-HF[16] studies, physician decision-making would be simplified, and treatment costs could be substantially reduced.

Anti-arrhythmic potential of CRT

The basis for the clinical benefit of CRT devices in HF patients is not yet fully understood. Nevertheless, in general terms, CRT improves a range of measures of cardiac function in the setting of moderate-to-severe HF and a prolonged QRS duration. Thus, CRT is accompanied by an increase (albeit usually modest) of LV ejection fraction, a decrease in LV end-diastolic dimension, and diminution in the magnitude of mitral regurgitation in many patients.[1,6,7] Furthermore, to the extent that the more physiological pacing offered by CRT systems may reduce ventricular volumes and improve cardiac output, it is reasonable to believe that both wall stretch[1,17] and levels of circulating catecholamines will be diminished;[18] as a partial consequence, tachyarrhythmia risk may be reduced. In this regard, in COMPANION[12] both CRT-P and CRT-D were comparable in terms of mortality benefit at least to the extent of study follow-up period [442 days for optimal pharmacological therapy (OPT), 495 days for CRT and 479 for CRT-D groups].

COMPANION was a prospective trial in which NYHA class 3 or 4 patients were randomized to OPT, OPT plus CRT-P, or OPT plus CRT-D groups. Compared with OPT alone, CRT-P and CRT-D (both in combination with OPT), reduced the

* Corresponding author. Tel: +1 612 625 4401; fax: +1 612 624 4937.
E-mail address: bendi001@umn.edu

© The European Society of Cardiology 2006. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org

Downloaded from https://academic.oup.com/europace/article/8/7/499/480622 by Akdeniz Universitesi user on 20 September 2021

risk of all-cause mortality or first HF hospitalizations by 34 and 40%, respectively ($P = 0.002$ and $P < 0.001$, respectively). In terms of mortality outcome, specifically compared with OPT alone, CRT-P reduced all-cause deaths by 24% ($P = 0.059$), whereas CRT-D in combination with OPT reduced the risk of all-cause mortality by 36% alone ($P = 0.003$). In brief, CRT-D may have been more effective in COMPANION, but the CRT-P effect was impressive nonetheless, and thereby becomes a potentially very cost-effective choice.

Additional evidence supporting an important CRT-P mortality benefit is provided in the relatively recently published CARE-HF study. CARE-HF was a randomized and controlled trial encompassing 813 HF patients (404 CRT-P vs. 409 medically treated), and was the first study to demonstrate a survival benefit attributable to cardiac resynchronization alone.[16] Although, in terms of the issues being considered in this communication, CARE-HF did not compare CRT-P with CRT-D directly, it nonetheless provided strong evidence in support of the potential for CRT-P alone to reduce mortality of HF patients significantly. In this regard, CARE-HF reported a 36% reduction of all cause mortality in patients receiving CRT-P compared with those treated by medical therapy alone. On the other hand, CRT-P impact on potentially life-threatening arrhythmias remains an unsettled question. For example, in CARE-HF, while overall mortality benefit was clear, the number of sudden deaths among all deaths (35%) was concerning. In this context, the potential pro-arrhythmic effects of LV epicardial stimulation have raised the disconcerting thought that CRT-P mortality benefits may be counter-balanced by adverse effect outcomes in large patient populations.[19]

Our own observations, although confined to a small non-randomized population, also suggest that CRT-P may provide an important anti-arrhythmic benefit in some patients, particularly those with the most severe HF.[20] In this regard, we examined ventricular arrhythmia burden and ICD treatment frequency in patients in whom worsening HF dictated the need for replacing a pre-existing conventional ICD system with a CRT-D. The availability in each of these individuals of a full-featured ICD, both before and after introduction of CRT, along with the absence of substantial alterations in drug therapy, permitted detailed assessment of the impact of CRT on arrhythmia susceptibility in these individuals. The study population comprised a consecutive series of 18 patients who underwent successful upgrade from conventional ICD therapy to a CRT-D-based solely on conventionally accepted HF indications. Patients in this study had been followed for 47 ± 21 months prior to CRT upgrade, and for an additional 14 ± 2 months after upgrade. Presenting arrhythmias were ventricular tachycardia in 55%, ventricular fibrillation in 28%, and non-sustained VT in 17%. The frequency of appropriate anti-tachycardia pacing (ATP) applications and ICD shocks was significantly reduced after CRT-D upgrade. During conventional ICD treatment, ATP was applied in 10/18 (56%) patients compared with 1/18 (3%) following CRT-D placement. Similarly, the number of patients receiving ICD shocks diminished following CRT. In essence, our experience suggests that in the setting of diminished LV systolic function and worsening HF, CRT-P does diminish tachyarrhythmia susceptibility as assessed by diminished need for either ICD shocks or ATP.

In conclusion, current evidence suggests that CRT-D therapy may offer a greater magnitude mortality benefit than does CRT-P alone when viewed over a wide range of HF patients, and therefore CRT-D remains the appropriate choice in most cases. On the other hand, as suggested by the findings in COMPANION, the additional CRT-D mortality benefit compared with CRT-P may be relatively small, and may not apply equally to all types of patients. In particular, individuals with severe LV dysfunction and apparently worsening HF may be more prone to die from disease complications other than ventricular tachyarrhythmias (particularly electro-mechanical dissociation and bradyarrhythmias) that are not readily reversed by defibrillation. These latter patients may be more cost-effectively served by CRT-P primarily for QoL reasons, and perhaps only secondarily for any mortality benefit that CRT-P may provide. This approach would be especially reasonable in those individuals with existing conventional pacemakers already in place. Placement of a single additional lead may provide months, even if not years, of more comfortable life.

A prospective clinical trial or at least a follow-up registry in patients with seemingly progressive systolic HF, evaluating QoL indices, and survival outcomes would prove helpful in terms of assessing whether a CRT-P treatment strategy is indeed effective. Such a study would assist physicians to understand better the relative roles of CRT-P and CRT-D in patient care, and would facilitate decision-making by payers (government and private) who inevitably must prioritize the manner in which limited health care resources are to be expended.

References

1. Park RC, Little WC, O'Rourke RA. Effect of alteration of the left ventricular activation sequence on the left ventricular end-systolic pressure-volume relation in closed-chest dogs. *Circ Res* 1985;**57**:706–17.
2. Blanc JJ, Etienne Y, Gilard M *et al*. Evaluation of different ventricular pacing sites in patients with severe heart failure. Results of an acute hemodynamic study. *Circulation* 1997;**96**:3273–7.
3. Leclercq C, Cazeau S, le Breton H *et al*. Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure. *J Am Coll Cardiol* 1998;**32**:1825–31.
4. Etienne Y, Mansourati J, Gilard M *et al*. Evaluation of left ventricular based pacing in patients with congestive heart failure and atrial fibrillation. *Am J Cardiol* 1999;**83**:1138–40.
5. Cazeau S, Leclercq C, Lavergne T *et al*. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;**344**:873–80.
6. Nelson GS, Berger RD, Fetics BJ *et al*. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left-bundle branch block. *Circulation* 2000;**102**:3053–9.
7. Mansourati J, Etienne Y, Gilard M *et al*. Left ventricular-based pacing in patients with chronic heart failure: comparison of acute hemodynamic benefits according to underlying heart disease. *Eur J Heart Fail* 2000;**2**:195–9.
8. Auricchio A, Stellbrink C, Sack S *et al*. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002;**39**:2026–33.
9. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E *et al.*; MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–53.
10. Higgins SL, Hummel JD, Niazi IK *et al*. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003;**42**:1454–9.

Downloaded from https://academic.oup.com/europace/article/8/7/499/480622 by Akdeniz Universitesi user on 20 September 2021

11. Young JB, Abraham WT, Smith AL *et al.*; Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA* 2003;**289**:2685–94.
12. 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**:2140–50.
13. Cazeau S, Ritter P, Lazarus A *et al*. Multisite pacing for end-stage heart failure: early experience. *Pacing Clin Electrophysiol* 1996;**19**:1748–57.
14. Blanc JJ, Benditt DG, Gilard M, Eteinne Y, Mansourati J, Lurie KG. A method for permanent transvenous left ventricular pacing. *Pacing Clin Electrophysiol* 1998;**21**:2021–4.
15. 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**:1567–73.
16. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L *et al.*; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**14**;352:1539–49.
17. Saxon LA, De Marco T, Schafer J, Chatterjee K, Kumar UN, Foster E; VIGOR Congestive Heart Failure Investigators. Effects of long-term biventricular stimulation resynchronization on echocardiographic measures of remodeling. *Circulation* 2002;**105**:1304–10.
18. Adamson PB, Kleckner KJ, VanHout WL, Srinivasan S, Abraham WT. Cardiac resynchronization therapy improves heart rate variability in patients with symptomatic heart failure. *Circulation* 2003;**108**:266–9.
19. Evonich RF, Maheshwari A, Gardiner JC, Khasnis A, Kantipudi S, Ip JH *et al*. Implantable cardioverter defibrillator therapy in patients with ischemic or non-ischemic cardiomyopathy and non-sustained ventricular tachycardia. *J Interv Cardiac Electrophysiol* 2004;**11**:59–65.
20. Ermis C, Seutter R, Zhu AX *et al*. Impact of upgrade to cardiac resynchronization therapy on ventricular arrhythmia frequency in patients with implantable cardioverter defibrillators. *J Am Coll Cardiol* 2005; **46**:2258–63.

Downloaded from https://academic.oup.com/europace/article/8/7/499/480622 by Akdeniz Universitesi user on 20 September 2021