

When Is It Too Late for Cardiac Resynchronization Therapy?

BENGT HERWEG, M.D. and S. SERGE BAROLD, M.D.

Arrhythmia Service and Division of Cardiology, Tampa General Hospital and University of South Florida, Tampa, Florida

Lehmann et al.¹ pointed out that taken together, the large cardiac resynchronization therapy (CRT) trials included 10,803 patients, the majority of who were in congestive heart failure (CHF) New York Heart Association (NYHA) class III, but only 451 patients (4.2%) were class IV. The role of CRT in NYHA class IV patients remained uncertain until recently when Lindenfeld et al.² reported the results of CRT in 217 such ambulatory patients (on no intravenous inotrope therapy) after a median follow-up of 14 months. Death or hospitalization for any cause was significantly improved in both CRT and CRT-defibrillator patients. The time to all-cause death and heart failure (HF) hospitalization was also significantly improved in the same groups.² However, the large CRT trials have generally excluded patients with refractory class IV CHF on intravenous inotropic therapy.³⁻⁵ Although cardiac resynchronization has revolutionized the treatment of CHF, its use in end-stage patients whose prognosis is poor and who are dependent on intravenous drugs has remained controversial and poorly defined. Furthermore, scientific guidelines have not addressed the role of CRT in this group of patients.⁶⁻⁷ The question arises as to whether the recent documentation of CRT benefit for NYHA class IV ambulatory patients can be extended to the much sicker group of class IV patients on inotropic support.

Negative Results

There is a prevailing belief that CRT is of little benefit in inotrope-dependent class IV CHF patients. In this regard, Auricchio and Abraham stated in 2004 that "isolated anecdotal experience suggests that CRT may be contraindicated in patients in whom weaning from parenteral inotropic therapy has not been possible."⁸ Table I shows the published results of CRT in NYHA class IV CHF patients on intravenous inotropic therapy at the time of implantation. Considering the high mortality in some of the reports shown in Table I, some

workers believe that CRT is of little or no benefit in this group of patients.

Makati et al.⁹ reported their disappointing experience with CRT in 15 patients with class IV CHF on continuous inotrope infusion and optimal medical therapy. Mortality and hospitalizations were compared retrospectively to outcomes in a similar group of 10 patients receiving a continuous inotrope infusion and optimal medical therapy (control group). The CRT and control group did not differ significantly with regard to age, etiology of CHF, left ventricular ejection fraction (LVEF), or implanted ICD. Mortality rates were not significantly different at 1, 3, 6, and 12 months between the two groups. At 12 months the mortality in the CRT group was 46.7% versus 60.0% in the control group ($P = 0.50$). Only one patient tolerated discontinuation of intravenous inotrope therapy. The hospitalization rate was similar in the two groups at 3-year follow-up.

Konstantino et al.¹⁰ also underscored the very high mortality in inotrope-dependent class IV CHF patients undergoing CRT in a series of 10 patients with ischemic cardiomyopathy (median QRS duration = 170 ms). Although eight patients improved (four remaining on intravenous (IV) inotrope therapy), the mortality rate was 60% during a median follow-up of 9.5 months.

Huneycutt et al.¹¹ also found CRT to be of questionable benefit in CHF patients requiring IV inotropic support (median duration of inotropic therapy was 6 days). They found no significant differences in length of hospitalization between 21 patients on inotropic support who were treated with CRT and a matched group that did not receive CRT, although 86% of the CRT patients were able to wean from inotropic support compared with 71% of the non-CRT group ($P = 0.03$). Only 29% of the CRT patients were alive at the 1-year follow-up.

Positive Results

In a retrospective observational study of patients undergoing CRT, Cowburn et al.¹² identified 10 patients who required inotropic support for refractory CHF and who underwent CRT while on intravenous inotropic agents (Table I). Patients

Address for reprints: Bengt Herweg, M.D., Division of Cardiology, University of South Florida, South Tampa Center for Advanced Healthcare, 2A Columbia Dr., Suite 5070, Tampa, FL 33606. Fax: 813-259-0665; e-mail: bherweg@health.usf.edu

Table I.

Published Reports of Cardiac Resynchronization in NYHA Class IV Patients on Intravenous Inotropic Therapy at the Time of Implantation

Reference	No. pts	Etiology	Follow-up (Months)	No. Pts Weaned Off IV Inotrope Therapy	Symptomatic Improvement (no. pts)	Long-term Mortality
Makati et al. ⁹	15	ICM 73%	12	1	NA	60%
Konstantino et al. ¹⁰	10	ICM 100%	9.5 median	4 (median 5.5 mths)	8	50%
Huneycutt et al. ¹¹	21	ICM 50%	12	18/21 (86%)	NA	71%
Cowburn et al. ¹²	10	NA	0.4 ± 0.4	All 2 ± 2 days post-CRT	NA	0% short-term
James et al. ¹³	6	NA	14 ± 11	All survivors	NA	50%
Simon et al. ¹⁴	18	NA	22 Median 5	6 (33%)	11	25%
Milliez et al. ¹⁵	14	ICM 5 NICM 9	36	All within 3 days	All survivors	15%
Herweg et al. ¹⁶	10	ICM 4 NICM 6	25 ± 13	9/10 ± 15 ± 14 days post-CRT	9	0%. 3 pts underwent orthotopic transplantation 56, 257, and 910 days post-CRT

No = number; pt = patient; mths = months; ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy; NA = not available.

had been hospitalized for 30 ± 29 days and had received inotropic support for 11 ± 6 days prior to CRT. All patients were weaned from inotropic support (2 ± 2 days post-CRT) and all patients survived to hospital discharge (12 ± 13 days post-CRT). James et al.¹³ evaluated the benefit of CRT in 38 class IV CHF patients who received IV inotropic therapy within 30 days of CRT, or only during CRT implantation (14 patients were recovering from major cardiac surgery). Of the six patients who received IV therapy only during CRT, half survived and came off IV therapy. Nine patients required inotropic therapy during and after CRT and seven underwent cardiac transplantation. The survival rate of the patients who did not have cardiac surgery or transplantation cannot be determined from the published data.

Simon et al.¹⁴ concluded that CRT can be safe and clinically effective in inotrope-treated class IV patients followed for a median of 156 days after implantation. Six of 11 patients on continuous inotropic therapy who were treated with CRT were weaned off inotropes, and the mean number of CHF hospitalizations decreased from eight to three over the course of 6 months pre- and postimplantation ($P = 0.09$). There were seven clinical events (four deaths, one transplant, and two ven-

tricular assist device implantation). Event-free survival was 61% at 6 months.

Milliez et al.¹⁵ recently reported their experience with CRT devices in 14 end-stage inotrope-dependent unstable CHF patients (five ischemic and nine nonischemic cardiomyopathy patients; left ventricular ejection fraction $20 \pm 10\%$). Dependence on vasopressor agents was defined as the inability to stop or reduce the drugs without occurrence of hypotension, oligoanuria (<20 mL/hour), and hypoxemia. All vasopressor agents were withdrawn within 72 hours. One patient with a CRT device died 24 hours after the procedure from a ventricular tachyarrhythmia. During the mean follow-up of 3 years (6 months to 4 years), one patient died of CHF. Hence, 12 of 14 patients (85%) were alive with improvement of their exertional tolerance by at least 1 NYHA functional class and LV ejection fraction by a mean of 5%.

We recently reported 10 consecutive patients, mean age 55 years, in sinus rhythm, with class IV heart failure who underwent CRT while receiving intravenous inotropic support with dobutamine or milrinone.¹⁶ One patient required ventilatory support during CRT implantation. All patients were alive after a mean follow-up of almost 3 years. Three patients underwent successful orthotopic

cardiac transplantation and in one, inotropic support was continued until transplantation. Nine of the other patients were able to discontinue IV inotropic therapy. LV end-systolic volume decreased significantly ($P < 0.01$), and LVEF increased significantly ($P < 0.05$). Our satisfactory results in consecutive patients may have been due to chance, operator experience, or less sick patients than those in the unfavorable reports because they were maintained alive a relatively long time on inotropic therapy before CRT. A selection bias^{7,8} was highly unlikely because the patients were all referred by heart failure specialists in our busy cardiac transplantation center.

CRT in Inotrope-Dependent Patients after Cardiac Surgery

There appears to be a potential role for CRT in inotrope-dependent class IV CHF patients after cardiac surgery. The report of James et al.¹³ exposed a potential new role for CRT in patients with significant LV dysfunction and refractory CHF immediately after cardiac surgery, especially coronary artery bypass surgery. In this respect, Fox et al.¹⁷ reported the remarkable benefit of CRT in one patient with refractory heart failure (preoperative LVEF = 25% and left bundle branch block: QRS duration = 170 ms) despite IV inotropic support and continuous positive airway pressure. The implantation of a CRT device produced a dramatic

improvement and the patient was found to be in class II NYHA 9 months after surgery.

Conclusion

The weight of evidence suggests that CRT should not be automatically dismissed as contraindicated in class IV CHF patients on inotropic support. Thus, it may be never too late to consider CRT and even the sickest end-stage patients might benefit. The selection of such class IV CHF inotrope-dependent patients for CRT must be individualized based on a number of factors, including clinical judgment, positive proof of potentially treatable LV dyssynchrony, need for an additional ICD, and operator skill. Permanent atrial fibrillation in such patients should not be an absolute contraindication because the results of a recent large prospective observational study clearly demonstrated that CRT (in patients with standard indications) coupled with atrioventricular junctional ablation yields long-term results comparable to those obtained in sinus rhythm.¹⁸ Although the prognosis of end-stage CHF patients on inotropic support is poor in terms of mortality, CRT is relatively safe and worthwhile in selected patients if only for symptomatic improvement even if it is of relatively short duration. Definitive answers regarding the role of CRT will be difficult to obtain as randomized trials are not feasible in patients with end-stage CHF in NYHA class IV on inotropic support.

References

- Lehmann MH, Aaronson KD. CRT-D therapy in heart failure: How much do NYHA class IV patients benefit? *J Cardiovasc Electrophysiol* 2006; 17:491–494.
- Lindenfeld J, Feldman AM, Saxon L, Boehmer J, Carson P, Ghali JK, Anand I, et al. Effects of cardiac resynchronization therapy with or without a defibrillator on survival and hospitalizations in patients with New York Heart Association class IV heart failure. *Circulation* 2007; 115:204–212.
- 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; 344:873–880.
- Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; 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; 352:1539–1549.
- McAlister FA, Ezekowitz J, Hooton N, Vandermeer B, Spooner C, Dryden DM, Page RL, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: A systematic review. *JAMA* 2007; 297:2502–2514.
- Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE Jr, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines/American College of Cardiology/American Heart Association/North American Society for Pacing and Electrophysiology Committee. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: Summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *J Cardiovasc Electrophysiol* 2002; 13:1183–1199.
- Authors/Task Force Members, Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, Gasparini M, et al.; ESC Committee for Practice Guidelines (CPG), Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Funck-Brentano C, Filippatos G, et al.; Document Reviewers, Priori SG, Blomstrom-Lundqvist C, Brignole M, Terradellas JB, Camm J, Castellano P, et al. Guidelines for cardiac pacing and cardiac resynchronization therapy: The task force for cardiac pacing and cardiac resynchronization therapy of the European society of cardiology. Developed in collaboration with the European Heart Rhythm Association. *Eurpace* 2007; 9:959–998.
- Auricchio A, Abraham WT. Cardiac resynchronization therapy: Current state of the art; Cost versus benefit. *Circulation* 2004; 109:300–307.
- Makati KJ, Dumitro I, Ewald G, Rogers J, Faddis MN. Cardiac resynchronization therapy does not change mortality in class IV CHF patients on continuous inotrope infusion with ICDs (Abstract). *Pacing Clin Electrophysiol* 2003; 26:362.
- Konstantino Y, Iakobishvili Z, Arad O, Ben-Gal T, Kusniec J, Mazur A, Porter A, et al. Urgent cardiac resynchronization therapy in patients with decompensated chronic heart failure receiving inotropic therapy. A case series. *Cardiology* 2006; 106:59–62.
- Huneycutt DC Jr, Langberg J, Leon AR, Smith AL. Experience with cardiac resynchronization in heart failure patients requiring inotropic support (Abstract). *Pacing Clin Electrophysiol* 2003; 26:1041.
- Cowburn PJ, Patel H, Jolliffe RE, Wald RW, Parker JD. Cardiac resynchronization therapy: An option for inotrope-supported patients with end-stage heart failure? *Eur J Heart Fail* 2005; 7:215–217.
- James KB, Militello M, Barbara G, Wilkoff BL. Biventricular pacing for heart failure patients on inotropic support: A review of 38 consecutive cases. *Tex Heart Inst J* 2006; 33:19–22.
- Simon MA, Saba S, Spates J, Murali S. Cardiac resynchronization therapy for inotrope-dependent advanced heart failure patients: Can we? Should we? (Abstract). *Heart Rhythm* 2004; 1:S248.
- Milliez P, Thomas O, Haggui A, Mebazaa A, Schurando P, Extramiana F, Beaufilets P, et al. Resynchronization as a rescue therapy in

HERWEG AND BAROLD

- unstable overt heart failure dependent of intravenous vasopressive agents (Abstract). *Heart Rhythm* 2006; 3:S132.
16. Herweg B, Ilercil A, Cutro R, Dewhurst R, Krishnan S, Weston M, Barold SS. Cardiac resynchronization therapy in patients with end-stage inotrope-dependent class IV heart failure. *Am J Cardiol* 2007; 100:90–93.
 17. Fox DJ, Petkar S, Davidson NC, Fitzpatrick AP. Biventricular pacing in a patient with ventilatory and inotropic dependent heart failure following coronary artery by-pass surgery. *Europace* 2005; 7:490–491.
 18. Gasparini M, Auricchio A, Regoli F, Fantoni C, Kawabata M, Galimberti P, Pini D, et al. Four-year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: The importance of performing atrioventricular junction ablation in patients with atrial fibrillation. *J Am Coll Cardiol* 2006; 48:734–743.