Cardiac resynchronization therapy in congestive heart failure

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WHICH FUTURE FOR CARDIAC RESYNCHRONIZATION THERAPY? A GOOD ONE, BUT AS A SERVANT OF IMPLANTABLE DEFIBRILLATORS

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Cardiac resynchronization therapy (CRT) has become a technique of choice for the treatment of advanced heart failure associated with electromechanical dyssynchrony. Recent evidence suggests that the role of CRT alone may be limited, and combination with implantable cardioverter-defibrillators should be used in the majority of cases of ischemic cardiomyopathy. However, more data are needed to expand this indication to patients with idiopathic dilated cardiomyopathy. CRT alone may prove to be useful instead of right ventricular pacing in patients with less severe left ventricular dysfunction.

Cardiac resynchronization therapy (CRT) has become an accepted therapeutic alternative in patients with chronic heart failure and intraventricular conduction delay. However, many of them also fall into the category of patients who might benefit from implantable cardioverter-defibrillators (ICD). Should all candidates for CRT receive a combined device with ICD capability?

The efficacy of cardiac resynchronization therapy

The principle of CRT is to employ appropriately timed biventricular (or single-site left ventricular) pacing to resynchronize ventricular contraction. Several studies have demonstrated acute hemodynamic benefit as represented by increased left ventricular contractility or pulse pressure[1]. Compared to administration of inotropes, these beneficial effects are associated with decrease in myocardial oxygen consumption[2] and result in reverse remodeling of the left ventricle in the long-term course[3]. Both early clinical studies and more recently, three randomized trials (PATH-CHF, MUSTIC, MIRACLE) evidencing data from 605 patients, have documented a significant improvement in NYHA functional class, an increase in the 6-min walking distance and oxygen uptake at peak exercise, and a better quality of life[4]. However, none of these studies was evaluating the impact of CRT on prognosis. Recent meta-analysis, incorporating 1634 cases, suggested that CRT is associated with a significant 51% reduction of mortality for progressive heart failure. On the other hand, all-cause mortality or non-heart failure deaths were not decreased[5]. Reassuring data have been obtained from another randomized multicenter study evaluating safety and effectiveness of CRT-ICD in 490 patients[6]. The study revealed no difference in the incidence of ventricular tachyarrhythmias when comparing CRT with no CRT. However, others have warned against a higher risk of torsade de pointes in CRT patients that may reflect pacing-induced increase in QT duration and transmural dispersion of repolarization[7].

Lessons from primary prevention implantable cardioverter-defibrillator trials

The ICD has been demonstrated in several clinical trials to be the most significant therapy available to treat life-threatening ventricular tachyarrhythmias and thus, to prevent sudden cardiac death in post-infarction population with impaired left ventricular function. Based on data from the MADIT and MUSTT studies, the ICD conferred an average 50% reduction of all-cause mortality as compared with conventional or antiarrhythmic drug therapy[8]. The latest primary

prevention ICD trial, MADIT II, confirmed again superiority of ICD therapy over the conventional one[9]. In this trial, post-infarction patients were enrolled based on documented depression of left ventricular function, without the need for inducibility of ventricular tachyarrhythmias. Interestingly, this trial reported that the incidence of new or worsened heart failure was higher in the ICD group than in the conventional therapy group (19.9 vs 14.9%, p = 0.09). As it was the only ICD trial that included dual-chamber ICDs and a larger proportion of more symptomatic patients with chronic heart failure, such data suggest that unnecessary right ventricular stimulation from dual-chamber ICD promotes progression of heart failure. This issue was further studied in the DAVID trial[10]. A total of 506 patients with a primary or secondary indication for ICD therapy, and with evidence of left ventricular dysfunction were implanted with dual-chamber ICD and randomized to either ventricular only back-up pacing or dual-chamber rate-responsive pacing. The trial was terminated early because a higher relative probability of death or hospitalization for new or worsened heart failure was documented for the latter group (p = 0.03). Thus, ventricular dyssynchrony resulting from right ventricular apical pacing seems to outbalance beneficial effects of dual-chamber ICDs (Fig. 1), and these patients may benefit from a combined device (ICD with CRT capability).

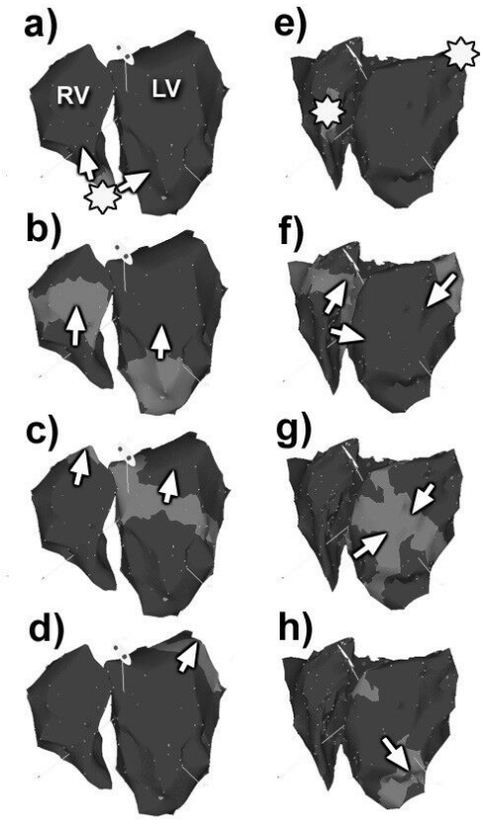

Figure 1. *Three-dimensional electroanatomical propagation maps of both ventricles (right ventricle-RV and left ventricle-LV) as seen from the left lateral view with caudal rotation in a patient with dilated cardiomyopathy and right ventricular apical pacing* (a-d), *and in a patient with the same diagnosis and biventricular pacing with right ventricular lead placed midseptally* (e-h). Asterisks *mark the pacing sites, activation wavefronts are depicted in light gray and direction of activation is highlighted by* arrows. *Note abnormal activation of the LV during right ventricular apical pacing that produces electromechanical dyssynchrony. Biventricular pacing simulates normal left ventricular activation and shortens its activation time.*

The future of cardiac resynchronization therapy

At present, accepted indications for CRT include NYHA functional class III and IV that results from severe left ventricular dysfunction. Candidates for secondary prophylactic ICD implantation of any etiology who fulfill these criteria should be implanted with CRT-ICD. Combining indications for CRT with indications for primary prophylactic ICD implantation, CRT-ICD should be considered for any post-infarction patient who also meets criteria for MADIT, MUSTT or MADIT II trial. This concept that CRT candidates need a device with ICD capabilities is supported by recently reported but unpublished results from the COMPANION trial[11]. This was a randomized study which has been terminated prematurely after the enrolment of 1600 of the 2200 patients planned due to early benefit associated with CRT. Preliminary results showed that both CRT and CRT-ICD significantly decreased the occurrence of the composite endpoint events – all-cause deaths and hospitalizations by 19%. However, only CRT-ICD reduced significantly total mortality by 43%. For CRT only, the reduction was non-significant (23%). The unresolved question remains how to proceed in patients with idiopathic dilated cardiomyopathy. Given unconvincing data on the role of primary prophylactic ICD implantation in this subset of chronic heart failure patients[12,13], we should wait for more conclusive data from ongoing trials.

Future studies are also needed to evaluate whether CRT is superior to right ventricular pacing in patients with less severe left ventricular dysfunction and the need for chronic ventricular stimulation. On the contrary, more data are required to support the notion that candidates for ICD with left ventricular dysfunction and less severe chronic heart failure (NYHA class II) should be implanted also with CRT-ICD system. This may be even more important in those who require, for any reason, dual-chamber ICD.

Conclusions

In summary, recent evidence suggests that the role of CRT alone may be limited, and combination with ICD should be used in the majority of cases of ischemic cardiomyopathy. More data are needed to expand this indication to patients with idiopathic dilated cardiomyopathy. CRT alone may prove useful instead of right ventricular pacing in patients with less severe left ventricular dysfunction. Ongoing and future trials will further refine the indications for CRT and CRT-ICD therapy.

References

1. Auricchio A, Stellbrink CH, Block M, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. Circulation 1999; 99: 2993-3001.
2. Nelson GS, Curry CW, Wyman BT, et al. Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. Circulation 2000; 101: 2703-9.
3. Auricchio A, Spinelli JC, Trautmenn SI, Kloss M. Effect of cardiac resynchronization therapy on ventricular remodeling. J Card Fail 2002; 8 (Suppl): S549-S555.
4. Abraham WT. Cardiac resynchronization therapy: a review of clinical trials and criteria for identifying the appropriate patient. Rev Cardiovasc Med 2003; 4 (Suppl 2): S30-S37.
5. 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: 730-40.
6. Higgins SL, Hummel JD, Niazzi 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.
7. Medina-Ravell VA, Lankipalli RS, Yan GX, et al. Effect of epicardial or biventricular pacing to prolong QT interval and increase transmural dispersion of repolarization: does resynchronization therapy pose a risk for patients predisposed to long QT or torsade de pointes? Circulation 2003; 107: 740-6.
8. Prystowsky EN. A guide to device selection: cardiac resynchronization therapy alone or in combination with an implantable cardioverter defibrillator. Rev Cardiovasc Med 2003; 4 (Suppl 2): S47-S54.
9. Moss AJ, Zareba W, Hall WJ, et al, for the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002; 346: 877-83.
10. Wilkoff BL, Cook JR, Epstein AE, et al, for the DAVID Trial Investigators. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002; 288: 3115-23.
11. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac resynchronization therapy (CRT) reduces hospitalizations, and CRT + an implantable defibrillator (CRT-D) reduces mortality in chronic heart failure: preliminary results of the COMPANION trial. www.uchsc.edu/cvi
12. Strickberger SA, Hummel JD, Bartlett TG, et al. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia - AMIOVIRT. J Am Coll Cardiol 2003; 41: 1707-12.
13. Bansch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). Circulation 2002; 105: 1453-8.