Review Article

Non-Classical Indications for Cardiac Resynchronization Therapy

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Cardiac resynchronization therapy (CRT) affords efficacious treatment for patients with New York Heart Association (NYHA) class III or IV heart failure despite optimal medical management, left ventricular ejection fraction (LVEF) ≤35% and ventricular dyssynchrony identified by prolonged QRS duration.[1-3] These indications are based on randomized controlled trials. However, most of the patients enrolled in these studies were in sinus rhythm, were not previously paced and had a left bundle branch block (LBBB) pattern or left intraventricular conduction delay.[4-9]

Uncertainties still remain regarding several subpopulations that are either not included or under-represented in the main studies. These populations include patients with the following: atrial fibrillation (AF); previous pacemakers, being considered for upgrade to CRT; a right bundle branch block (RBBB) pattern; QRS <120 ms; NYHA class II; low EF, who need pacemakers for other indications and who do not have a wide QRS; and finally those patients with predominant right heart failure. We reviewed the literature and our experience in order to survey the benefits of CRT in these specific subpopulations.

Patients with chronic atrial fibrillation (Table 1)

Heart failure is commonly associated with AF, known to be present in up to 50% of patients with NYHA class III-IV.[10] Patients with permanent AF are excluded from most of the major studies, and therefore some indications for CRT guidelines do not refer specifically to them.[1] While others require that patients be in sinus rhythm,[3] the European guidelines also recommend biventricular pacing in patients with permanent AF and indications for atrioventricular junction ablation.[2] However, there are several studies that investigated this specific population and demonstrated the benefits of CRT, most of them showing a similar or somewhat decreased but significant benefit in AF patients when compared to patients paced in sinus rhythm.[11-21] Some observational studies have suggested that CRT is only beneficial following atrioventricular junction ablation, when a high percentage of biventricular pacing may be achieved.[14,22] Notably, there are unique programming features of CRT devices that tend to maintain a high percentage of biventricular pacing in patients with atrial fibrillation. This special type of algorithm, called "rate regularization" or "conducted atrial fibrillation response", reduces RR variability and preserves CRT delivery at a rate that slightly exceeds that of the intrinsic ventricular response, which is calculated on the basis of several preceding RR intervals. Rate regularization may be beneficial, not only because of its effect on maintaining biventricular capture, but also because ventricular cycle-length irregularity *per se* may se-

Table 1. Patients with chronic atrial fibrillation.

Author	# of pts	Inclusion criteria	Assessed Parameters	Results
Leclercq[11]	15	NYHA class III/IV, EF<35%, DCMP, LVEDD>60 mm, QRS>120	NYHA, Peak VO_2, QRS duration, EF	Improvement in exercise tolerance. Benefit tended to be greater in patients with atrial fibrillation
Etienne[12]	11	NYHA class III/IV, first-degree atrioventricular block and/or LBBB	Systemic and pulmonary arterial pressure, pulmonary capillary wedge pressure, cardiac index	Comparable to patients with sinus rhythm
Garrigue[13]	13	NYHA class III/IV, EF<40%, LVEDD>60 mm, QRS>140 ms (AV ablation)	LVEF, QRS duration, 6MW, Peak VO_2.	Better hemodynamic performance than LV pacing
Leon[14]	20	NYHA class III/IV, EF≤35%, Prior AV ablation	LVEF, LVEDD, LVESD, QRS duration, NYHA, QOL, hospitalizations	Improvement in LV function and symptoms
Leclercq[15]	59	NYHA Class III, EF<35%, LVEDD >60 mm, prior RV paced QRS duration >200 ms, 6MW<450 m	NYHA, QOL, 6MW, hospital admissions, QRS duration, LVEF, Peak VO_2	Improvement in exercise tolerance
Molhoek[16]	30	NYHA class III/IV, EF<35%, QRS>120 ms, CLBBB	NYHA, QOL, 6MW	Benefit from CRT comparable to those who had sinus rhythm
Linde[17]	35	NYHA class III, EF<35%, LVEDD>60 mm, 6MW<450 m, QRS>150 ms (>200 ms in paced patients)	6MW, peak VO_2, QOL, NYHA, blood pressure, body-weight, QRS duration, LVEF, hospitalizations, mortality	Favorable results
Doshi[18]	103	NYHA I-III, requirement for AV ablation, 6MW<450 m	6MW, QOL, LVEF	Improvement in 6MW and EF
Kies[19]	74	NYHA class III/IV, LVEF<35%; QRS>120 ms (>200 ms for a paced QRS), CLBBB	NYHA, QOL, 6MW, LVEF, LVEDD, LVESD, LA	Benefit with significant left atrial and LV reverse remodeling
Khadjooi[20]	86	NYHA class III/IV, EF<35% QRS>120 ms	NYHA, 6MW, QOL, LVEF, LVEDV, LVESV	Similar prognostic and symptomatic benefits
Delnoy[21]	96	NYHA class III/IV, QRS>120 ms, EF<35%	NYHA, 6MW, QOL, LVEF, LVEDV, LVESV, MR	Clinical and echocardiographic improvement
Gasparini.[22]	48	NYHA II-IV, EF<35%, QRS>120 ms	NYHA, 6MW, peak VO2, LVEDV, LVEDD, LVESV, LVESD, LVEF, MR	Improvement of LV function and functional capacity, especially after AV ablation

6 MW – six minute walk; AV – atrioventricular; CLBBB – complete left bundle branch block; CRT – cardiac resynchronization therapy; DCMP – dilated cardiomyopathy; LA – left atrium; LBBB – left bundle branch block; LVEDD – left ventricular end-diastolic diameter; LVEDV – left ventricular end-diastolic volume; LVEF – left ventricular ejection fraction; LVESD – left ventricular end-systolic diameter; LVESV – left ventricular end-systolic volume; MR – mitral regurgitation; NYHA – New York Heart Association; QOL – quality of life; RV – right ventricular.

verely affect quality of life as well as myocardial function.[23]

In addition, it should be noted that Efremidis et al described a novel alternative approach to treating these patients. They found that AF ablation used in patients with heart failure and a low EF was relatively effective. In this study, 62% of the patients remained in sinus rhythm at the end of the follow up, and improved left ventricular systolic function, as well as atrial and ventricular reverse remodeling, were observed.[24] More recently, the PABA-CHF investigators reported that AF ablation was superior to atrioventricular-nodal ablation with CRT implantation in patients with heart failure who had drug-refractory AF.[25] It should be emphasized, however, that AF ablation is not suitable for all patients and its efficacy is limited. Moreover, the data supporting this approach need to be verified in additional large-scale randomized studies.

Since it has also been our experience that patients with AF improve with CRT, as long as consistent pacing in the ventricles is achieved with appropriate rate control or with atrioventricular nodal ablation (the so called "ablate-and-CRT" approach), we believe that CRT is indicated in patients with AF who would otherwise be candidates for CRT implantation according to the available guidelines.

Patients with previous pacemakers (Table 2)

Patients with systolic heart failure who had previously implanted pacemakers were not included in most of the major CRT trials and only a few studies have examined the clinical outcome in patients with a preexisting right ventricular pacemaker or intra-cardiac defibrillator (ICD) undergoing upgrade to CRT. The beneficial results from most of these studies were similar to or even greater than those demonstrated in the traditional CRT population.[14,15,26-29] Similarly, a somewhat better response to CRT has been shown in 25 patients with prior pacing compared to patients with *de novo* CRT implantation.[30]

Selection criteria for upgrading to CRT among pacemaker patients have not yet been established, but it is conceivable that paced QRS width may not be an appropriate selection criterion and measures of mechanical dyssynchrony may have to be taken into account.[31,32] In addition, the relationship between pacing and dyssynchrony is not entirely clear. Both Schmidt et al and Bordachar et al found that mechanical dyssynchrony was present in the majority of patients with pacemakers and low EF, whereas it was much less common in pacemaker patients with normal or near normal EF.[31,32] To the best of our knowledge, the value of various measures of mechanical dyssynchrony in selecting pacemaker patients for upgrading has not yet been systematically studied. Nevertheless, we and others believe that patients with pacemakers who develop systolic dysfunction with heart failure have a greater chance of improvement when upgraded to CRT.

Patients with RBBB

Although patients with RBBB have been included in several major trials[6,7,33] and are not excluded from present indications in the current guidelines,[34,35] their results were analyzed separately only a relatively short time ago. Recently, an experimental animal model revealed that the magnitude of cardiac dyssynchrony in a failing heart with a pure RBBB pattern was considerably less than in a heart with LBBB, despite similar prolongation of the QRS. Moreover, although CRT improved dyssynchrony in failing hearts with RBBB, this effect was smaller than that observed in LBBB hearts. In this model there seemed to be little or no advantage of biventricular over right ventricular single-site pacing therapy in improving left ventricular synchrony, and both modes enhanced right ventricular EF to a similar extent.[36] Furthermore, Egoavil et al showed only a slight benefit of CRT in RBBB patients in an analysis based on more than 60 cases.[33] In contrast, Garrigue et al[37] demonstrated a beneficial effect of CRT in a very small series of patients with RBBB, but only in those having measures of mechanical dyssynchrony. It is conceivable that an RBBB pattern serves as a marker of left ventricular dyssynchrony in many but not all CRT candidates, and it is therefore reasonable to opt for CRT implantation in patients with an RBBB pattern based on measures of mechanical dyssynchrony, such as tissue Doppler imaging.

Patients with narrow QRS complex

Information is scarce regarding CRT in this population. As research in this field expands, it is becoming evident that the traditional selection criteria of wide QRS are limited in their ability to predict CRT success and that they are only markers of mechanical dyssynchrony, measures of which may provide better prediction of success.[38] In addition, it has been shown that mechanical dyssynchrony detected by echocardiography is present in up to 43% of congestive heart

Table 2. Patients with previous pacemakers.

Author	# of pts	Inclusion criteria	Assessed Parameters	Results
Leon[14]	20	NYHA class III/IV, EF≤35%, prior AV ablation and RV pacing	LVEF, LVEDD, LVESD, QRS duration, NYHA, QOL, hospitalizations	Improvement in left ventricular function and symptoms
Leclercq[15]	59	NYHA class III, EF<35%, LVEDD>60 mm, prior RV paced QRS duration>200 ms, 6MW<450 m	NYHA, QOL, 6MW, hospital admissions, QRS duration, LVEF, Peak VO_2	Improvement in exercise tolerance
Baker[24]	60	NYHA III/IV, previous RV pacing	NYHA, QRS duration, QOL, EF, MR	Improvement
Witte[14]	32	NYHA class III/IV, EF≤35%, previous RV pacing	NYHA, QOL, QRS duration, VO_2, LVEF, LVEDD, LVEDV, dyssynchrony parameters	Similar improvements in clinical, hemodynamic, and dyssynchrony variables
Marai[28]	25	NYHA III/IV, LVEF<35%, QRS>120, previous RV pacing	NYHA, 6MW, LVEF, LVEDD, LVESV, dyssynchrony parameters, PAP, LA, MR	Results comparable to patients with no previous PMI
Duray[26]	18	NYHA III/IV, LVEF≤35%, RS>120, previous RV pacing	NYHA, BNP, LVEF	Clinical response as good as in patients with no PMI
Leclercq[27]	56	NYHA III/IV, EF<35% dyssynchrony (interventricular delay >40 ms or LV pre-ejection delay >140 ms) with need of pacemaker replacement	NYHA, 6MW, QOL, LVEF, LVEDD, LVESD, dyssynchrony, QRS duration, hospitalizations	Upgrading might significantly alleviate symptoms, increase exercise tolerance and reduce hospitalizations

6MW – six minute walk; AV – atrioventricular; BNP – brain natriuretic peptide; LA – left atrium; LVEDD – left ventricular end-diastolic diameter; LVEDV – left ventricular end-diastolic volume; LVEF – left ventricular ejection fraction; LVESD – left ventricular end-systolic diameter; MR – mitral regurgitation; NYHA – New York Heart Association; PAP – pulmonary artery pressure; PMI – pacemaker implantation; QOL – quality of life; RV – right ventricular.

failure (CHF) patients with a narrow QRS complex (<120 ms), and these patients may benefit from CRT.[39-41] Yu et al compared patients with a narrow QRS complex and predefined dyssynchrony by tissue Doppler imaging to similar patients with a wide QRS complex. They concluded that CRT for CHF patients with narrow QRS complexes and coexisting mechanical dyssynchrony results in left ventricular reverse remodeling and improvement of clinical status. Furthermore, the benefit was similar to that of the wide-QRS group, provided that a similar extent of dyssynchrony was selected.[42] In contrast, in a recently published study, 172 patients who had a standard indication for an ICD but narrow QRS were randomly assigned to CRT. The implantation showed no benefit in this patient population, although a significant benefit was shown in a subgroup of patients with a QRS interval of 120-130 ms.[43] Similar results were also shown by others.[44] This topic is the subject of intensive research in ongoing randomized controlled trials, but at this juncture we, like others,[45] cannot justify CRT implantation in patients with a narrow QRS based on the current literature.

Patients without overt heart failure

Some of the major CRT trials have included a few patients with NYHA class II heart failure.[4,46,47] These studies demonstrated an effect of CRT on echocardiographic measures of cardiac remodeling, but a very limited clinical effect on heart failure symptoms. In contrast, the MIRACLE ICD II trial showed that CRT offers important benefits to mildly symptomatic NYHA class II heart failure patients with ventricular dyssynchrony and an indication for an ICD, although no significant differences were noted in 6-minute walk distance or quality-of-life scores.[48] Cleland et al recently published a sub-analysis from the CARE-HF trial[49] and found that the severity of symptoms was not an important determinant of the prognostic effects of CRT. Similar results were also shown by Landolina et al,[50] where CRT induced significant improvements in EF and left ventricular dimensions in patients with NYHA class II, indicating that CRT promotes long-lasting reverse remodeling, even in patients with less symptomatic CHF.

Currently, the evidence is insufficient to recommend CRT implantation in patients with NYHA functional class I or II.[51] Large randomized controlled trials dealing with this question are currently underway. The preliminary results of the REVERSE trial have just been presented but not yet published. They indicated some benefit of CRT in this group of patients with regard to several parameters of CHF and left ventricular function. However, the clinical relevance of their findings as well as the long-term effects in this patient group remain to be established.[52]

Prophylactic CRT in patients requiring pacemaker implantation

We often face patients with some degree of heart failure who need pacemaker implantation for bradycardic indications, but who do not have a wide QRS. When paced, however, they are likely to develop dyssynchrony and may further deteriorate. Chiladakis et al reported that ventricular pacing in patients with normal left ventricular systolic function who underwent conventional dual chamber pacemaker implantation for sick sinus syndrome was associated with impaired left ventricular systolic function. They also reported a moderate degree of worsening of left ventricular diastolic function, based on tissue Doppler imaging, color M-mode echocardiography and brain natriuretic peptide levels.[53] Thus, the pertinent question is whether a conventional or CRT pacemaker should be implanted in these patients.

Interestingly, this issue was addressed by the PAVE trial, which demonstrated a beneficial effect from CRT implantation versus traditional pacing in patients undergoing atrioventricular nodal ablation, especially in those with EF <45% and with CHF symptoms (NYHA II-III).[18] Kindermann et al recently published their analysis from 30 patients with standard indications for permanent ventricular pacing and EF<40%, who were prospectively randomized in a crossover design to three months of right ventricular pacing and three months of biventricular pacing. They found that biventricular stimulation was superior to conventional right ventricular pacing with regard to left ventricular function, quality of life, and maximal as well as sub-maximal exercise capacity.[54] Albertsen et al also reported that biventricular pacing protects against the left ventricular dysfunction otherwise seen after conventional right ventricular pacing, but observed no clinical improvement.[55] Conversely, Brignole et al found no or only modest superiority of biventricular pacing over right ventricular pacing.[56] Whether this approach should be applied to all patients requiring pacemaker implantation will depend upon the results of ongoing trials, such as the BLOCK HF study, which addresses this specific question.[57]

While we await the results of further randomized controlled trials to better define this group, our current practice is to use conventional pacing for those who do not fit into CRT criteria, and to upgrade to CRT those patients who deteriorate on conventional pacing. We implant CRT defibrillators with a plug-in left ventricular port in ICD borderline recipients who might need an upgrade to CRT in the future.

Patients with right heart failure

This subgroup of patients is mixed within the large trial populations and very few studies have looked specifically at these patients as candidates for CRT. A small series of congenital heart disease patients have demonstrated beneficial results from CRT, but this population is unlike the typical CRT candidate.[58] We have previously shown a beneficial effect of CRT on the myocardial performance index of the right ventricle,[59] and also demonstrated a beneficial effect of CRT on the functional capacity of 7 patients with combined left and right heart failure.[60] Similar results were noted by Rajagopalan et al, who also showed that improvement in right ventricular function was independent from improvement in LVEF.[61] In addition, Bleeker et al assessed the influence of CRT on right ventricular remodeling, using the diameter of the tricuspid valve annulus, the maximal dimension of the middle third of the right ventricle, and the distance from the right ventricular apex to the mid-point of the tricuspid annulus. They found that all of these parameters showed a significant decrease after six months of CRT, and concluded that CRT results in significant reverse remodeling of the right ventricle.[62] Another study that assessed the influence of biventricular pacing on right ventricular systolic function showed a significant improvement from biventricular pacing, compared with AAI, right or left ventricular pacing in CRT recipients.[63]

Overall, evidence is scarce regarding the benefit of CRT in patients with isolated or predominant right heart failure.

Conclusions

Whereas the role of CRT is established in patients with classical indications, its role has not yet been established in several subgroups of patients reviewed in this paper. CRT seems to benefit patients with AF and those with preexisting pacemakers, while its role in patients who are in NYHA class I-II or who have a narrow QRS complex remains unclear. Uncertainties also exist regarding CRT in patients with an RBBB pattern, in patients who need pacing for other indications and who do not have a wide QRS, and in those with predominant right heart failure. Many of these questions may be solved in the future by the use of better predictors of success, such as echo tissue Doppler imaging, and will eventually be answered by ongoing clinical trials.

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