

Cardiac Resynchronisation Therapy and Heart Failure: Perspective from 5P Medicine

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Abstract

Chronic heart failure is still a major challenge for healthcare. Currently, cardiac resynchronisation therapy (CRT) has been incorporated into the updated guideline for patients with heart failure, left ventricular ejection fraction $\leq 35\%$ and prolonged QRS duration. With 20 years of development, the concept of 'from bench to bedside' has been illustrated in the field of CRT. Given the fact that the indications of CRT keep evolving, the role of CRT is not limited to the curative method for heart failure. We therefore summarise with the perspective of 5P medicine – preventive, personalised, predictive, participatory, promotive, to review the benefit of CRT in the prevention of heart failure in those with conventional pacemaker indications, the individualised assessment of patient's selection, the predictor of responders of CRT, and the obstacles hindering the more application of CRT and the future development of this device therapy.

Keywords

Heart failure, cardiac resynchronisation therapy, 5P medicine

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The prevalence of heart failure (HF) is still high¹ and is rising in developing countries.² Despite optimal medical therapy, refractory HF is a common occurrence and remains a "global disease requiring global response."³ The emergence of cardiac resynchronisation therapy (CRT), has brought a new paradigm in the management of HF. CRT has been the most promising device therapy in mild-to-severe HF over the past two decades,⁴ has improved the prognosis of HF and has been incorporated into therapeutic guidelines.^{5,6} The 20-year history of CRT illustrates the concept of "from bench to bedside" and this article aims to review the use of CRT in the context of 5P medicine-prevention, personalisation, prediction and participation as well as promotion.

Preventive Role of Cardiac Resynchronisation Therapy in Heart Failure

The role of CRT is continually evolving, and recently has extended to patients with bradycardia requiring frequent ventricular pacing ($> 40\%$) and left ventricular ejection fraction (LVEF) $\leq 35\%$,⁵ who are candidates for a conventional pacemaker. A growing body of evidence shows that right ventricular (RV) pacing has a detrimental effect on left ventricular (LV) function and remodeling despite normal ejection fraction before implantation. Both pacing-induced cardiomyopathy⁷ and new-onset of HF⁸ are frequently encountered in patients undergoing RV pacing, even in those with less than 40% accumulative pacing and in the short-term (less than one month) pacing. Despite satisfactory response to CRT upgrading in patients with RV pacing-induced LV remodeling or

HF,⁹ this is a "wait-and-see" approach, especially for outpatients with infrequent echocardiographic examination. Therefore, pacing-induced LV dysfunction might be avoided with de novo implantation of CRT. The results of the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF trial) supported the superiority of CRT to RV pacing as demonstrated by the significant reduction of total mortality, urgent HF care, or an increase in LV end-systolic volume index in patients with HF and conventional indications for pacing.¹⁰ The inclusion criteria for the BLOCK-HF trial included patients with LV ejection fraction $< 50\%$, not confined to $< 35\%$ as in other HF and CRT trials. In terms of patients with bradycardia and normal ejection fraction, the Pacing to Avoid Cardiac Enlargement (PACE) trial and extended follow-up consistently demonstrated the superiority of CRT over RV pacing in prevention of LV remodeling and deterioration of systolic function, as well as reduction of HF in the long-term follow-up.^{11–13} However, preliminary results of the Biventricular pacing for atrioventricular Block to Prevent cArDiac dEsynchronisation (BIOPACE) trial showed that CRT failed to significantly improve outcomes compared to RV pacing in atrioventricular (AV) block (preliminary result, in annual scientific meeting in ESC 2014). Nevertheless, data from this trial should be interpreted with care due to the relatively high failure rate of implantation and lower accumulative ventricular pacing percentage (90% at one month), which might have an impact on the primary end-point. Currently, CRT is unlikely to completely replace conventional RV pacing, even in patients with high-degree AV block;

however, its preemptive role in HF deterioration and HF occurrence should be acknowledged although further study is necessary to fully elucidate its effects.

Personalisation and Predictive Medicine in Cardiac Resynchronisation Therapy

Non-responder and Super-responder

The concept of non-responders^{14,15} was proposed in CRT therapy since there is a wide range of response to CRT and around 30 % of patients do not respond to CRT. There remains a lack of standard criteria to define non-responders, but LV reverse remodeling is considered to be an acceptable parameter with better predictive value for cardiovascular mortality compared with other criteria.¹⁶ Numerous studies aiming to predict CRT responders have been conducted, including clinical, electrical and imaging predictors at time points pre-, during and post-implantation.¹⁷ Potential parameters to facilitate patient selection have included QRS pattern and width, LV ejection fraction and dyssynchrony parameters. However, no parameters have been found to conclusively identify responders to CRT; a composite scoring system with several strong predictors may be needed.

In addition, some patients demonstrate dramatic improvement after CRT, even approaching normal cardiac function; they are termed "super-responders".¹⁸ In these patients, a reduction of risk of ventricular arrhythmias has also been observed.¹⁹ Compared to non-responders, super-responders are understudied but the concept is clinically relevant for the secondary prevention of sudden death with CRT-defibrillator or CRT-pacemaker.²⁰

Vulnerable Patients in Conventional Pacemaker Indications

Despite encouraging outcomes of CRT in bradycardia patients, LV dysfunction does not develop in all patients receiving RV pacing; a proportion of population may be resistant to pacing-induced systolic dyssynchrony.^{21,22} Therefore not every patient should be given CRT due to its high cost and relatively high complication rate. It is important to select vulnerable patients who are likely to develop systolic dyssynchrony when undergoing frequent ventricular pacing in bradycardia. Although it would be desirable to identify baseline predictors related to pacing-induced systolic dyssynchrony, there are a lack data to inform patient selection. The presence of RV pacing induced ventricular dyssynchrony may direct DDDR/CRT-Pacemaker device implant in patients with heart block and normal LVEF. The Efficacy of the Presence of Right Ventricular Apical Pacing Induced Ventricular Dyssynchrony as a Guiding Parameter for Biventricular Pacing in Patients with Bradycardia and Normal Ejection Fraction (ENHANCE) trial aims to address this crucial clinical issue.

Identification of Candidates Developing CRT-induced Proarrhythmia

Another emerging issue is that CRT-induced proarrhythmia, which might be related to the LV lead located within the epicardial scar.²³ This is a rare but serious complication and is refractory to antiarrhythmic drugs. Switching off LV pacing presents a clinical dilemma since HF may deteriorate. Arrhythmia recurrence can be managed with catheter ablation but patients require a further intervention. An enhanced understanding of this complex clinical entity and early identification of patients developing CRT-induced proarrhythmia is important, and may amplify our knowledge of the potential complications of CRT.

Women and CRT

Clinical data have shown that women benefit more from CRT in comparison with men²⁴; however, fewer women than men were enrolled in CRT clinical trials. Greater recruitment of female candidates may improve the non-responders rate.²⁴ Although CRT is not recommended in narrow QRS patients,²⁵ in a study of individual patient data, women demonstrated benefit from CRT-defibrillator at a shorter QRS duration compared to men,²⁶ which highlights the importance of gender-specific medicine.

Participation of Cardiac Resynchronisation Therapy in Clinical Practice

Despite demonstrating substantial benefits, CRT is underutilised even in developed countries like US and Europe.²⁷ It was estimated that, between 2002–2013, 100,000–430,000 HF patients in the US were potential candidates for CRT but did not receive the implantation.²⁷ There are several reasons for the apparent gap between guidelines and real-world practice, the most important being risk and cost-related issues.

(1) CRT is an expensive therapy, which is an obstacle in terms of reimbursement. Currently, the benefit of CRT outweighs the cost of HF within health systems and CRT is considered a cost-effective treatment compared with optimal medical therapy or implantable cardioverter-defibrillator (ICD). Data shows that the additional cost-effectiveness ratio is \$7,320 per quality-adjusted life year. A study conducted in Europe (Belgium) found that CRT in New York Heart Association (NYHA) class III and IV patients resulted in an incremental cost-effectiveness ratio of about €11,200 per quality-adjusted life year.²⁸ Though CRT is a worthwhile investment in severe HF, its high expense hinders its use in developing countries.

(2) Another issue affecting the use of CRT in clinical practice is its relatively high complication rate due to the complicated anatomy of the coronary vein. Implantation requires greater experience, skill and training compared with ICD or RV pacing implantation. Risks associated with CRT implantation include implantation dissection, lead displacement and dislodgement as well as phrenic nerve stimulation.

(3) During a 20-year history, it is unsurprising that the benefits of CRT have been challenged, and was doubted its long-term results. A large percentage of patients received ICD despite showing indications for CRT. In addition, around on quarter of HF patients were implanted with RV pacing with frequent ventricular pacing percentage. More education with guideline-directed medical therapy in both patients and physician groups is required to tackle the low participation rate.

Promotion of Cardiac Resynchronisation Therapy in the Future

The development of CRT keeps evolving, and is now applied in hypertrophic cardiomyopathy; congenital heart disease with different phenotypes of HF (systemic LV failure, RV failure and single ventricular failure); RV failure due to pulmonary hypertension and in patients with HF with preserved ejection fraction.²⁹ The effectiveness of CRT is attenuated in atrial fibrillation, therefore a multimodal therapeutic approach, such as AV junction ablation³⁰ or pulmonary vein isolation combined with CRT, may accentuate the response to CRT by means of rate control. In order to overcome technical hurdles to the wide application of CRT, the development of new technology is required. Access route of LV leads need to be improved in difficult patients including transventricular passage or percutaneous

subxiphoid approach. The implantation of CRT using a sensor-based electromagnetic tracking system to facilitate LV placement has proven safe and successful.³¹ Multisite stimulation has emerged as a method of potentially overcoming non-response; this may be achieved by means of multiple leads or multipolar (quadripolar) LV leads.³² A leadless ultrasound-based technology for LV endocardial resynchronisation showed promising results in a pilot study.³³ Safer and more effective lead and system extraction will be required in the

event of system infection or dislodgement for CRT system. Last but not least, stand-alone devices with lower cost and remote monitoring will further consolidate the advantages of CRT.

In summary, from proof-of-concept studies to clinical trials, CRT is undoubtedly an important therapy for a subgroup of HF patients. Further studies and initiatives are required to increase its utilisation in eligible patients. ■

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