Cardiac resynchronisation therapy (CRT) is the most established non-pharmacological therapy for patients with advanced heart failure in the last decade. It is a device-based treatment modality which involves the implantation of an additional left ventricular lead through the coronary sinus to reach the free wall. This allows the simultaneous pacing of the septal wall with the use of the right ventricular lead, which can either be a pacing or defibrillator electrode. The right atrial lead will help to maintain atrioventricular synchrony, unless patients are having persistent atrial fibrillation. There has been compelling evidence from a number of multicentre clinical trials that CRT improves symptoms, exercise capacity and cardiac function as well as reduces heart failure hospitalisations and cardiovascular mortality in patients with advanced congestive heart failure. In the current American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines for heart failure and device-therapy, CRT in the form of pacemaker alone (CRT-P) or combined with implantable cardioverter defibrillator (CRT-D) is a class I recommendation (means absolutely indicated as supported by clinical trials) with level of evidence A (means good evidence from multi-centre clinical trials) for patients with New York Heart Association (NYHA) functional class III or ambulatory class IV heart failure symptoms despite optimal medical therapy, with left ventricular ejection fraction (LVEF) ≤35%, with sinus rhythm and QRS duration ≥120ms. However, the beneficial effects of CRT have recently been demonstrated in some selected subgroups of patients who may not fulfil the aforementioned criteria. The ESC 2010 updated guideline has recently included patients with mildly symptomatic heart failure, permanent atrial fibrillation (AF) and standard pacemaker indication which will be elaborated below.

CRT in NYHA class I or II heart failure

The effect of left ventricular (LV) reverse remodelling caused by CRT in patients with NYHA class II symptoms was previously reported in a few small-scale observational studies. However, it is not until the recent publications of the 2 randomised control trials, i.e. the REsynchronization reVerses Remodeling in Systolic left vEntricular dysfunction (REVERSE), and the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT), that the incremental benefit conferred by CRT in patients with NYHA class I or II heart failure symptoms has been confirmed. The REVERSE trial enrolled 610 patients with NYHA functional class I (18% patients) or II symptoms, sinus rhythm, LVEF ≤40%, QRS duration ≥120ms, and LV end-diastolic diameter ≥55mm. They were randomly assigned to CRT-ON or CRT-OFF group, and followed up for 12 months. The primary endpoint was the percentage of clinically worsened patients assessed by a clinical composite parameter, while the prospectively powered secondary endpoint was the change in LV end-systolic volume index (reverse remodelling) measured by echocardiography. At the end of 12 months, no significant difference was observed in the primary endpoint that 16% of patients in CRT-ON worsened in the clinical composite score when compared with 21% in CRT-OFF (P=0.10). However, a significant degree of reverse LV remodelling was observed among patients who received CRT-ON, and time to first heart failure hospitalisation was obviously delayed (hazard ratio [HR], 0.47; P=0.03). Interestingly, the extended follow up for 24 months was conducted in European patients (n=262) of the REVERSE trial, which gave rise to more promising results than that of the main study. In the CRT-ON group, 19% patients worsened compared with 34% in the CRT-OFF group (P=0.01). A progressive reverse remodelling was observed with CRT that accompanied by a significant delay in time to first heart failure hospitalisation or death (HR, 0.38; P=0.003). Of note, in both 12- and 24-month analyses, there was evidence of a significantly higher proportion of patients who showed an improvement of clinical composite score in the CRT-ON group. The MADIT-CRT trial included 1,820 patients with NYHA functional class I (15%) symptoms of ischaemic aetiology or class II of any causes, sinus rhythm, LVEF ≤30%, and QRS duration ≥130ms. Patients were assigned to implantable cardioverter defibrillator (ICD) or CRT-D treatment. During a mean follow up of 2.4 years, a 41% reduction in the risk for non-fatal heart failure events was demonstrated with CRT-D, whereas the annual mortality rate showed no difference between the groups. The CRT-D group had more significant LV reverse remodelling than those treated with ICD only, which was also predictive of favourable clinical outcomes. Furthermore, in pre-specified subgroup analyses of both REVERSE and MADIT-CRT trials, patients with QRS duration ≥150ms exhibited the greatest benefit from CRT. Therefore, in the “2010 Focused Update of ESC guidelines on device therapy in heart failure”, CRT preferentially by CRT-D has been recommended to patients in NYHA functional class II who have a LVEF ≤35%, QRS duration ≥150ms, and sinus rhythm, as a new class I indication, to reduce morbidity or to prevent disease progression.
CRT in permanent AF

The prevalence of AF is increasingly high with the severity of heart failure, that estimated from 5-20% in NYHA class I or II to 25-50% in class III or ambulatory class IV patients. Its occurrence is usually associated with older age, more comorbidity and worse prognosis. As large, multicentre CRT clinical trials enrolled predominately patients with sinus rhythm, there are inadequate data with regard to the impact of CRT in patients with AF. However, several prospective observational cohort studies compared the effect of CRT between patients with permanent AF and sinus rhythm, which were further reported in a meta-analysis. It is concluded that patients in permanent AF benefit substantially and significantly from CRT, with greater improvement in echocardiographic measurements and smaller improvement in functional outcomes, when compared with patients in sinus rhythm. Since the majority of AF patients enrolled had atrioventricular nodal ablation and a wider QRS duration of ≥130ms, the evidence-based consideration considered the inclusion of these criteria. In the 2010 update of ESC guideline, CRT is recommended for patients with permanent AF who have NYHA class III or ambulatory class IV symptoms, LVEF ≤35%, and QRS duration ≥130ms (IIa indication). The requirements are similar in the current ACC guideline except that QRS duration ≥120ms is adopted instead. In both, complete ventricular capture to maximise the benefits is emphasised, in the form of either pacemaker dependency induced by atrioventricular nodal ablation or adequate rate control such as through beta-blockers or digoxin therapy.

CRT in standard pacemaker indication

It has been recognised that the detrimental effects of conventional right ventricular apical (RVA) pacing on LV function and symptoms, in particular in patients with congestive heart failure. Such pacing causes an abnormal LV electrical activation sequence, manifested as LBBB on surface ECG, which leads to an electromechanical dyssynchrony and subsequent asymmetric hypertrophy, increased mitral regurgitation, and decreased EF. Several observational studies demonstrated that in patients with preexisting LV dysfunction and an indication for standard pacing, CRT improved LV systolic function, exercise capacity and quality of life, when compared with RVA pacing. Moreover, a reverse remodelling effect of upgrading to CRT from long-standing RVA pacing was observed in patients with severe ventricular dysfunction and NYHA function class III symptoms, regardless of QRS width or duration of prior RVA pacing. Therefore, CRT is recommended for patients with a concomitant class I pacemaker indication (ESC guideline) or anticipated frequent ventricular pacing (ACC/AHA guideline), who have LVEF ≤35%, QRS <120ms, and NYHA class III or ambulatory IV symptoms (IIa indication) and NYHA class I or II (IIb indication).

Future perspectives on exploration of new indications for CRT

CRT is intended to treat cardiac dyssynchrony commonly observed in heart failure, which is manifested as a prolonged QRS complex of ≥120ms and being adopted in current guidelines. However, the ECG criteria are not ideal in identifying mechanical dyssynchrony. With the application of different imaging modalities such as echocardiography, lack of mechanical dyssynchrony has been found to occur in about one-third of patients with a wide QRS complex (≥120ms). Conversely, on the other hand, presence of systolic dyssynchrony occurs in 40-50% of heart failure patients with a narrow QRS complex (<120ms). Therefore, it has been suggested that patients who have a narrow QRS complex and coexisting evidence of systolic dyssynchrony may also benefit from CRT. Several single-centre studies were initiated to observe the role of CRT in this special group of patients, which resulted in the improvements of functional class, exercise tolerance, quality of life and LV remodelling after a follow up at 3 to 6 months. However, in a multi-centre trial, the Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ), failed to provide promising results. RethinQ was the first randomised study in patients with a narrow QRS complex, which recruited 172 patients in NYHA class III heart failure and with an indication for ICD implantation. All patients had a QRS width of <130ms but presence of mechanical dyssynchrony assessed by echocardiography. The primary endpoint, i.e. the increase in peak oxygen consumption, did not reach a significant difference between CRT and control groups. However, improvement of NYHA class was observed in the CRT arm. Nonetheless, it is worthy of note that the selection of echocardiographic dyssynchrony parameter was not stringent, and the primary endpoint using gaseous exchange assessment was a tedious procedure. Furthermore, the choice of echocardiographic equipment could have been suboptimal while follow up was short. The ongoing study, Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) trial, which will enrol more than 1,000 patients, utilises advanced echocardiographic techniques and investigates all-cause mortality and hospitalisation for cardiovascular events. This will, hopefully, provide a more definite answer.

The benefits of CRT in patients with a normal EF and standard indications for pacing were investigated in a first prospective, randomised, controlled study, the Pacing to Avoid Cardiac Enlargement (PACE). This study enrolled 177 patients who were implanted with CRT device and randomly assigned to biventricular pacing and RVA pacing arms, where the primary endpoints were LVEF and LV end-systolic volume at 12 months. As a result, conventional RVA pacing induced adverse LV remodelling with a reduction of LVEF, which was prevented by bi-ventricular pacing. However, due to the low rate of clinical events within a relatively short period of follow up, the study was not powered to test the significant differences in clinical outcomes. Therefore, it is unknown if the favourable responses to CRT measured by echocardiographic parameters would be translated into a better prognosis in these patients. This will be addressed by the BIOPACE study which is currently underway.
Conclusion

CRT is one of the most rapidly evolving fields in heart failure management. It requires concerted efforts of heart failure specialists, electrophysiologists as well as cardiac imaging specialists, in particular echocardiographers. Therefore, a multi-disciplinary approach for patient management is essential, which starts from patient assessment, stretches through device implantation, and continues with patient follow up. Currently, researchers are actively exploring ways of fine-tuning this therapy to reach an even higher response rate, and exploring new indications to benefit more patients. Despite published data from multi-centre trials that have included more than 7,000 patients to date, more study results are expected in the few years to come. As the evidence of CRT benefits is compelling, primary care physicians and specialists who encounter heart failure patients shall bear the possibility of including CRT as an effective treatment option.

References