Introduction

Heart failure (HF) is one of the most important causes of morbidity and mortality in the industrialized world.[1] The prevalence of symptomatic HF is estimated to range from 0.4 to 2.0% in general European population.[2] The incidence increases rapidly with age, and in Europe, the mean age of HF population is 74 years.[3–6]

Left ventricular (LV) activation delay, as indicated by widening of the QRS complex on a twelve lead electrocardiogram (ECG), is present in approximately one-quarter to one-third of heart failure patients. This dyssynchrony leads to physiological changes in the structure of the heart, an enlargement and rounding of the left ventricle referred to as "remodeling". Widening of the QRS complex is also a significant predictor of worsened LV systolic dysfunction and poorer outcomes in patients with heart failure.[7] Cardiac resynchronization therapy (CRT) has been used to improve both the electrical and mechanical dyssynchrony in heart failure patients to improve patient morbidity and mortality, and prevent and potentially reverse the remodeling.[8]

Cardiac resynchronization is a pacing modality utilizing an LV pacing lead with the goal of re-synchronizing myocardial contraction in patients with heart failure, depressed systolic function, and significant LV activation delay. CRT is thought to produce a reduction in intraventricular dyssynchrony and more favorable hemodynamics by placement of a pacing lead, either endovascularly via a coronary sinus tributary, or epicardially with direct placement on the lateral LV wall via a thoracotomy. CRT was originally indicated in patients with significant LV dysfunction, defined as a left ventricular ejection fraction (LVEF) $\leq$ 35%, with New York Heart Association (NYHA) class III-IV heart failure symptoms, and with a QRS duration $\geq$120ms on optimal medical therapy, which varies in definition.[9-12] Therefore, the focus of CRT has expanded to include not only the treatment of advanced heart failure but also the prevention of clinical deterioration in patients with milder heart failure.[13-17] More recently, the indications for CRT have expanded to include patients with an LVEF $\leq$35%, a QRS duration $\geq$120ms, and minimally symptomatic heart failure (NYHA class I-II) on optimal medical therapy.

Multiple large scale clinical trials have been conducted demonstrating the benefits of CRT. Early trials of CRT compared CRT pacemakers with optimal medical therapy alone in patients with advanced heart failure.[13,14] With the concomitant development of the intracardiac defibrillator (ICD), comparisons

used in the large clinical trials changed to compare patients with ICDs with and without CRT.[17] Currently, the vast majority of candidates for CRT devices also have an indication for an ICD, therefore, the large majority of patients receiving CRT receive a CRT defibrillator (CRT-D) as opposed to a CRT pacemaker (CRT-P). CRT-P devices are occasionally placed in patients who wish to avoid ICD shocks or in patients with an indication for frequent ventricular pacing due to conduction disease who have a left ventricular ejection fraction between 36-50%. Only one randomized trial of CRT contained arms with both CRT-P and CRTD and was underpowered to compare them. Therefore, the incremental benefit of a CRT-D over CRT-P in terms of survival is unclear.[15] The early trials of CRT focused on "softer" endpoints including changes in quality of life (QoL) scores, NYHA functional class, and six minute hall walk times.[7] As these benefits of CRT were repeatedly seen, the benefit of CRT in terms of "harder" endpoints was also established, including reversal of ventricular remodeling (reduction in LV volumes and return to more normal shape with improvement in function), improvement in maximal oxygen consumption (MVO2), reduction in heart failure admissions, and improvement in all-cause mortality.[11-17]

While CRT has been one of the most important therapeutics for the treatment of heart failure over the past 15 years, not every patient who meets the guideline criteria for this therapy responds to the intervention. While the percentage of "non-responders" to CRT fluctuates greatly based on how one defines "response "(e.g., reduced mortality, decreased readmissions, or improved patient report of symptoms), it is generally estimated that 30-40% of patients meeting implantation guidelines fail to respond.[11] Therefore, how to predict who will respond to CRT remains an important and largely unanswered question.[11] Prediction of response to CRT is an important goal in order to tailor this therapy to patients most apt to derive benefit.[11] In addition, the specter of patient harm in certain subgroups has been raised.[12] More recently, based on subgroup analyses from the large randomized controlled trials as well as single center cohort studies, bundle branch morphology has been shown to be an important predictor of response; patients with a left bundle branch block (LBBB) are more likely to respond than patients with a non-LBBB morphology (right bundle branch block (RBBB) or non-specific intraventricular conduction delay(IVCD)).[12,18,19] In addition, QRS duration is also an important factor independent of its linkage to bundle branch block morphology. In a recent study from Medicare claims data, patients with a LBBB morphology and a QRS duration $\geq$150 ms had better outcomes following CRT compared with patients with either a LBBB and a QRS duration $\leq$150 ms or a non-LBBB regardless of QRS duration.[20]

The new 2013 United States guidelines for the implantation of CRT capable devices take both bundle branch block morphology and QRS duration into consideration in determining appropriateness for device implantation.[21] It is not yet clear how these new guidelines will improve response rates, but the improvements are expected to be incremental, with the issue of non-responders not completely resolved. Not all potential causes of non-response were included in the new guidelines or established in individual studies.[22]