INTRODUCTION
Heart failure accounts for more than 1.1 million hospitalizations and 58,000 deaths per year in the United States, with an estimated prevalence of 5.7 million patients (1). Accordingly, a significant amount of health care resources are devoted to caring for patients with heart failure with an estimated cost of $32.7 billion per year (1). While refinement of medical therapy has led to impressive improvements in morbidity, an important role for implantable rhythm management devices in the treatment of heart failure has emerged. In addition to the use of implantable cardioverter-defibrillators (ICDs) for prevention of sudden cardiac death (SCD), biventricular (BiV) pacing devices have been increasingly used in treatment of dyssynchronous heart failure. This strategy is referred to as cardiac resynchronization therapy (CRT) and will be the focus of this lecture.

MECHANISM OF DYSSYNCHRONY – DEFINING SUCCESS WITH CRT
Conduction abnormalities are a common feature of systolic heart failure. Approximately 25-40% of patients with cardiomyopathy have a prolonged QRS complex (>120ms) on the ECG indicating electrical dyssynchrony of the left ventricle (LV) (2-4). Delayed activation occurs as depolarization spreads slowly through the myocardium without the aid of a healthy bundle branch and/or Purkinje conduction pathway, causing intraventricular dyssynchrony (lateral and inferolateral segments of the LV contract later than the septal segments) and/or interventricular dyssynchrony (between RV and LV). Dyssynchronous contraction that ensues is mechanically less efficient at ejecting blood from the ventricle into the systemic circulation, and additionally, further impairs diastolic filling (5,6). Hemodynamic derangements associated with ventricular dyssynchrony lead to both valvular and contractile dysfunction. The goal of CRT, thus, is to restore synchronous contraction of the LV and optimize the delay in contraction between LV and RV. CRT is typically accomplished through BiV pacing using a standard right ventricular lead and a left ventricular lead placed adjacent to the inferolateral or lateral wall via the coronary sinus under fluoroscopic guidance. Electrical stimulation delivered at both sites restores synchronous ventricular activation, resulting in improved hemodynamic parameters and favorable remodeling of the LV. Specifically, systolic blood pressure, stroke volume, cardiac output, dP/dtmin (active relaxation), dP/dtmax, end-systolic elastance, stroke work, and ventricular-arterial coupling are improved with CRT (7,8). Furthermore, CRT therapy has been shown in multiple randomized controlled studies to improve functional status and exercise capacity (9-16) and to reduce hospitalizations and mortality (12,13,17).

The underlying mechanisms of the demonstrated benefits of CRT are an exciting area of ongoing clinical and laboratory investigations. Successful CRT results in improved left ventricular ejection fraction (LVEF) and decreased end diastolic and end systolic dimensions (i.e., reverse ventricular remodeling) (9,13,15). The restoration of mechanical myocardial contractile synchrony optimizes the effort and energy expenditure in the left ventricle. In contrast to pharmacologic means of improving systolic function (β-agonists), improvements in cardiac performance with CRT are achieved with slight reductions rather than increases in myocardial metabolic demand (18). Additionally, CRT has been shown to reduce mitral regurgitation (MR) (9,13,15,19). Acute improvements are observed when papillary muscle dyssynchrony is a contributing factor in MR, while reverse ventricular remodeling with chronic CRT contributes to further reductions in MR (19-22). Although substantial improvements in quality of life scores and New York Heart Association (NYHA) functional class have been consistently reported, changes in global LVEF after instituting CRT are relatively small (~5%). It has been suggested that restoration of rotational dynamics and global cardiac mechanics may be more important than improving LVEF in determining effectiveness of CRT. Indeed, it has been recently demonstrated that improvements in ventricular twist mechanics correlate well with response to CRT therapy (23,24).

Though CRT is capable of acutely improving global ventricular systolic and diastolic function by improving mechanical function of the heart, the precise molecular and electrophysiological mechanisms contributing to benefits in long-term functional status and mortality are still actively being studied. Enduring benefits may be
related to the impact of CRT on the derangements in the cardiac autonomic system and pathologic changes that occur at the cellular and molecular level in heart failure. Initial causes of cardiac insult (i.e. infarct) lead to acute adaptations which seek to overcome depressed cardiac function. If the depressed pump function becomes chronic, these compensatory mechanisms can lead to maladaptive remodeling with detrimental effects on outcome. In addition to remodeling that occurs at a macroscopic level, expression of autonomic receptors and contractile elements are altered with progression of heart failure. CRT has been shown to reverse molecular remodeling, restoring gene expression in contractile elements (more fast α -myosin) and improving excitation-contraction coupling and calcium handling (increased sarcoplasmic reticulum calcium ATPase 2-a) (25). In animal models of dysynchronous heart failure, greater rest and β-adrenergic stimulated myocyte function was demonstrated with CRT in association with upregulation of β1-adrenergic receptors and improvement in adenylate cyclase activity (26). This is a potential contributing mechanism of improved functional capacity observed with CRT. Furthermore, regional heterogeneity of action potential duration and alterations in potassium and calcium currents that exist in cardiomyopathy were attenuated using CRT in an animal model of heart failure(27). As many as 50% of deaths due to heart failure are sudden and unexpected, largely due to lethal arrhythmias(28). These arrhythmias are primarily re-entry in origin and arise under conditions with regional differences in electrical conduction and refractoriness such as that occurring with pathological electrophysiologic remodeling seen in heart failure. Mitigation of this remodeling may play a role in the observed reduction in arrhythmias and mortality with CRT(27).

INDICATIONS, PATIENT SELECTION AND OPTIMIZATION

Standard indications for CRT are LVEF < 35% with QRS >120 msec, sinus rhythm, and NYHA III or ambulatory class IV after optimal medical therapy (Class I, Level of Evidence A) (29) according to the published ACC/AHA/HRS guidelines. Left bundle branch block (LBBB) is the most common conduction abnormality in patients undergoing CRT (~75%), with the inferolateral segments of the LV activated last (3). CRT can be employed in patients with similar clinical and ECG criteria but who are in atrial fibrillation rather than sinus rhythm (Class IIa, Level of Evidence B) as well as in patients with advanced heart failure with frequent dependence on ventricular pacing(Class IIa, Level of Evidence C). More recent trials have employed CRT in less symptomatic patients (NYHA I or II) resulting in some reduction in heart failure events as well as reverse remodeling and improvements in ejection fraction(30-32).

Although the demonstrated benefits of CRT are impressive, approximately 30% of patients meeting standard selection criteria are non-responders who show no functional benefit or regression of disease process after initiation of therapy. This may be due to heterogeneity of the disease process leading to end-stage heart failure (ischemic vs. non-ischemic, LBBB vs. RBBB, degree of inter/intra-ventricular conduction delay) as well as variability in the procedural aspects (precise lead location, device settings/optimization). An association has been shown between higher non-response rates and patient parameters such as ischemic cardiomyopathy, sustained pre-implant monomorphic ventricular tachycardia, severe mitral regurgitation, larger LV dimensions (>75mm LVEDD)(33). Refinement of selection criteria for patients who will benefit from CRT is an evolving area in which echocardiography is playing a prominent role.

Though electrical dyssynchrony typically is associated with mechanical dyssynchrony, each may occur in isolation. Patients with isolated electrical dyssynchrony and synchronous ventricular contraction prior to therapy would be unlikely to respond to CRT. On the other hand, some patients have evidence of isolated mechanical dyssynchrony and QRS duration less than 120 msec (not meeting standard CRT indications). Several smaller studies in these patients with isolated mechanical dyssynchrony demonstrated clinical response to CRT(34-36) although a recent prospective, randomized controlled trial was unable to demonstrate clear improvement(37). These discrepant results may be due in part to the lack of an ideal or standardized method of assessing mechanical dyssynchrony.

By measuring mechanical dyssynchrony, echocardiography has been used as a screening tool for identifying patients who will benefit from CRT. Various techniques have been used with variable success, including M-mode definition of septal to inferolateral wall motion delay, pulsed wave tissue Doppler delay of peak systolic velocity, color Doppler tissue imaging with offline analysis of segmental velocity or longitudinal strain, and speckle-tracking echocardiography used to determine segmental longitudinal or radial strain delay. A multicenter trial evaluating several conventional echocardiographic modalities- M-mode, pulsed wave Doppler and tissue Doppler methods as predictors of clinical or LV remodeling response with CRT was unable to recommend any of these methods for improving patient selection despite promising single center studies (38). Other new echocardiographic techniques
such as radial strain determined by speckle-tracking analysis may help identify patients who will respond to CRT. In brief, routine B-mode gray-scales images are analyzed by specialized software for frame-by-frame movement of natural acoustic markers (i.e. speckles) present in ultrasound tissue images over the cardiac cycle. Strain, defined as change in length along a given axis, is quantified and reflects expansion or compression of tissue. In cardiac tissue this generally measured longitudinally (base to apex), circumferentially, or radially (epicardial to endocardial towards a central point). Commercially available software packages can average regional strain values according to standard LV segmental divisions, allowing comparison of amplitude and timing of cardiac mechanical activity between segments. Recent studies suggest that radial strain dyssynchrony (differences in timing of peak systolic strain) may be a good discriminator of echocardiographic improvement with CRT when compared with other techniques (39,40).

Several 3-dimensional (3D) echocardiographic techniques have been used to identify mechanical dyssynchrony in patients who are candidates for CRT. Using ECG-gated full volume 3D echocardiography, quantification of mechanical dyssynchrony based on volumetric changes has been described (41), and has correlated well with Doppler based techniques (42). Real time 3D echocardiography is encouraging and permits comparison of mechanical synchrony in all segments of the ventricle within the same cardiac cycle, however it is currently limited by low temporal resolution. Amongst the latest advances in this field is the merging of speckle tracking technology and 3D echocardiography allowing for measurement of dyssynchrony between regional myocardial segments in a 3D volumetric space (43). It is important to recognize that although speckle tracking based strain imaging and 3D-echocardiography are being increasingly used, they have not yet positioned themselves as mainstream modalities at this time. A recent consensus statement by the ASE recognizes that many of these parameters are under investigation and that an ideal approach has not yet been identified. While echocardiographic measures of dyssynchrony can contribute to the decision whether or not to undergo CRT in patients with unclear indications (borderline LVEF, ambiguous NYHA status), it is not recommended to use these parameters as a sole basis to withhold CRT from patient otherwise meeting accepted standard criteria at this point (44).

Besides improving patient selection, echocardiography also aids in optimizing CRT settings. In CRT devices, the A-V delay should be programmed to provide consistent ventricular pacing without competition from intrinsic pathological conduction. This typically means a shorter A-V delay than is set with standard dual-chamber pacers, in which intrinsic A-V conduction is preferable and encouraged with device settings. While standard settings usually suffice, pulsed wave Doppler interrogation of transmittal diastolic flow can help customize A-V delay to optimize atrial contribution to preload. This is achieved by identifying an interval that results in clear and separate E and A waves and ensuring termination of the A wave prior to the onset QRS. The delay between the pacing stimulus delivered through the RV and LV leads can also be customized. While this interventricular (V-V) delay is typically initially set at zero (i.e. simultaneous delivery of pacing stimuli to the LV and RV) by the device manufacturer, it can be varied to optimize stroke volume or minimize mechanical delay based on echocardiographic parameters. Some non-responders will improve with optimization of V-V delay. In a single center study, the rate of non-responders was reduced from the typically reported 20-30% range to 10% with optimized V-V delay (45). Unfortunately, due to the resource intensive nature of echocardiographic optimization of device settings, this approach is often reserved for patients who meet traditional selection criteria but fail to respond with basic initial settings (46).

PERIOPERATIVE ANESTHESIA CONSIDERATIONS

Anesthetic management of patients undergoing placement of CRT devices is primarily complicated by underlying advanced heart failure and other co-morbidities. This, in combination with variable tolerance of the supine position by NYHA class III or IV patients will influence the choice of sedation versus general anesthesia. Monitoring of electrical and mechanical cardiac activity (heart rate and pulse rate) is crucial in any EP procedure. Of the standard monitors, continuous ECG and peripheral pulse monitoring are particularly useful, and the need for invasive arterial monitoring is typically dictated by the patient’s preoperative condition. Cardiac arrhythmias are common during intracardiac lead placement and may not be tolerated well hemodynamically. As many of patients presenting for CRT have LBBB, transient complete heart block due to inadvertent manipulation of the right bundle during lead placement is a particular concern. Surface defibrillation/pacing pads should be placed in all patients and a functional defibrillator should be readily available. Many patients eligible for CRT therapy will also meet criteria for ICDs. In some patients a BiV-ICD is implanted as their initial device, while others may have an in situ ICD replaced with a BiV-ICD (“BiV upgrade”). In the latter situation, the procedure is typically shorter, involving only replacement of the generator and the addition of one pacing lead (CS lead to the LV). In either case, defibrillator function is often tested at the time of implant and should be anticipated. Myocardial pacing thresholds during lead placement can be
affected by clinical conditions including acidosis, electrolyte abnormalities, or myocardial ischemia. Of note, LV pacing may capture the phrenic nerve, resulting in stimulation of the diaphragm. This may be masked by paralytic agents, therefore, communication with the proceduralist regarding timing and use of neuromuscular blockade is recommended. Proper placement of the LV lead in the coronary sinus may vary significantly in difficulty and duration amongst patients and is often not predictable. Uncommon complications such as coronary sinus dissection or perforation can occur. Cardiac perforation leading to tamponade is a potentially life-threatening complication and must be considered in the differential diagnosis of hypotension in patients undergoing CRT. Occasionally the procedure is abandoned due to unfavorable coronary venous anatomy, great difficulty in accessing existing veins, or inability to secure the lead in an acceptable position; these patients can be referred for surgically placed epicardial leads.

Perioperative management of patients with CRT devices undergoing non-EP related surgical procedures is similar to patients with other cardiac rhythm management devices with some notable exceptions. It is important to recognize that the settings on a typical dual chamber pacer (right atrial and right ventricular leads) are chosen to minimize RV pacing, while CRT devices are programmed to achieve ventricular pacing virtually 100% of the time. While RV pacing produces a LBBB pattern that is easily recognizable, the 12-lead ECG with biventricular pacing may show a narrow-complex QRS with a different axis. Programming the device to an asynchronous mode above the intrinsic rate is usually sufficient to maintain consistent ventricular pacing. However, some biventricular pacing devices lack a DOO setting. Fortunately, the use of electrocautery discrimination software in modern devices may reduce pacer inhibition, especially if the electrocautery dispersion pad is placed at a remote site from the device and electrocautery use is limited to short bursts. Pacer dependence should be determined pre-operatively; brief periods of inhibition may be tolerated well as many patients with a CRT device are not dependent. Electrocautery has the potential for causing device reset, this should be addressed with post operative interrogation as recommended by society guidelines and individual manufacturers. As the majority of CRT devices are combined with ICDs, the pacing features are not altered by placement of a magnet over the device. That is, a pacing inhibited mode can not be changed to asynchronous pacing by placing a magnet over the device. Standard perioperative management of pacing and ICD devices otherwise applies. This subject is discussed in detail in a practice advisory published by the American Society of Anesthesiologist(54) and includes preoperative device interrogation to determine underlying rate and rhythm, adequacy of battery life, pacing and sensing thresholds, and adjustment of rate responsiveness/rest modes. ICD functions should be disabled if monopolar electrocautery use is planned and monitoring of rhythm and rate should be continued in the postoperative period until defibrillation capabilities are re-enabled. Consideration should be given to choice of surgical cauterization methods, availability of emergency pacing/defibrillation, postoperative monitoring of rate and rhythm and follow-up interrogation of device to verify or restore settings as well (54,55).

SUMMARY

CRT represents a valuable therapeutic modality that allows optimization of ventricular function in patients with heart failure and electrical conduction delays. The benefits of CRT are well established and the success rate of therapy will likely improve as procedural techniques and patient selection criteria are further refined. Improved understanding of these CRT devices and the principles behind the therapy will aid practitioners caring for patients with heart failure.

REFERENCES


2. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008;52:1834-43.


Winter S, Nesser HJ. Echocardiographic aspects of multisite pacing in patients undergoing cardiac resynchronization therapy. Anaesthesiol 2007;20:261

Rozner MA. The patient with a cardiac pacemaker or implanted defibrillator and management during anaesthesia. Curr Opin Anaesth 2007;20:261-8.