

Prediction of Response to Cardiac Resynchronization Therapy

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Abstract

Cardiac resynchronization therapy with biventricular pacing improves quality of life and survival in individuals with systolic heart failure. A significant issue with cardiac resynchronization therapy at the present time is the clear identification of responders versus non-responders. Various clinical, electrocardiographic and echocardiographic predictors of response have been described. Most clinical trials have utilized QRS widening as marker of ventricular dyssynchrony. However, 20 – 30% of patients satisfying these criteria do not respond well to resynchronization. Newer criteria for detection of ventricular dyssynchrony are emerging. Echocardiographic evidence of ventricular dyssynchrony has been found in those with normal QRS duration. Standard deviation of time to peak myocardial velocity measured by tissue Doppler imaging is a promising parameter which predicts reverse remodeling after resynchronization. Non-contact mapping and magnetic resonance imaging have been used in identifying optimal site for left ventricular pacing. Newer magnetic resonance imaging techniques are being developed for the evaluation of ventricular dyssynchrony.

Keywords: cardiac resynchronization therapy; biventricular pacing; heart failure; echocardiography.

Introduction

Several randomized trials [1] [2] [3] [4] [5] and meta-analyses [6] [7] have shown that cardiac resynchronization therapy (CRT) with biventricular pacing provides symptomatic relief in patients with heart failure refractory to pharmacological therapy. A systematic review including a meta-analysis of nine trials concluded that CRT also reduces all-cause mortality [7]. The recently published Cardiac Resynchronization - Heart Failure (CARE-HF) trial has also confirmed the mortality benefit of CRT [8]. All clinical trials to date, have used prolonged QRS duration, 120 milliseconds or longer, as entry criteria. However, these studies have documented that about 30% of patients do not improve as a result of CRT [9]. It is also possible that selection of left ventricular pacing sites may predict response rates. Since CRT is an expensive treatment modality, beyond the reach of most of the world's population, accurate methods of identifying those who will respond to it are essential. This review aims at evaluating the current evidence to support the various parameters useful in identifying the potential responders.

Various methods of predicting the response to CRT has been investigated. Electrocardiography [10], non-contact mapping [12], echocardiography [11], radionuclide angioscintigraphy and magnetic resonance imaging [13] have been utilised for identifying patients who are likely to respond to CRT as well for selection of optimal pacing site.

Clinical Selection Criteria

Patients in NYHA Class III – IV heart failure, not responding to optimal pharmacological therapy are generally considered for CRT. Response to CRT is similar in those with ischemic cardiomyopathy and idiopathic dilated cardiomyopathy. The percentages of responders with improvement in NYHA class of one or more grade is comparable in both groups - 65% vs 71% [14].

Electrocardiographic Parameters

QRS Duration

The 12 lead ECG has been the mainstay of patient selection for CRT. A broad QRS complex indicates electrical delay that may correlate with the mechanical dyssynchrony and reversible by CRT. QRS duration of more than 120 milliseconds (ms) is the criterion that is widely used in clinical trials [7] and the basal QRS duration significantly correlates with the improvement in left ventricular systolic function [15]. There is a correlation between the QRS width and the degree of dyssynchrony. Severe dyssynchrony as evidenced by septal to lateral wall delay of more than 60 ms was observed in 27% of patients with narrow QRS complex (<120 ms), 60% with intermediate QRS duration (120 – 150 ms), and 70% with wide QRS complex (>150 ms) [16].

Responders exhibit a significant reduction in QRS duration after CRT. More than 50 ms reduction in QRS duration is highly specific (88%) but not sensitive (18%) to predict response to CRT [17]. This conventional wisdom of choosing only patients with wide QRS has been questioned recently. About one fourth to half of patients with heart failure and “normal” QRS duration (< 120 ms) have intraventricular dyssynchrony [18] [15] and may improve with CRT [19].

Bundle Branch Block Pattern

Left Bundle Branch Block

Left bundle branch block (LBBB) is associated with dyssynchrony of contraction between the septum and lateral wall of the left ventricle. The contraction of interventricular septum is early relative to the delayed contraction of the posterolateral free wall. Failure of simultaneous contraction of opposing LV walls reduces peak systolic pressure. Twenty to 30% of patients with symptomatic heart failure have ECG evidence of LBBB [11].

Right Bundle Branch Block

Patients with RBBB have also been shown to have significant improvement in functional class, exercise time and peak oxygen consumption with CRT. But most patients with RBBB (82%) also had either left anterior fascicular block or left posterior fascicular block. Hence the improvement may be due to concomitant left-sided conduction abnormalities [20].

Non-Contact Left Ventricular Endocardial Mapping

Non-contact mapping can identify regions of slow conduction within the left ventricle. Pacing outside these slow conduction areas increases cardiac output and dt/dt_{max} significantly. In patients in whom leads have already been implanted in these slow conduction areas, better results can be obtained by pacing the left ventricle 32 ms before the right ventricle [21].

Radionuclide Angioscintigraphy

Basal ventricular asynchrony and resynchronization by CRT can be measured by radionuclide angioscintigraphy [22]. Both interventricular and apicobasal dyssynchrony can be calculated. Patients with large electromechanical dyssynchrony benefit most from CRT. A significant interventricular dyssynchrony (> 60 ms) has a positive predictive value of 83% to predict an improvement of LVEF [22].

Two novel parameters which can be measured by equilibrium radionuclide angiography are synchrony (S) and entropy (E). Complete synchrony is indicated by an S value of 1 and its

absence by 0. Entropy measures the disorder in the region of interest, a value of 1 denotes random contraction and 0 full synchrony. Phase angle (ϕ) which represents the timing of regional contraction has also been used in the evaluation of synchrony. Phase angle is calculated from gated blood pool time versus radioactivity curve. Standard deviation of phase angle used as a marker of synchrony has been shown to indicate the beneficial effects of CRT. It has strong prognostic value in patients with non-ischemic dilated cardiomyopathy, which is superior to LVEF [23].

Echocardiography

Atrioventricular, intraventricular and interventricular dyssynchrony can be measured by echocardiography. Left ventricular filling time will be reduced in the presence of atrioventricular dyssynchrony. It is measured from the onset of the E wave to the end of the A wave on mitral Doppler and if less than 40% of the cardiac cycle is indicative of dyssynchrony [11]. A prolonged aortic pre-ejection time (> 140 ms) is a marker of intraventricular dyssynchrony. It is measured as the time from the onset of QRS to the beginning of flow in the aortic Doppler. Pulmonary pre-ejection time is measured on similar lines and a difference of more than 40 ms between aortic and pulmonary pre-ejection periods indicates interventricular dyssynchrony [11]. M mode echocardiography has been used to calculate the septal-to-posterior wall motion delay measured as the time difference between the maximum displacements of septum and posterior wall. A delay of > 130 ms has been shown to predict reverse remodeling after CRT with a positive predictive value of 80% [24]. Echocardiography may also facilitate the placement of the left ventricular lead in an optimal position based on identification of dysynchronous segments.

Tissue Doppler Imaging

Tissue Doppler Imaging (TDI) can be used to assess the regional electromechanical delays. This can be measured from the onset of QRS to the start of systolic shortening (S wave). Difference between the regions of earliest and latest regions of contraction gives the dispersion of intraventricular contraction. Dispersion of more than 40–50 ms may provide an index of intraventricular dyssynchrony. The extent of the LV base displaying delayed longitudinal contraction, as detected by TDI before CRT, predicts long-term efficacy [25]. The greatest difference in time to peak velocity between any of 12 left ventricular regions also indicates intraventricular dyssynchrony. Standard deviation of time to peak myocardial velocity from 6-basal and 6-mid left ventricular segments has been shown to be a powerful predictor of reverse remodeling after CRT [26].

Strain Rate Imaging

Strain Rate Imaging (SRI) data is calculated from TDI data. The strain rate (velocity of deformation) can be estimated by calculating the velocity gradient between two points with the equation: strain rate = $(v[r] - v[r + \Delta r]) / \Delta r$ [26]. It is less dependent on image quality and less subjective than visual assessment of endocardial border motion. Tracking of myocardial deformation with this technique has a higher time resolution than magnetic resonance imaging. Hence it can document transient changes in deformation patterns such as post-systolic shortening [27]. CRT can reverse abnormal myocardial strain distribution. Septal-lateral wall difference in mid-segmental peak strain has been reversed by CRT [28].

Post Systolic Shortening

Techniques of TDI and SRI are combined to look for post systolic shortening (PSS) or delayed longitudinal contraction. It is an early diastolic contraction after the closure of aortic valve and is an indirect marker of systolic asynchrony, though it may rarely occur in normal individuals [29].

Contrast Variability Imaging

Contrast variability imaging has been used to quantify cardiac dyssynchrony to assess resynchronization achieved by CRT. In this technique, echo-contrast is infused slowly and gated images are acquired before and during contrast appearance. Quantitative assessment of resynchronization similar to that obtained by tagged magnetic resonance imaging (MRI) is feasible [30].

Three – dimensional Echocardiography

Three-dimensional echocardiography allows rapid and accurate evaluation of LV volumes and performance. Coupled with appropriate analytic software, this technique allows the detection of delayed contraction of LV segments and can be used to select the optimal pacing site during CRT [31]. Real-time three-dimensional echocardiography has been used calculate systolic dyssynchrony index (SDI), derived from the dispersion of time to minimum regional volume for all 16 LV segments. SDI decreases significantly in those who respond to CRT with reverse remodeling. SDI is low in healthy individuals/ patients with normal LV function and increases with worsening LV function regardless of the QRS duration [32].

Magnetic Resonance Imaging

Magnetic resonance (MR) tagging is a type of labeling of the myocardium by manipulating the magnetization of the tissue. These tags appear as hypointense stripes and move with the tagged segment of myocardium [33]. Analysis of these tags can be used to calculate the local myocardial strain. Harmonic phase analysis (HARP) is a method of rapidly analyzing MR tagged data. HARP method has been used in analyzing dyssynchrony in ischemic cardiomyopathy. Strain-encoded (SENC) MRI is a new method for direct imaging of regional strain. [34]. MRI-guided CRT has been performed with a left ventricular epicardial lead at the lateral region where a 4-mm thickening during systole had been proven [13].

Conclusion:

Various new imaging techniques have been tested as a measure of cardiac mechanical dyssynchrony. However, only criteria based on the surface electrocardiogram and echocardiography have been tested for outcome with cardiac re-synchronization therapy. At the present time, a wide QRS in excess of 120 msec with or without echocardiographic dys-synchrony appears to offer the best prediction in terms of response. Clinical trials are in progress examining the role of CRT in imaging based diagnosis of dys-synchrony in patients with narrow QRS.

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