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·综 述·

Predicting patient response to cardiac resynchronization therapy by gated SPECT myocardial perfusion imaging

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Introduction

Heart failure(HF) is widely prevalent(> 6 million cases) and rapidly growing(> 0.6 million new cases annually) in the United States[1]. Although the prevalence of HF in China is less than that in the United States, the total number of HF patients in China exceeds 4 million[2].

Cardiac resynchronization therapy(CRT) has shown benefits in patients with end-stage HF, such as improved HF symptoms, exercise capacity, quality of life, left-ventricular (LV) function, and mortality benefits[3-10]. The standard criteria for CRT, according to the ACC/AHA/HRS guidelines[11], are end-stage drug-refractory HF with New York Heart Association (NYHA) class III or IV symptoms, LV ejection fraction (LVEF)≤35%, sinus rhythm with QRS duration ≥120ms on surface eletrocardiogram(ECG). However, using these conventional criteria for selecting patients for CRT, up to 40% of pa-

tients fail to respond to this therapy according to clinical[8-9] as well as echocardiographic endpoints[12-15].

Efforts have been made to identify predictors for response to CRT. One mandatory parameter is LV mechanical dyssynchrony. Echocardiography with tissue Doppler and/or speckle tracking has been most widely used to measure LV mechanical dyssynchrony and shown to predict patient response to CRT[13]. However, reliable echocardiography measurements require expertise to obtain reproducible results. Due to high variability, the Predictors of Response to Cardiac Resynchronization Therapy(PROSPECT) trial found that under "real-world" conditions the current available echocardiographic techniques are not ready for routine practice to clinically predict CRT response[16]. These results have prompted the search for a more reproducible method of measuring LV mechanical dyssynchrony.

Another important issue related to CRT response is the position of the LV pacing lead. One study showed that pacing at the site of latest mechanical activation, as determined by echocardiography with speckle tracking radial strain analysis, resulted in superior echocardiographic response after 6 months of CRT and better prognosis during long-term follow-up[17]. Another study showed that CRT resulted in clinical and echocardiographic nonresponse when there was myocardial scar in the lateral or posterior wall, the usual position of the LV pacing lead[18]. These studies suggest that the optimal LV pacing lead position is the site of latest mechanical activation outside myocardial scar.

Phase analysis has been developed and validated to assess LV mechanical dyssynchrony from ECG-gated single photon emission computed tomography (SPECT) myocardial perfusion imaging(MPI)[19-20]. It has recently been shown to identify the site of latest mechanical activation as the optimal LV pacing lead position[21]. Most importantly, phase analysis has shown great reproducibility and repeatability for assessing LV mechanical dyssynchrony[22-23] as well as for identifying optimal LV pacing lead position[21]. This review demonstrates how this technique assesses those parameters individually and comprehensively for selection of patients for CRT.

Phase Analysis and LV Mechanical Dyssynchrony

Phase analysis of gated SPECT MPI is based on the partial volume effect, which states that regional myocardial wall thickness is approximately proportional to the maximum counts of the same region. Figure 1 shows the processing steps in phase analysis. The gated SPECT MPI data are first reconstructed and reoriented to generate a gated short-axis image. Regional maximal count detection is performed in 3D for each temporal frame of the gated short-axis image. Then, the first-harmonic Fourier function is used to approximate the discrete sample points into a continuous curve. As the regional maximum counts are approximately proportional to the regional myocardial wall thickness, such continuous curve represents myocardial wall thickening over the cardiac cycle. For each region, the wall-thickening curve provides a phase angle that represents the onset of mechanical contraction of the region. Once the phase angles of all regions (>600 regions over the entire LV) are obtained, a phase distribution is generated that provides information on the degree of mechanical dyssynchrony for the entire ventricle. The phase distribution can be displayed in polar map as well as in histogram as shown in Figure 2. For a normal subject, the entire LV starts contraction almost at the same time, so that the phase polar map is uniform and the phase histogram is narrow and highly peaked. Two quantitative indices, phase standard deviation (the standard deviation of the phase distribution) and histogram bandwidth (the range of 95% of the phase angles) are well studied for assessing LV mechanical dyssynchrony. As all processing steps in the phase analysis tool are automated, phase analysis has shown superior reproducibility and repeatability to echocardiography[22-23].

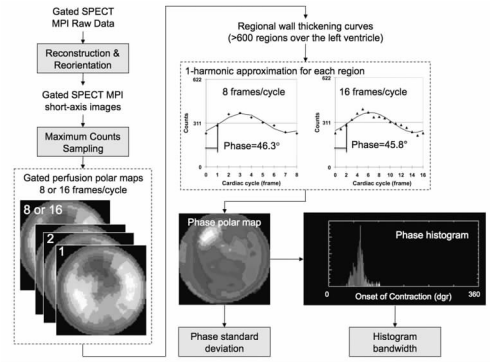

Figure 1 Processing steps of phase analysis of gated SPECT MPI

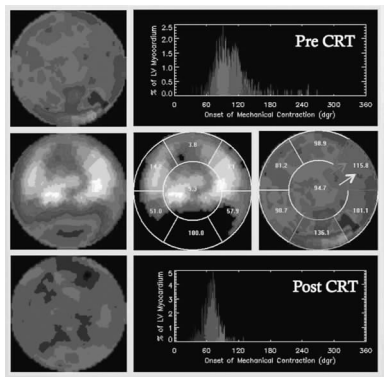

Figure 2 A patient with favorable response in LV synchrony immediately post CRT

Gated SPECT MPI studies are often perceived to have a low temporal resolution as the data are usually acquired using 8 to 16 frames per cardiac cycle. Since the discrete points of regional maximum counts are transformed into the continuous wall thickening curves by the first-harmonic Fourier approximation, the actual temporal resolution of the phase analysis technique is greatly enhanced. A simulation study demonstrated that with a count level achieved during routine clinical gated SPECT MPI the phase analysis tool was able to detect a minimum phase delay of 5.6 degrees, representing 1/64 of a cardiac cycle[24].

LV mechanical dyssynchrony measured by phase analysis of gated SPECT MPI has shown to correlate with that meas-

ured by 2D tissue Doppler imaging in 75 patients undergoing CRT[20]. The correlation coefficients were 0.80 ($P<0.000\ 1$) and 0.89 ($P<0.000\ 1$) for phase standard deviation and histogram bandwidth, respectively. Phase analysis of gated SPECT MPI has been evaluated for predicting clinical response after 6 months of CRT in 42 patients with end-stage HF[25]. Based on the improvement of ≥1 NYHA functional class, 30 patients were classified as responders and the other 12 patients as non-responders. Both histogram bandwidth ($175\pm63°$ vs $117\pm51°$, $P<0.01$) and phase standard deviation ($56.3\pm19.9°$ vs $37.1\pm14.4°$, $P<0.01$) were significant higher in responders as compared to non-responders. Moreover, the optimal cutoff values of histogram bandwidth (135°) and phase standard deviation (43°) for predicting CRT response were derived by receiver operating characteristic analysis. With these optimal cutoff values, phase analysis showed sensitivity and specificity of 70% and 74%, respectively in predicting clinical response to CRT.

Phase Analysis and Optimal LV Pacing Lead Position

Echocardiographic studies have suggested that the site of latest mechanical activation outside myocardial scar is the optimal LV pacing lead position for CRT[17-18]. Recently phase analysis has been evaluated for assessing regional mechanical activation and shown to identify the site of latest mechanical activation as the optimal LV pacing lead position[21]. That study enrolled 90 patients, who were indicated for CRT based on the standard criteria. In 52 patients, the LV lead was positioned at the site of latest mechanical activation (concordant), and in 38 patients the LV lead was positioned outside the site of latest mechanical activation (discordant). CRT response was significantly more often documented in patients with a concordant LV lead position than in patients with a discordant LV lead position (79% vs. 26%, $p<0.01$). After 6 months, patients with a concordant LV lead position showed significant improvement in LVEF and reduction in LV end-systolic and end-diastolic volumes ($p<0.05$), whereas with a discordant LV lead position showed no significant improvement in these variables. It must be noted that in the 52 patients, 7 of them had myocardial scar at the site of latest mechanical activation, suggesting that these patients should be considered having non-optimal LV lead position even if it was at the site of latest mechanical activation. Taking this into account, 45 patients had optimal LV lead position and the response rate in this group was >90%. This finding indicated that the comprehensive phase analysis approach, which assesses LV mechanical dyssynchrony, site of latest mechanical activation, and myocardial scar, has a high positive predictive value in predicting CRT response and can significantly improve CRT response rate.

Patient Examples of Using the Comprehensive Phase Analysis Approach to Predicting CRT Response

Three cases are shown below to demonstrate the comprehensive phase analysis approach to predicting CRT response.

Case 1 (Figure 2): A 72-year-old male with ischemic cardiomyopathy had NYHA class III symptoms. This patient had substantial LV mechanical dyssynchrony pre CRT, as reflected by a nonuniform phase polar map and a wide phase histogram. He had a large myocardial scar. Regional scar extent analysis using a 7-segment model showed that 51%, 100%, and 58% of the septal, inferior, and posterior wall had myocardial scar. Regional phase analysis showed that the inferior wall had the latest activation (the white arrow), whereas the lateral wall had the latest mechanical activation without substantial myocardial scar. The LV pacing lead was positioned at the lateral wall (the red arrow), pacing the site of latest activation with viable myocardial. Comparing the pre-CRT phase polar map and phase histogram to those immediately post CRT, this patient had favorable acute response to CRT (phase standard deviation from 28.9° to 15.4°, histogram bandwidth from 88° to 50°). His QRS duration also reduced from 142 ms to 132 ms. This patient had been followed up for 1 year, and showed no endpoint outcomes (cardiac death, HF hospitalization, ICD shocks, CRT deactivation).

Case 2 (Figure 3): A 65-year-old female with non-ischemic cardiomyopathy had NYHA class III symptoms. This patient had substantial LV mechanical dyssynchrony pre CRT, as reflected by a nonuniform phase polar map and a wide phase histogram. She had no myocardial scar. Regional phase analysis showed that the posterior wall had the latest mechanical activation (the white arrow), however, the LV pacing lead was positioned at the anteroseptal wall (the red arrow). Comparing the pre-CRT phase polar map and phase histogram to those immediately post CRT, this patient had deteriorative acute response to CRT (phase standard deviation from 19.8° to 37.4°, histogram bandwidth from 59° to 113°). This patient had CRT deactivation due to worsened symptoms 15 days post CRT.

The gated SPECT MPI data are reconstructed and reoriented to generate a gated short-axis image. 3D sampling is performed on each temporal frame of the gated short-axis image to detect regional maximum counts, which are approximately proportional to regional myocardial wall thickness. The points shown in the plots are regional wall thicknesses over the cardiac cycle. The first harmonic Fourier function is used to approximate the wall thicknesses (shown as the solid line) to calculate a phase angle for each region. Once the phase angles of all regions are obtained, a phase distribution is generated and displayed in polar map or in histogram. Note that the phase difference between 8 vs. 16 frame/cycle is very small - 0.5 (360 corresponding to one cardiac cycle) demonstrating that the first harmonic approximation improves the temporal resolution of the phase measurement. Also note that the phase polar map shows a significant phase delay (bright region) at the anterior and apical wall, where the perfusion polar maps shows a severe defect.

The first row shows the phase polar map and phase histogram of the patient pre CRT. The left panel of the second row shows the perfusion polar map of the patient. The middle panel of the second row shows the myocardial scar analysis. The pixels in the perfusion polar map, whose counts are less than 50% of the maximum counts in the perfusion polar map, are black-

ened out. The perfusion polar map is divided into 7 segments, and the scar extents are calculated and displayed for the 7 segments. The right panel of the second row shows the regional mean phases of the 7 segments. The white arrow indicates the segment with the latest mechanical activation (having the largest mean phases) and viable myocardium. The red arrow indicates the actual LV pacing lead position. The third row shows the phase polar map and phase histogram of the patient immediately post CRT.

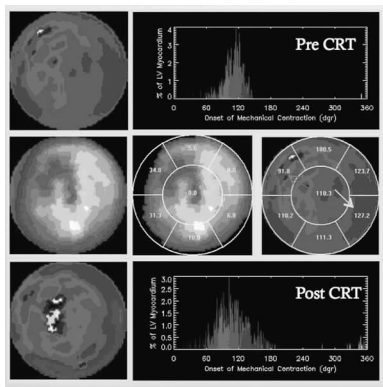

Figure 3 A patient with deteriorative response in LV synchrony immediately post CRT due to inappropriate LV pacing lead position

The first row shows the phase polar map and phase histogram of the patient pre CRT. The left panel of the second row shows the perfusion polar map of the patient. The middle panel of the second row shows the myocardial scar analysis. The pixels in the perfusion polar map, whose counts are less than 50% of the maximum counts in the perfusion polar map, are blackened out. The perfusion polar map is divided into 7 segments, and the scar extents are calculated and displayed for the 7 segments. The right panel of the second row shows the regional mean phases of the 7 segments. The white arrow indicates the segment with the latest mechanical activation (having the largest mean phases). The red arrow indicates the actual LV pacing lead position. The third row shows the phase polar map and phase histogram of the patient immediately post CRT.

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Case 3 (Figure 4): A 61-year-old female with ischemic cardiomyopathy had NYHA class III symptoms. This patient had substantial LV mechanical dyssynchrony pre CRT, as reflected by a nonuniform phase polar map and a wide phase histogram. She had a very large myocardial scar. The scar extent was 52% of the left ventricle. Regional phase analysis showed that the posterior wall had the latest activation (the white arrow), and the LV pacing lead was positioned at the posterior wall (the red arrow). Although there was a concordant LV pacing lead position, there was a large myocardial scar in the posterior wall. Comparing the pre-CRT phase polar map and phase histogram to those immediately post CRT, this patient had deteriorative acute response to CRT (phase standard deviation from 33.4° to 229°, histogram from 49.1° to 259°). This patient had HF hospitalization about 4 months post CRT.

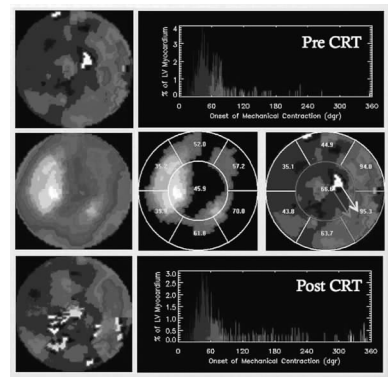

Figure 4 A patient with deteriorative response in LV synchrony immediately post CRT due to large myocardial scar burden

Conclusion

Phase analysis of gated SPECT MPI is a promising approach to predicting CRT response. It applies to conventional, widely available gated SPECT MPI studies with high reproducibility and repeatability. It has been shown to comprehensively assess LV mechanical dyssynchrony, myocardial scar, and site of latest mechanical activation from a single gated SPECT MPI scan. Integrated analysis of these parameters, once validated, can be a viable clinical approach to consistently and reproducibly predicting CRT response in HF patients.

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