ROLE OF QRS DURATION AND MORPHOLOGY IN PREDICTING RESPONSE TO CARDIAC RESYNCHRONIZATION TREATMENT

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Cardiac resynchronization therapy (CRT) has become a standard treatment for patients with congestive heart failure (CHF) who remain symptomatic despite maximum medical therapy.[1] Initially indicated for patients in sinus rhythm, recent guidelines have extended CRT to patients with atrial fibrillation with frequent dependence on ventricular pacing and those with Class I or Class II heart failure symptoms in whom ICD and/or permanent pacemaker is being implanted with anticipated frequent dependence on ventricular pacing.[2] What remains unchanged is the requirement of wide QRS (≥120 ms) and no inclusion of mechanical asynchrony as a criterion for patient selection. This article reviews evidence behind ECG morphology and duration as determinant for CRT response.

Randomized Trials in Cardiac Resynchronization Treatment. In over 4000 patients enrolled thus far in CRT trials, ECG of ≥120 ms width has been the sole asynchrony criterion for patient selection.[3] These randomized controlled trials have now proven functional, cardiac structural as well as survival benefits of CRT. While patients with left bundle branch block (LBBB) comprised great majority of patients in these randomized trials as well as in small single center studies that enrolled another 2000 patients, patients with intraventricular conduction delay (IVCD) and those with right bundle branch block (RBBB) were also included. In all studies that evaluated QRS width post CRT, a significant reduction in ECG width was noted, although no correlation was found between magnitude of QRS narrowing and clinical response.[4]

Prognostic Role of QRS in Medical Population. QRS duration predicted mortality in approximately 47000 patients that comprised a general medical population.[5] After adjusting for age, gender, and heart rate, the QRS duration score was a strong independent predictor of cardiovascular mortality with an 18% increase in cardiovascular risk for every 10-ms increase in QRS duration. Results were similar for wide QRS with or without BBB or paced rhythm. Within each LBBB and RBBB group survival was worse for those with QRS width > than 150 ms vs. < 150 ms. Annual mortality was 3.9% vs. 7.0% ($p<0.001$) and 3.1% vs. 4.8% ($p<0.01$) in those with LBBB < vs. > and RBBB < vs. > 150 ms respectively. Another study evaluated the prognostic role of complete RBBB in over 7000 patients referred for nuclear stress testing.[6] Patients with heart failure and paced rhythm were excluded. Prevalence of RBBB and LBBB was 3% and 2% respectively. At approximately 7 years of follow up, all cause mortality was 24% each in complete LBBB and RBBB group vs. 11% in the remaining cohort (both p 0.0001). Complete RBBB was as important a predictor of all cause mortality as LBBB with a hazard ratio of 1.5 for both. Incomplete RBBB did not confer an increased risk.

Prognostic Role of ECG in Heart Failure. Prolongation of QRS (≥120 ms) occurs in 14% to 47% of patients with HF and is generally accepted as occurring in approximately 30%.[7,8] LBBB occurs more commonly than RBBB (25% to 36% vs. 4% to 6%, respectively).[9] In Multicenter Unsustained Tachycardia Trial (MUSTT) comprising of 1638 patients, LBBB and intraventricular conduction delay were associated with a 50% increase in the risk of both arrhythmic and total mortality after adjustment for other significant factors, whereas RBBB was not

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associated with arrhythmic or total mortality.[10] A combination of QRS prolongation and LVEF <35% carries the highest mortality.[11,12] Increased prevalence of intraventricular asynchrony was present in patients with RBBB and left anterior fascicular block (50%) similar to that in LBBB (54%) unlike in patients with pure RBBB alone (33%) in a study that evaluated the prevalence of mechanical asynchrony in 200 CRT eligible patients with CHF.[13] This study found an increased prevalence of intraventricular asynchrony only in those with LBBB (58%) compared to those with RBBB and LAFB (42%) and those with pure RBBB alone (28%). In another small study of 12 patients with complete RBBB and left anterior or posterior fascicular block and QRS width of >145 ms, CRT conferred significant benefit in exercise capacity and NYHA class.[14] There was a significant and sustained improvement in aortic velocity time integral and reduction in mitral regurgitation severity and QRS width along with a reduction in LV diameter at 12 months.

LBBB was associated with an increased 1 year all cause mortality as well as sudden death in over 5500 patients with CHF in the Italian Network on Heart Failure Registry with a hazard ratio of 1.7 and 1.58 respectively.[15] Prevalence of LBBB was 25%. LBBB remained significant even after adjusting for age, underlying cardiac disease, measures of heart failure severity and prescription of beta blockers and ACE-inhibitors.

LBBB causes a delay in the left ventricular lateral wall activation resulting in delay in mechanical activation of lateral wall that contracts when interventricular septum has started to relax.[16] By placing LV lead in the lateral/posterolateral wall, this delayed LV lateral wall activation is abolished resulting in synchronized contraction of LV segments, improved diastolic filing and improved cardiac output. Surface QRS in LBBB correlates with both transseptal time as well the endocardial activation time.[17] There is a relationship between surface QRS and mechanical asynchrony, albeit weak, in patients with end stage CHF[18] and the relationship between surface QRS is stronger for interventricular than intraventricular asynchrony.[19] In addition surface QRS correlates with magnitude of acute increase in LV performance.[20] These studies suggest that a crude measure such as surface QRS does reflect underling substrate for mechanical asynchrony.

Surface QRS also predicted magnitude of CRT response in a recent study comprising of 286 patients who were followed for 22 months post CRT. Twenty two percent of patients were super-responders with a ≥30% reduction in LV end systolic volume at 6 months, another 35% were responders with a >15% and <30% decrease in LV end systolic volume. Forty three percent were non responders, including 22% of study patients in whom LV end systolic volume increased post CRT. There was a 3% vs. 37% risk of death, heart transplantation, or heart failure hospitalization in super-responders vs. non-responders. QRS width was 142, 156, 163 and 161 ms respectively in the negative responders, non-responders, responders and super-responders ($p<0.001$). While assessment of mechanical septolateral delay appeared to separate the responder group as well, this parameter was shown to have high variability and low sensitivity and specificity in a recently published PROSPECT study.[21]

Magnitude of QRS Shortening and CRT Response. While no tight correlation is seen between baseline or post CRT QRS duration and functional response, in general, an increased QRS shortening post CRT is associated with a better responder rate. In a retrospective study of 139 patients, among multiple demographic, clinical, and ECG variables, the amount of QRS shortening with Biv stimulation was the only independent predictor of a positive (37+23 ms) vs. negative (11+23 ms) response to CRT (P , 0.001). CRT responders were those alive, without heart failure hospitalization and with at least one full grade improvement of NYHA or an improvement in 6 MWH or peak VO2 increase of 10%.[22] Other smaller studies have found similar results.[23,24,25,26] In a study of 61 patients and 45 responders, the QRS duration at baseline was not predictive of CRT response, however, a significant shortening in QRS duration after six months of CRT was observed only in responders.[27] A reduction in QRS duration >10 ms had a high sensitivity (73%) with low specificity (44%) in prediction of responders. Conversely, a reduction in QRS duration >50 ms was highly specific (88%) but not sensitive (18%) to predict response to CRT. In 337 patients who underwent a 22 month follow up, post CRT QRS by tertile (hazard

ratio 1.5) was an independent predictor of cardiac mortality or heart transplantation along with older age (hazard ratio 1.03) and lack of treatment with ACE inhibitor or receptor blocker (hazard ratio 2.17). On the other hand improvement in hemodynamics with single chamber LV pacing which is invariably associated with prolonged QRS duration may be related to improved interventricular synchrony particularly in the presence of LBBB as well as improved diastolic filling due to a shorter AV delay during LV or Biv pacing.[28]

Selecting Site of RV Lead Placement. Recent studies have focused on "dialing up" CRT response by selecting right ventricular lead placement at RV apex, vs. mid interventricular septum vs. right ventricular outflow tract based on electroanatomical mapping to cause maximum QRS shortening and/or maximum improvement in LV dp/dt.[29]

Unresolved Questions. The question of whether to withhold CRT in those with wide QRS but without mechanical asynchrony and to provide CRT in those with narrow QRS with mechanical asynchrony has been raised.

CRT in Narrow QRS Heart Failure. Reserving CRT to a small proportion of those with wide QRS excludes over 50% of CHF population with narrow QRS. A number of observational studies have shown presence of mechanical asynchrony in patients with narrow QRS CHF.[30,31] An acute improvement in cardiac hemodynamics occurred by LV and Biv pacing in patients with narrow QRS.[32] The same group showed that Lead electrograms from the LV free wall were later in the LBBB patients in absolute terms and also relative to the surface QRS and improved inter as well as intraventricular synchrony occurred in both LBBB and narrow QRS patients with Biv pacing.[33] A few single center studies found that CRT produces as much benefit in narrow QRS CHF patients who have mechanical asynchrony, as measured by tissue Doppler imaging, as those with wide-QRS.[34,35,36] This initial data appeared promising, however was not borne out by subsequent multicenter randomized, controlled study that used similar selection criteria.[37] No change in primary outcome of increase in VO2 max or in secondary outcome measures of improvement in LV volumes or size was found at the end of 6 months in those randomized to CRT (n=76) vs. managed medically (n=80).

Mechanical Asynchrony and Response to CRT in Wide QRS Patients. A number of single center studies have shown better predictive role of mechanical asynchrony measures compared to ECG measures. Multiple asynchrony parameters have been evaluated using echocardiography based on pulsed wave Doppler,[38] M-mode[39,40] tissue Doppler[41-55] three-dimensional imaging[56] and now speckled tracking methods.[57,58] Online evaluation of mechanical asynchrony can be represented as color encoded time to peak velocity maps in tissue synchronization imaging, which allows evaluation of mechanical asynchrony and predicts CRT response.[59,60] Methods have evaluated time differences of global ejection or segmental velocities between right and left ventricle as well as within the left ventricle. Radial, longitudinal and circumferential motion has been evaluated using M-mode, tissue Doppler velocity, displacement, deformation and rotation. However none of the asynchrony measures were felt to be robust enough or provided enough incremental predictive power in a multicenter study, Predictor of Response to CRT (PROPSECT)[21] in wide QRS patients to be recommended as criteria for CRT patient selection. Large variability of tissue Doppler measures of asynchrony was found. Another prospective randomized controlled trial RETHINQ study[61] in patients with QRS width of ≤130 ms did not find improvement in primary end point of increase in VO2 max or secondary end point of LV size of volumes in control vs. CRT patients. However improvement in VO2 max occurred in patients with QRS width between 120-130 ms compared to those below 120 ms.

More recently use of multi-parameter approach in both wide[62] and narrow[63] QRS patients has been used with a significant improvement in sensitivity and specificity.

Based on failure of mechanical asynchrony indices in multicenter studies such as PROSPECT and RETHINQ studies to predict responders to CRT, ACC/AHA/HRS guidelines for CRT selection continue to be wide QRS of ≥120 ms without use of mechanical asynchrony measures. Lack of investigator and core lab training in collecting and analyzing TDI measures of asynchrony, selection of

inappropriate or inadequate asynchrony measures, use of single instead of multiple asynchrony measures as well as variability of TDI measures of asynchrony have been attributed to result in failure of these studies. More prospective, randomized studies need to be conducted to evaluate role of CRT in narrow QRS patients using multi asynchrony parameter approach. In the meantime responder rate amongst those currently eligible for CRT needs to be improved by focusing on role of viability, coronary sinus venous anatomy, site of electromechanical delay, and pacemaker optimization.

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