When Right May Not Be Right
Right Bundle-Branch Block and Response to Cardiac Resynchronization Therapy

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Cardiac resynchronization therapy (CRT) in appropriately selected patients has been shown to improve cardiac function, heart failure symptoms, and survival. On the basis of results of large, randomized trials, current American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines recommend consideration of CRT in patients with cardiomyopathy on optimal medical therapy with left ventricular ejection fraction <35%, New York Heart Association class III or IV symptoms, and QRS duration >120 ms. The idea of resynchronization therapy was derived from the seminal observations that intraventricular conduction abnormalities, extensively characterized in patients with left bundle-branch block (LBBB), adversely affect left ventricular mechanics. LBBB produces predictable changes in the left ventricular activation sequence. Abnormal activation of the interventricular septum and markedly delayed activation of the lateral left ventricle are typically seen in patients with LBBB. However, left ventricular activation patterns may be highly variable and more complex in patients with underlying cardiomyopathy. Delayed, dyssynchronous electromechanical activation in these segments leads to increased cardiac work, less efficient cardiac contraction, and lower cardiac output. Electric (and mechanical) preactivation of the late-activating left ventricular region with CRT has been accepted to be prerequisite for successful clinical response. Although remarkable symptomatic improvement is seen in many patients, up to 30% of subjects who participated in CRT trials failed to respond to therapy or may have worsened. Several clinical features have been identified that carry adverse clinical prognosis and predict less response to CRT therapy (Table). Despite extensive efforts, preimplant identification of nonresponders remains a significant problem and erodes the overall clinical (and cost) effectiveness of CRT therapy.

Benefits of CRT therapy in the setting of right bundle-branch block (RBBB) have been debated with arguments for both sides. It is hard to find a compelling physiological explanation for left ventricular pacing in simple RBBB because left ventricular activation is largely not affected. The situation is more complex, however, when the picture is complicated by the presence of cardiomyopathy. Richman and Wolff described a particular ECG pattern that fulfilled RBBB criteria on the basis of the precordial leads but LBBB criteria by the limb leads (“LBBB masquerading as RBBB”). It was proposed that the ECG pattern may have been the result of extensive infarction of the interventricular septum and myocardial region around the septum. Further pathological studies have questioned the idea of masquerading block and have shown that patients with these mixed ECG patterns were often characterized by diffuse pathophysiological changes in both left and right bundles and marked destruction of the interventricular septum and other wall segments with a large scar burden. These observations were made in patients with ischemic cardiomyopathy, and pathological features of this ECG pattern have not been studied in nonischemic cardiomyopathy patients.

In a more recent work by Fantoni et al, right and left ventricular electroanatomic activation maps were evaluated in 100 consecutive patients who were referred for CRT therapy. Significant delay in the left ventricular endocardial activation sequence was seen in most patients with RBBB morphology and left axis deviation. In these patients, equal delay was seen in the right ventricular and left ventricular activation. Interestingly, the average left ventricular endocardial activation time in RBBB was even longer than in LBBB before data were adjusted for ischemic heart disease, underscoring the significance of ischemic heart disease and delayed left ventricular activation in this patient subset. Increased left ventricular activation time was also correlated with prior myocardial infarction in LBBB patients in another study. Bundle-branch block, in general, may be localized to the proximal portion of the His-Purkinje conduction system only and allow relatively normal conduction in the rest of the His-Purkinje system when the activation front reaches it, or, on the contrary, bundle-branch block may extensively involve the distal arborization of the His-Purkinje system, such as seen after myocardial infarction, and allow only slow intramyocardial conduction. In a severely diseased His-Purkinje system, conduction may be slow in both bundles, and ECG manifestation with a RBBB or LBBB depends on relative differences in conduction time. In other cases, although the ECG morphology may resemble RBBB, change in QRS axis and width may indicate the presence of other myocardial processes, such as right ventricular hypertrophy; QRS prolongation in these cases is due to only a right
ventricular abnormality. Thus, many underlying pathophysiological processes may provide similar ECG features, whereas these ECG morphologies result from quite different patterns of left ventricular activation.

Most available clinical data regarding the effects of CRT in RBBB are derived from retrospective data analyzing only a relatively small number of patients. Data from a cohort of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study ($n=43$) and from pooled data of the MIRACLE and CONTAK Cardiac Defibrillator Trial (CONTAK CD) studies ($n=61$) reveal no clinically significant improvement with CRT in this patient subgroup.$^{13,14}$ Prospective data are available in a very small number of patients with RBBB and CRT ($n=12$). In this study, benefit was seen only if delayed left ventricular activation was shown with tissue Doppler.$^{15}$ In another study, acute hemodynamic improvement was present but was less with RBBB than with LBBB (increase in $\Delta p/dt_{max}$ with biventricular pacing: LBBB, 11.4% versus RBBB, 5.5%).$^{16}$ A recent retrospective, single-center observational study by Adelstein et al.$^{10}$ showed worse survival in the RBBB group in addition to minimal symptomatic benefits (percentage of patients with improved symptoms: RBBB, 14% versus LBBB, 60%). Echocardiographic evidence of reverse remodeling was also markedly decreased with RBBB. Another single-center study revealed similar results regarding symptomatic or echocardiographic changes after CRT in RBBB patients,$^{17}$ but the study was underpowered to make conclusions regarding survival difference.

In the current issue of Circulation, Bilchick et al.$^{18}$ reported results from a retrospective study examining clinical predictors of death and the composite of death and heart failure hospitalization in patients with CRT implantable cardioverter-defibrillator (CRT-D) therapy. Patients were selected from the Iowa Foundation for Medical Care patient registry (which later became the National Cardiovascular Data Registry ICD) over a 16-month period between 2005 and 2006. By this time, most CRT device implants were based on results of the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization - Heart Failure (CARE-HF) studies. Participation in this registry was mandatory for all Medicare patients. Patient demographic information and device implant–related clinical data were gathered, and $>94\%$ of procedure questionnaire data were then successfully matched with Medicare hospital claims and outcome data (based on International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes and diagnosis related group codes) for a median follow-up of 40 months. Outcomes were analyzed in 14,949 patients who received CRT during the screening period and in addition had QRS duration $>120$ ms and left ventricular ejection fraction $<35\%$. Although heart failure class was not included as a patient selection criterion in this study, $\approx86\%$ of patients had New York Heart Association class III or IV symptoms. Baseline clinical data showed predominantly ischemic cardiomyopathy as the underlying etiology for heart failure (69%) and high rates of atrial fibrillation (35%). The mean QRS duration was 157 ms, with LBBB in 69% and RBBB in 11% (compared with 71% and 10%, respectively, in the COMPANION study). Most patients were treated with an appropriate heart failure medication regimen. During the follow-up, 52% of patients died or had heart failure admissions, and total mortality was 37%. Mortality rates at 30 days (1.4%) and 1 year (12.6%) were in agreement with those shown in the COMPANION study. It is clear, however, that the mortality rate remained high at an average of 10%/y after the first year after device implantation. The presence of RBBB was associated with worse overall survival compared with LBBB (40.3% versus 29.7% at 3 years). Adjusted clinical predictors of death after CRT therapy were identified as New York Heart Association class IV heart failure (1-year and 3-year mortality, 21% and 44%) and age $>80$ years, followed by RBBB, ischemic cardiomyopathy, diabetes mellitus, and atrial fibrillation. A stunning difference was seen in 3-year mortality if combined adverse risk predictors were present (ischemic cardiomyopathy plus RBBB, 41.9% versus nonischemic cardiomyopathy plus LBBB, 22.4%; $P<0.0001$).

How can we reconcile these findings with the currently available data, and should we make changes in our practice on the basis of these results?

This study delivers a strong message in accordance with analyses from prior studies that baseline RBBB is a significant negative predictor for clinical outcomes in CRT. Extrapolation of these results would suggest that CRT in a RBBB population may not be effective. It is important to realize, however, that this type of information cannot prove lack of efficacy because of the absence of a control group, and increased hazard associated with certain clinical features may simply indicate a higher-risk population. Thus, it remains unclear whether outcomes with RBBB are worse because of the compounding effects of adverse predictors and disease severity or decreased efficacy of (or maybe harm from) CRT. In our opinion, when CRT is considered in the presence of RBBB, it should be weighed significantly in addition to other negative predictors (such as heart failure class, ischemic heart disease, renal dysfunction, advanced age, atrial fibrillation) in an individualized decision process to recommend for or against CRT.

Could we improve the response to CRT in RBBB patients? Where should we look for answers?

There are only very limited data to offer guidance in this respect, but several avenues may be explored. Patient selection may be important, as suggested by prior data,$^{15}$ and the role of mechanical or electric dyssynchrony in both the left

### Table. Adverse Clinical Predictors in CRT

- Advanced age
- Male gender
- Ischemic cardiomyopathy
- Baseline non-left bundle-branch block
- QRS duration $<150$ ms
- Lack of mechanical dyssynchrony
- Significant left ventricular scar
- New York Heart Association class IV symptoms
- Severe noncardiac comorbidities (eg, pulmonary disease, pulmonary hypertension, renal dysfunction, diabetes mellitus)
Disclosures

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