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Editorial commentary: Harm from left bundle branch block: We are the tortoise, not the hare

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Left bundle branch block (LBBB) was first described by Eppinger and Rothberger in 1909 [1]. They injected silver nitrate into various areas of the canine left ventricle (LV) and observed that the electrocardiogram (ECG) changed more by destroying a small part of the ventricular septum (where the fibers of the left and right bundle branch emerge) compared to relatively larger sections of the left ventricular (LV) free wall. The prognostic significance of LBBB on patient outcomes was first explored nearly 50 years later by Johnson et al. in a case series of 555 patients with heart failure. They found that LBBB was associated with an average survival of 3.3 years and longer QRS durations portended an even shorter survival [2]. Unfortunately, early studies were confounded by the higher prevalence of comorbid heart disease among patients with LBBB compared to normal conduction. More recent studies of isolated LBBB occurring in the absence of other cardiovascular disease report disparate results. Some studies show LBBB in the absence of cardiac co-morbidity is associated with a 10 fold increase in risk of sudden death [3], and higher incidences of coronary artery disease [4], while others have found no difference in mortality or sudden death among patients with LBBB compared to normal ventricular conduction [5,6]. Controversy remains whether LBBB is simply an indicator of underlying cardiomyopathy or whether LBBB may directly contribute to the development of dilated cardiomyopathy [7,8].

In this setting, Smiseth et al. offer a comprehensive review highlighting how LBBB may contribute to the development of dilated cardiomyopathy [9]. They highlight that while LBBB is often tolerated in otherwise healthy patients, when it accompanies clinical heart failure, LV systolic function is often more severely reduced than in similar patients with normal conduction. The authors point to the at least partial reversibility of this LV dysfunction and improvement in clinical heart failure symptoms through the use of cardiac resynchronization therapy (CRT) to "correct" LBBB as indirect evidence that LBBB plays some mechanistic role in the reduced ejection fraction and chamber dilatation seen in patients with heart failure and LBBB.

The authors conclude that the primary mechanism by which LBBB likely affects LV mechanical function is the temporal separation of the septal and lateral wall contractions. In LBBB, early contraction occurs in the RV and the LV septum which squeezes blood into a relaxed and compliant LV resulting in stretch of the lateral wall rather than ejection through the aorta. This increased stretch (pre-load) of the LV lateral wall results in enhanced contraction (via the Frank-Starling mechanism) to effectively shift the workload of the LV disproportionally to the lateral wall. This imbalance in workload drives structural remodeling of the LV with thinning of the septum and hypertrophy of the lateral wall. Perfusion to the septum is reduced due to the prolonged septal systole and autoregulation (less workload results in lower blood flow). The inefficiency of this contraction pattern can be quantitatively expressed in terms of myocardial work that the authors use to highlight the degree of inequality between the septal and lateral walls.

In addition to its direct effects on LV contraction, LBBB may also promote adverse cardiac remodeling by causing or worsening pre-existing mitral regurgitation. Without the rapid conduction down the left anterior and posterior fascicles, the papillary muscles lose their head start on contraction that normally enables early tightening of the chordae tendineae to maintain the competence of the mitral valve during ventricular systole. The mitral valve then partially prolapses into the left atrium resulting in regurgitation. Worsening LV dilation then compounds the problem by further drawing the mitral leaflets apart, worsening valve leaflet coaptation and promoting regurgitation. Mitral regurgitation frequently improves with the use of CRT, suggesting that these mechanisms of LV dysfunction may also be correctable with elimination of LBBB.

In addition to the adverse mechanical consequences of LBBB on systole, LBBB may also directly and indirectly compromise diastole. First, as a result of prolongation of both the LV isovolumetric

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contraction and isovolumetric relaxation times and the requirement to maintain LV ejection time, the critical LV diastolic filling period is shortened in LBBB compared to normal conduction. The impaired LV filling time may result in higher LA pressures, pulmonary congestion, and can directly worsen clinical heart failure symptoms even in the absence of LV systolic dysfunction. Second, the dyssynchronous repolarization pattern of LBBB may adversely alter the suction force of active LV relaxation, further hindering LV filling. While early data suggest that these mechanisms may contribute to the development of clinical heart failure, perhaps even in the absence of systolic dysfunction, the authors correctly point to the need for further study of the role of the mechanisms of diastolic dysfunction in patients with LBBB and the potential role of CRT to correct these mechanisms.

While a majority of patients with LBBB maintain a normal LVEF, more than a third develop systolic dysfunction within 5 years and patients with LBBB and normal LV function are 3.8 times more likely to develop incident LV dysfunction than matched patients with normal conduction. The authors hypothesize that LBBB may initially cause a subclinical decline in LV systolic function and a reduction of afterload tolerance that makes patients more susceptible to additional stressors such as hypertension. While LBBB may increase susceptibility to additional cardiac insults, it also may serve as the "second hit" to patients with pre-existing cardiac conditions. Prior studies of right ventricular pacing (often viewed as an experimental surrogate of LBBB) have shown that the degree of LV dyssynchrony induced by activating the septum prior to the LV lateral wall is significantly greater in patients with lower baseline LV ejection fraction (LVEF) [10]. Not only does LBBB frequently coexist with other cardiac conditions, the dyssynchrony LBBB induces may work synergistically with those conditions to further worsen ventricular function.

This review highlights several important mechanisms by which LBBB impairs LV systolic function, often working in concert with other comorbid conditions to hasten remodeling and worsen prognosis. The authors compare several available imaging methods used to assess the magnitude of LV dysynchrony and its consequences on LV mechanical function. Future work optimizing and comparing these methods for upstream identification of high-risk patients with LBBB may facilitate the use of interventions such as CRT *before* their clinical decline.

In their initial manuscript, Eppinger and Rothberger were surprised that disruption of a small septal structure could precipitate more severe ECG changes than disruption of larger areas in the free wall. More than a century later we have a much better understanding of LBBB (including the fact that they misidentified LBBB and RBBB), but we still do not fully understand whether LBBB independently affects the prognosis of otherwise healthy patients, or how LBBB may cause LV dysfunction. As is evident in the review by Smiseth and colleagues, we have made slow, steady progress towards this goal. It is our hope that like the famous story of the tortoise and the hare, slow and steady progress will win this race towards improving the prognosis of patients with LBBB.

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