

EDITORIAL COMMENT

When Cardiac Function Dangles on a Thread of Conduction

Dyssynchronopathy in Patients With Left Bundle Branch Block*

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When Willem Einthoven gave his Nobel Lecture in 1925, he presented the case of a 79-year-old patient. The laureate had been puzzled by a capillary electrometer tracing taken back in 1894, showing a shape that was “markedly diverging from curves up till then recorded.” Investigating the same person 31 years later, using the modern string galvanometer, he had found the electrocardiographic pattern, with ventricles that “execute abnormal contractions and produce dextrograms,” remarkably unchanged (1). By this time science had provided an explanation for the irregularity: “a block in the left branch of the bundle of His.” It was intriguing to Einthoven that the patient could have had this anomaly for such a long time “without experiencing excessive discomfort.”

See page 1089

Today, the presence of left bundle branch block (LBBB) on the 12-lead electrocardiogram is widely recognized as an emblematic marker of structural heart disease. Among 5,209 subjects followed for 18 years in the Framingham study, 55 developed LBBB at a mean age of 62 years (2). Newly acquired LBBB was typically associated with hypertension, cardiac enlargement or ischemic heart disease, and constituted a powerful risk factor for subsequent clinical manifestations of coronary disease or congestive heart failure. However, in rare cases LBBB may also occur in the absence of any apparent structural cardiac abnormality. In a large Irish cardiovascular disease prevention program, the prevalence of “isolated” LBBB in the general population was estimated at 0.1% (3). Possibly, Einthoven’s patient was the first documented example of this kind.

The study of such patients has provided fundamental insights into the deleterious effects of abnormal electromechanical activation on left ventricular (LV) function and central hemodynamics. In their pivotal study Grines et al. (4) demonstrated abnormal activation, contraction, and relaxation sequences in patients with isolated LBBB, leading to delayed LV systole and diastole and prolonged isovolumetric contraction and relaxation periods.

It has been argued that LBBB per se does not cause adverse outcomes in patients with underlying heart disease but rather reflects the confounding effect of age, comorbidities, LV dysfunction, and other conditions (5). However, the marked clinical and hemodynamic improvements with cardiac resynchronization therapy (CRT) in patients with heart failure and intraventricular conduction indicated by LBBB or a wide QRS complex strongly suggest that cardiac dyssynchrony accounts for a substantial part of cardiac pathophysiology in these subjects. Recent research has greatly increased our detailed knowledge of the electrical, mechanical, and molecular aspects of dyssynchrony (6) and subanalyses from large clinical trials have consistently confirmed the important role of QRS duration, and, in particular, typical LBBB configuration, as powerful predictors of clinical success of CRT (7). Furthermore, the potential of CRT to reverse global functional and structural abnormalities induced by isolated LBBB has been demonstrated in a canine model (8).

Another convincing piece of evidence for the existence of an LBBB induced dyssynchronopathy syndrome comes from studies of conventional right ventricular (RV) pacing. Although the electromechanical features of RV pacing and LBBB are not completely identical, the conditions share a similar electrocardiographic and mechanical activation pattern. Trials in patients with normal and depressed LV function have delivered compelling evidence for an adverse effect of long-term RV stimulation on the risk of heart failure hospitalization (9,10) which was likely linked to the induction of cardiac dyssynchrony. Moreover, it has been shown in human studies and animal models that frequent premature ventricular contractions can induce dyssynchrony-related ventricular dysfunction and cardiomyopathy in otherwise structurally normal hearts (11,12), and that normal cardiac function can be restored after curative ablation of the arrhythmogenic focus.

These data strongly suggest that patients with LBBB but initially normal hearts may develop a progressive disorder in which dyssynchrony induces reduced LV performance, cardiac remodeling, and eventually the manifestation of clinical heart failure. In this issue of the *Journal*, Vaillant et al. (13) provide evidence that such a syndrome exists in clinical practice. By careful retrospective analysis of a large CRT population, the authors were able to identify a small group of patients with LBBB and structurally normal hearts in whom the transition from normal LV function to dyssynchronopathy and clinical heart failure could be tracked over

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time. Isolated LBBB had been present for a long time prior to the onset of heart failure and alternative causes of deteriorating LV function were virtually excluded. Given the conflicting results of previous cohort studies (3,14–16) the report from these well-characterized patients adds important information about a possible unfavorable clinical course in patients with isolated LBBB.

Notably, CRT almost completely reversed LV dysfunction in 6 of 8 patients. While such a remarkable improvement is rarely observed in patients with underlying structural damage, the curative effect of CRT demonstrated in isolated LBBB suggests that a similar mechanism may be active in many so called super-responders to CRT. In the MADIT-CRT trial, super-response was predicted by female sex, absence of prior myocardial infarction, QRS duration ≥ 150 ms, LBBB, body mass index < 30 kg/m², and a smaller left atrial volume index at baseline (17). These characteristics are similar to those of the subjects studied by Vaillant and coworkers, although the comparison is restricted by the small sample size. Nevertheless, assuming that CRT super-response may often occur in patients with isolated LBBB-induced dyssynchronopathy, it is likely that the prevalence of the latter condition among patients with dilated cardiomyopathy would be larger than the 1.6% reported in the present paper.

The study leaves some important questions unanswered. It remains unclear what proportion of patients with isolated LBBB will ultimately suffer a progression to dyssynchronopathy and overt heart failure. As indicated by Einthoven's patient case, LBBB is not always necessarily associated with an adverse clinical course but appears to affect only a subset of patients. This pattern of individual predisposition appears similar to other transient and reversible forms of cardiomyopathy such as those induced by tachycardia, stress, drugs, toxic agents and other causes. The pathophysiology underlying an increased susceptibility to dyssynchronopathy induced by isolated LBBB remains to be identified (6) but may include abnormal mitochondrial function, myocytic calcium processing, and other mechanisms. Given the dissimilar effects of resynchronization observed in men and women, sex differences in the vulnerability to LBBB and dyssynchrony should also be further explored.

Although the thorough diagnostic evaluation undertaken by the investigators did not reveal any underlying structural cardiac disease in the 6 super-responders, it cannot be excluded that LBBB was an early marker of a global progressive inflammatory and fibrotic remodeling process affecting the conductive tissue and eventually also the contractile myocardium. Possibly, the diagnostic methods used (magnetic resonance imaging was not an option because of the implanted device) were not sensitive enough to detect indicators of subtle structural abnormality. In the 2 patients with isolated LBBB who did not normalize within 12 months after CRT, however, alternative causes of LV dysfunction likely played a role.

A more detailed pathophysiological characterization of electromechanics would be necessary to clarify whether isolated LBBB evolves from minimal local injury and disruption of the electrical properties of the left bundle branch or from a functional block. While the former mechanism would be expected in purely isolated LBBB, the latter form would support the presence of a globally diseased myocardium. Auricchio et al., studying patients with LBBB and LV dysfunction with 3-dimensional contact and non-contact mapping, found that LBBB resulted from conduction delays at several anatomic levels of the activation sequence (18). In a third of cases, LBBB morphology primarily emerged from a prolongation of the intramural rather than the transeptal activation time, supporting the presence of a diffuse myocardial process. Unfortunately, the nature of LBBB was not known in the present study. Finally, the patients described by Vaillant and coworkers received concomitant drug therapy for their heart failure, and the relative contributions of medical therapy and resynchronization respectively remain unknown (13). Even if the distinct improvement after introduction of CRT strongly suggests a causal effect of dyssynchrony, we do not know to which extent reverse remodeling would persist without support by angiotensin-converting enzyme inhibitors and beta-blockers.

The paper by Valliant et al. (13) expands our knowledge about the interrelation between electrical and mechanical heart failure and calls for close attention to patients who present with the rare finding of LBBB in the absence of any apparent structural cardiac abnormality. It appears plausible that such individuals should be subjected to regular follow-up in order to timely detect any need for more advanced heart failure therapy, in particular CRT. Yet, there is no proof to date that these patients would benefit from prophylactic treatment. While the present findings may suggest that the fate of cardiac function dangles on a thread of conduction, future prospective studies need to establish the true lifetime risk of developing LV dysfunction and heart failure associated with isolated LBBB. Einthoven's case indicates that some patients are protected against this hazard.

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