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Review

Left Bundle-Branch Block—Pathophysiology, Prognosis, and Clinical Management

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Summary: Given its broad use as a screening tool, the electrocardiogram (ECG) has largely become one of the most common diagnostic tests performed in routine clinical practice. As a result, the finding of left bundle-branch block (LBBB) in the absence of a well-defined clinical setting has become relatively frequent and raises questions and often concerns. While in the absence of clinically detectable heart disease LBBB does not necessarily imply poor outcomes, physicians should be aware of the role of LBBB in stratifying risk of cardiovascular events and death in subjects with both ischemic and nonischemic heart disease. This paper reviews historical landmarks, pathophysiologic features, prognostic implications, and clinical management of LBBB in apparently healthy subjects and those with heart disease.

Key words: left bundle-branch block, electrocardiogram, history of medicine

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Evolving Concepts, Misunderstandings, and Current Appraisal of Left Bundle-Branch Block

As early as the beginning of the past century, Eppinger and Tothberger, by means of a rudimental but efficient experimental model, performed experiments destroying pieces of dog myocardium by injecting silver nitrate and then observing the induced electrocardiographic (ECG) changes.[1] By means of a single esophageal-anal lead, these and other investigators found that injuring the left and right bundle branches resulted, respectively, in an upward and a downward QRS deflection on ECG.[2] Ironically, the mere extrapolation of data obtained from this experimental canine model resulted in a 25-year misunderstanding of the real electrical abnormalities. Left bundle-branch block (LBBB) pattern was incorrectly identified as right bundle-branch block (RBBB), and vice versa. In fact, since the esophageal-anal lead was erroneously judged to be "vertical" in the dog, the presence in humans of a wide downward deflection in leads II and III was considered to disclose RBBB.[3]

Almost 70 years after elucidation of this long-lasting misinterpretation, the electrogenesis and ECG pattern of LBBB appear to be fully clarified. Under normal conditions, the electrical impulse from the His bundle passes through a narrow anterior fascicle, a broader early branching posterior fascicle, and a third septal segment composed of many branches originating from each of the fascicles. The electrical impulse then spreads through a rich peripheral Purkinje network that couples with individual myocardial cells.[4, 5] The simultaneous electrical activation of the right ventricle from its own branch results in the QRS complex, which then represents the "sum" of two parallel and independent electrical phenomena. Left bundle-branch block completely modifies the electrical activation of the left ventricle and QRS complex on ECG. The activation of the interventricular septum, which is left-sided in physiologic conditions, originates on its right side. The electrical impulse propagates then inferiorly, to the left, and slightly anteriorly. This results in a nonhomogeneous and delayed depolarization of the left ventricle, which can be only partially preserved in the presence of an efficient distal left bundle branch and Purkinje network.[6]

Findings from three-dimensional (3-D) nonfluoroscopic contact and noncontact mapping have recently provided new insights into left ventricle activation sequence in patients with LBBB and heart failure.[7] From its site of earliest left ventricular (LV) breakthrough, activation wave front spreads both superiorly and inferiorly, but it is unable to cross from the anterior to the lateral wall because of the presence of a line of block

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oriented from the base toward the apex of the left ventricle. The wave front reaches the lateral and posterolateral regions by propagating inferiorly around the apex and across the inferior wall, thus defining a U-shaped activation pattern.[7] The ECG shows wide QRS complexes (>120 ms), increased intrinsecoid deflection time (80–120 ms), rS complexes in V_1–V_2, and loss or large reduction of Q waves in leads I and aVL. Likewise, repolarization forces mirror the electrical abnormality induced by the sequential activation of the two ventricles. Since they early originate from the right ventricle, left leads (I, aVL) usually show a negative ST-T pattern.

Asymptomatic Left Bundle-Branch Block: Prevalence, Prognosis, and Concerns

Since its wide diffusion, undemanding feasibility, and low cost, the ECG has become one of the most commonly performed investigations in routine clinical practice in the last 30 years. Given its broad use as a screening tool in the general healthy population, the finding of abnormal ECG patterns in the absence of a well-defined clinical setting has become frequent. Are we dealing with the preclinical stage of a structural heart disease or rather with a borderline physiologic phenomenon not necessarily implying future clinical consequences? This is exactly the case of LBBB in apparently healthy subjects, a paradigmatic example of "medical rebus." In the setting of LBBB and apparent structural heart diseases, the available observational studies suggest caution and often concern in the prognostic evaluation.[8–10] On the other hand, new onset LBBB in asymptomatic subjects raises several questions concerning the diagnostic algorithm and the clinical behaviour, with particular regard to the need for further investigation, intensity and nature of follow-up, and indications for specialist referral.

In epidemiologic studies conducted during the last 30 years, the prevalence of LBBB in the general population has been reported to vary considerably according to population size and sampling criteria, ranging from 0.1–0.8%[11–15] (Table 1). Of note, there is no consensus on LBBB-related prognosis, as the latter is clearly influenced by study design, population size, and heterogeneity. In a large population sample (3.983 subjects) with a 29-year follow-up, Rabkin *et al.*[16] found that the incidence of LBBB was 0.7%. Of interest, in this study >50% of subjects with LBBB had a normal ECG before the conduction disturbance was detected. During follow-up, subjects with LBBB displayed increased cardiovascular morbidity and mortality compared with control subjects, with sudden death frequently being the first clinical disease expression.

In 1979, the Framingham Study[17] (5,209 subjects, 55 with LBBB) showed a clear association between LBBB and main cardiovascular diseases, such as hypertension, cardiac enlargement, and coronary heart disease. Coincident with or subsequent to the detection of LBBB, 48% of these individuals developed coronary artery disease (CAD) or congestive heart failure (CHF). Within 10 years from LBBB detection, cardiovascular mortality was 50%, and at 18 years follow-up only 11% of subjects with LBBB remained free of detectable cardiovascular abnormalities (Table 2).

In a large population of 110,000 subjects with a mean follow-up of 9.5 years, Fahy *et al.*[18] reported no difference in total actual survival between subjects with LBBB and their controls. However, the LBBB group showed an increased prevalence of cardiovascular disease at follow-up (21 vs. 11% in controls) (Table 2).

In a formerly published review article, Rowlands[19] summarized the follow-up data from many studies concerning intraventricular conduction defects. He concluded that mortality risk in pre-existent LBBB without overt cardiac disease is only 1.3. On the other hand, a newly acquired LBBB confers a mortality risk of 10.0, mainly in subjects aged >44 years at LBBB onset.

Left Bundle-Branch Block and Risk Stratification in Heart Disease

In several studies on chronic and acute CAD, LBBB was found to be an excellent predictor of mortality and events[20–24] (Table 2). In 681 patients with acute myocardial infarction (AMI) enrolled in the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 9 and Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO) 1 protocols,[25] the incidence of LBBB was found to be 7%. The occurrence of both RBBB and LBBB was closely related to factors indicating more extensive myocardial damage (such as number of diseased vessels, peak creatinine phosphokinase, ejection fraction) and mortality. In patients showing persistent rather than transient BBB, the 30 days-risk of death was six times higher than in those without BBB, patients with LBBB mostly contributing to this outcome.

TABLE 1 Studies of left bundle-branch block (LBBB) in apparently healthy populations

First author (Ref. No.)	Year	n	Mean age (years)	Male/female ratio	Prevalence (%) of LBBB
Rodstein (12)	1951	30,000	51		131 (0.43)
Hiss (13)	1962	122,043	30	All male	231 (0.19)
Ostrander (56)	1965	5,129	40	0.9	18 (0.35)
Rotman (15)	1975	237,000			394 (0.16)
Siegman-Igra (57)	1978	5,204	50	All male	43 (0.82)

Modified from Ref. No. (18).

TABLE 2 Outcomes in subjects and patients with left bundle-branch block (LBBB)

First author (Ref No.)	Year	n	Mean age (years)	Sample	Outcome
Eriksson (28)	1998	855	70	Men born 1913	Increased mortality for LBBB only in conjunction with CAD
Fahy (18)	1995	100,000	44	Screening	Increased prevalence of cardiovascular disease at follow-up Increased cardiac mortality for LBBB+CAD No differences in all-cause mortality for LBBB
Schneider (17)	1981	5,209	50	Framingham	Increased mortality for LBBB
Rotman (15)	1975	237,000	35	U.S. Air Force	No increased mortality for LBBB
Hesse (58)	2001	7,073	60	Stress testing	Increased all-cause mortality for LBBB
Freedman (20)	1987	15,609	55	Chronic CAD	Increased mortality for LBBB
Wong (24)	2006	17,073	68	Acute MI	Increased 30-day mortality for LBBB
Guerrero (23)	2005	3,053	69	Acute MI	Increased in-hospital death for LBBB
Stenestrand (27)	2004	88.026	77	Acute MI	Increased unadjusted 1-year mortality
Brilakis (26)	2001	894	76	Acute MI	Lower pre-discharge ejection fraction Higher in-hospital and long-term unadjusted mortality
Baldasseroni (10)	2002	5.517	63	CHF	Increased 1-year mortality and sudden death

Abbreviations: CAD = coronary artery disease, MI = myocardial infarction, CHF = congestive heart failure.

Even when a community-based population of patients with AMI and longer (3 years) follow-up was considered, unadjusted postdischarge mortality was higher in subjects with LBBB[26] (Table 2).

To assess the independent contribution of LBBB to cause-specific mortality in ischemic heart disease, Stenestrand *et al.* recently analyzed data from a large cohort of patients with AMI[27] (Table 2). In striking contrast with the previous studies, these authors reported that the extent of comorbidities such as previous myocardial infarction, CHF, hypertension, diabetes, renal failure, chronic pulmonary disease, and history of stroke substantially reduces the independent prognostic impact of LBBB in AMI, thus minimizing the differences in 1-year mortality between subjects with and without LBBB. This finding supports the concept that unadjusted differences in mortality are mainly due to poorer LV function and concomitant diseases.

In a random-sampled population of 855 men aged 50 years in 1963, Eriksson *et al.*[28] (Table 2) did not describe a significant relationship between bundle-branch block and ischemic heart disease in a 30-year follow-up. On the other hand, men who had developed BBB also had a greater heart volume at age 50 years and were more often diagnosed with CHF compared with control subjects during follow-up. These findings suggest that BBB results from a progressive disease affecting not only the conduction system but the myocardium itself. Furthermore, no increased mortality was noted in men with BBB at follow-up, and there was no difference in the incidence of ischemic heart disease or death due to cardiovascular diseases compared with control subjects. Although these results cannot be readily extrapolated to subjects with LBBB, the impressive length of follow-up gives reason for a detailed analysis and perhaps clarifies discrepancies with other studies. Left bundle-branch block early affects prognosis of ischemic heart disease; several different mechanisms account for such an effect. When LBBB expresses an unrecognized underlying non-ischemic structural heart disease, LV performance may be depressed and inadequate to face up to an acute ischemic event. Moreover, LBBB itself induces intra- and interventricular asynchrony,[29, 30] abnormal LV diastolic filling patterns,[31, 32] and impairment of LV systolic performance.[33] Finally, in LBBB the prolongation of the depolarization phase and the subsequent increase in vulnerable repolarization time heightens the risk of life-threatening ventricular arrhythmias in the presence of frequent ventricular ectopic beats, a common finding in the setting of ischemic heart disease.[34, 35] In the study by Eriksson *et al.*, the 30-year follow-up allowed the detection of a slowly progressing degenerative heart disease-related BBB, thus unmasking the real incidence of initially silent CAD-unrelated dilated cardiomyopathy. Moreover, the long observational period likely balanced CAD-related mortality in subjects with BBB compared with those with normal intraventricular conduction.

On the basis of the evidence presented so far, it is imperative in clinical practice to consider the possibility that LBBB represents the clinical onset of an idiopathic dilated cardiomyopathy[36] or an infective, hypertensive, or valvular "dilated heart disease." This is particularly true in "tricky" forms of clinically silent structural heart disease, often characterized by borderline values of LV volume and ejection fraction.

The Issue of Advanced Atrioventricular Block

Several studies published during the last three decades have shown that patients with chronic BBB and nonfunctional atrioventricular (AV) block induced by incremental atrial pacing and/or infranodal conduction time (His to ventricle interval, HV) ≥ 70 ms had a significantly higher incidence of progression to spontaneous second- or third-degree AV block, with subjects with HV interval ≥ 100 ms presenting the highest risk.[37–39]

Taken together, these studies claim that surface ECG analysis is of limited value in identifying patients with LBBB at higher risk for AV block, and that electrophysiologic evaluation is of great help in defining prognosis of patients with BBB. On the other hand, it has been reported that in symptomatic patients with BBB the practical usefulness of electrophysiologic study is questionable, since risk stratification can be easily obtained by ECG.[40] Moreover, Rosen *et al.* failed to demonstrate any relationship between prolonged HV interval and occurrence of spontaneous AV block.[41]

Recent data from the International Study on Syncope of Uncertain Etiology (ISSUE)[42] show that in patients with BBB (patients with LBBB representing 38% of the study population), syncope, and negative electrophysiologic study, most syncopal recurrences are due to prolonged asystolic pauses mainly attributable to paroxysmal AV block, as assessed by implantable loop recorder traces. This finding claims a very low negative predictive value of an invasive electrophysiologic study in ruling out a paroxysmal AV block as the cause of syncope, since 33% of the patients with a negative study had a documented episode of AV block. Notably, the study failed to identify any risk predictor of future AV block. The authors conclude that in patients with symptomatic BBB and negative electrophysiologic study, an implantable loop recorder-guided strategy is reasonable, with pacemaker implantation safely delayed until symptomatic bradycardia is documented.

The Long and Winding Road of Clinical Management

As stated in a consensus document of the Study Group of Sport Cardiology of the European Society of Cardiology,[43] subjects who have positive findings at basic clinical evaluation, as in the case of LBBB, should be referred for additional testing, initially noninvasive such as echocardiography, 24-h ambulatory Holter monitoring, and exercise testing. In selected cases, invasive tests such as coronary angiography and electrophysiologic study may be necessary to confirm or rule out the suspicion of heart disease.

Complete LBBB is also listed among the medical disqualifications for flying duties.[44] Both the U.S. Federal Aviation Administration (FAA) and the Joint Aviation Requirements standards (the European approach to medical standards for flying fitness)[45] consider LBBB as a disqualifying condition unless structural heart disease is excluded. According to the UK Civil Aviation Authority policy, the exact requirements to rule out heart disease in the presence of LBBB are set out in a specific CAA Medical Division protocol. The finding of LBBB on resting ECG requires a complete cardiology evaluation including exercise ECG, 24-h ECG, echocardiogram, evaluation of possible CAD at least with myocardial perfusion scan in subjects aged > 40 years, and electrophysiologic study in the presence of LBBB and I degree AV block. Class 1 certificate applicants need to show no abnormal instrumental findings and a 3-year period of stability before a certificate can be issued.

Unless we are dealing with such particular kinds of patients, it is reasonable that routine patients with new onset LBBB undergo second-step investigations, that is, echocardiogram and Holter ECG. This latter is particularly helpful in identifying both advanced AV blocks and heart disease-related tachyarrhythmias. The clinical suspicion of ischemic heart disease, based on the presence of risk factors and typical symptoms, should lead the physician to assess myocardial perfusion by means of imaging techniques, given the low specificity of ECG ST-segment changes during stress test in the presence of

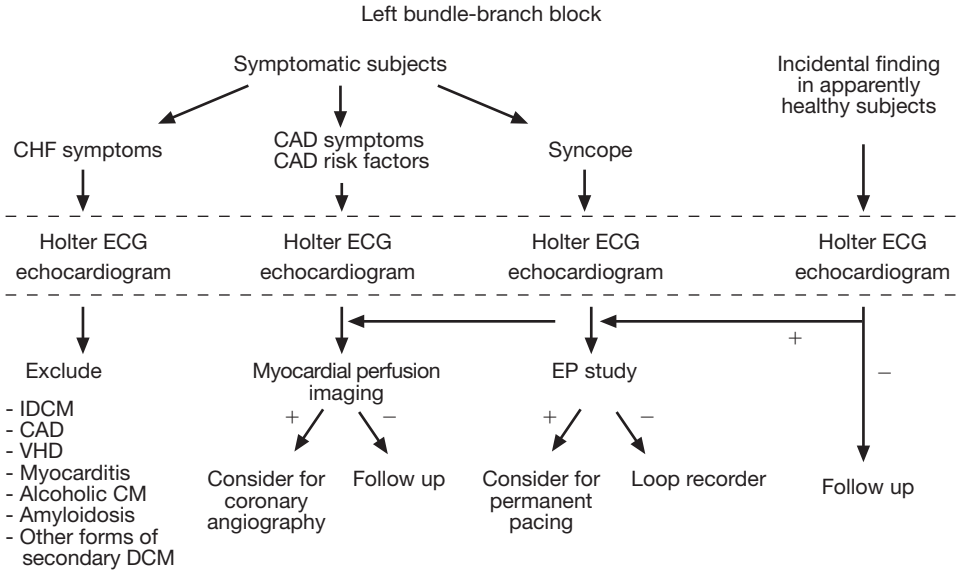

FIG. 1 Flow-chart of proposed clinical approach to an individual or patient presenting with left bundle-branch block. CHF = congestive heart failure, CAD = coronary artery disease, EP = electrophysiologic, IDCM = idiopathic dilated cardiomyopathy, VHD = valvular heart disease, CM = cardiomyopathy, DCM = dilated cardiomyopathy.

LBBB. In the absence of significant instrumental and clinical findings, a cautious "wait and see" attitude is probably the preferred choice, and annual clinical follow-up may be scheduled. Only apparent anomalous clinical and/or instrumental findings should lead to a third-step investigation (i.e., coronary angiography or electrophysiologic study) (Fig. 1).

Future Perspectives: Should We Treat Patients or Electrocardiographic Traces?

Recent successes of cardiac resynchronization therapy (CRT) in chronic heart failure[46–49] highlight the hemodynamic effects of LBBB, so far considered roughly an electrocardiographic entity. Prolongation of QRS complex >120 ms results in some degree of intra- and interventricular dyssynchrony, usually characterized by noncoordinated contraction of interventricular septum and LV posterior or posterolateral wall. This results in waste of energy contraction, inability to generate effective intraventricular pressure, and increased wall tension at the level of latest activated regions of the LV.[50] Conventional echocardiography- and TDI-based techniques for intra- and interventricular dyssynchrony quantification currently offer the potential for an accurate definition of the effects of LBBB on cardiac contraction[51–53] and seem to identify with some degree of accuracy those patients who will most benefit from CRT.[54, 55]

While referral for resynchronization therapy currently applies to subjects with severe heart disease, indications for physiologic pacing are expanding. The new millennium is marking the transition of LBBB from risk stratification factor to rational therapeutic target.

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