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REVIEW

Left bundle branch block: from cardiac mechanics to clinical and diagnostic challenges

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Left bundle branch block (LBBB) results in an altered pattern of left ventricular (LV) activation and subsequent contraction, causing remarkable changes in LV mechanics, perfusion and workload and ultimately leading to pathologic cardiac remodelling. Clinical and diagnostic notions about the LBBB phenomenon had evolved from just an electrocardiographic pattern to a critically important finding affecting diagnostic and clinical management of many patients and adversely influencing their outcomes. Recent advances in imaging techniques significantly improved the assessment of patients with LBBB and provided additional insights into pathophysiological mechanisms of LV remodelling. In the current review we summarized currently available data on the LBBB epidemiology, diagnosis, its impact on clinical management and prognosis, and the role and place of various imaging modalities in assessing cardiac mechanics and perfusion abnormalities, as well as their potential implications for diagnostic and treatment strategies.

Keywords Left bundle branch block • Electrocardiography • Cardiovascular imaging • Left ventricular remodelling • Prognosis

Introduction

Left bundle branch block (LBBB) was first described on the electrocardiogram (ECG) more than 100 years ago.[1] Over the years, the interest to this disorder of cardiac ventricular conduction has increased significantly and evolved from just an electrocardiographic finding to the 'cardiac clinical entity'[2] posing multiple challenges to the clinicians. Its presence affects patient's management in acute clinical conditions, such as myocardial infarction (MI), and provides additional insights into the prognosis of patients with chronic cardiovascular diseases. Moreover, LBBB has been reported to adversely affect prognosis even in individuals who have no symptoms or known cardiovascular disorders and LBBB has been an incidental finding on ECG. Finally, LBBB is an important factor affecting patients' management, and performance and interpretation of diagnostic tests.

Attention regained by LBBB in the last decade was largely associated with the implementation of the cardiac resynchronisation therapy (CRT) and accumulation of data demonstrating considerably higher rate of responders in patients with LBBB QRS morphology. The interest to this disorder was further promoted by increasing numbers of patients with iatrogenic LBBB after transcatheter aortic valve replacement (TAVR), which constitutes one of the most frequent complications of this procedure and significantly affects outcomes.

The purpose of this review was to summarize currently available data on the LBBB epidemiology, diagnosis, its impact on patients' management and prognosis, and the role and place of various imaging modalities in detection of the changes in cardiac mechanics and their potential implications on treatment strategy.

Aetiology and epidemiology

LBBB is a rare finding in young individuals and almost never occurs before 35 years of age, suggesting it could be an acquired condition.[2] In asymptomatic adults, including athletes, an estimated prevalence of LBBB ranges between 0.1 and 0.8%.[3–5]

In prospective population studies, the prevalence of LBBB strongly correlates with age with an average age at LBBB diagnosis being 70 ± 10 years in men and 68 ± 11 years in women.[6] Proportion of

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those with LBBB increases progressively from <1% at age of 50 to 6% by 80 years.[6,7]

Relatively little is known about the aetiology of LBBB, because it usually has a silent onset. In several longitudinal studies, factors found to be associated with its development included arterial hypertension, coronary artery disease (CAD), valvular heart disease, cardiomyopathies, myocarditis, as well as various electrocardiographic abnormalities, such as left ventricular (LV) hypertrophy and ST-T changes.[2,6] In some individuals, however, LBBB develops in the absence of any of these risk factors.

Currently available evidence suggests that LBBB development can be modulated by genotype. The recent meta-analysis identified common variants in 22 loci associated with QRS duration and cardiac ventricular conduction.[8] Gene expression data derived from human and animal studies have shown that variations in connexin 40 (expressed in atria, proximal conduction system) and connexin 43 (expressed in Purkinje cells and cardiomyocytes) are associated with cardiomyopathy and can cause LBBB.[9,10] These findings are supported by large genome-wide association studies demonstrating strong associations of genetic markers close to the gene for connexin 43 (GJA1) with QRS duration.[11] Moreover, connexin 43 is downregulated in end-stage heart failure (HF), and this altered expression is associated with an increased risk of ventricular arrhythmias.[10] Connexin 43 can be regulated at the post-transcriptional level, thereby affecting its turnover and function.[12] Ischaemia induces dephosphorylation of connexin 43 and its translocation from the gap junction to intracellular stores, resulting in reduced intraventricular conduction.[13] However, the role of molecular mechanisms in the pathogenesis of LBBB and patients' response to CRT remains to be clarified.

Over the last decade it became apparent that LBBB could also develop as a complication after TAVR. The incidence of TAVR-induced LBBB varies widely between 7% and 83% most likely depending on the device used.[14–16] A recent systematic review reported mean post-TAVR LBBB rates of 14.0% (from 4.0 to 30.2%) and 45.2% (from 22.0 to 65.0%) for the Sapien and CoreValve prostheses, respectively.[17] The mechanism of development of LBBB associated to TAVR can be explained by the proximity of the atrioventricular node and the left bundle branch of the cardiac conduction system to the aortic valve and a likely mechanical interaction of the implanted valve frame with the conduction system structures.[16] Other factors, including device geometry and mechanical characteristics, baseline QRS duration, pre-procedural right bundle branch block (RBBB), male gender, history of MI, previous coronary artery bypass grafting, and depth of implantation were reported as main predictors of new onset of LBBB after TAVR.[17]

Definition and ECG criteria

Identification of complete LBBB on the ECG may not be so straightforward and it is not fully standardized yet. Widely recognised conventional criteria for LBBB, also applied in large trials investigating the effectiveness of CRT,[18,19] include prolongation of the QRS complex (≥120 ms) due to delayed activation of the LV, accompanied by a characteristic morphology of the QRS complex, such as QS or rS pattern in lead V1, and a monophasic R wave with no Q waves in leads V6 and I,[20] which may be completed by delayed intrinsicoid deflection >60 ms in the same leads, QS pattern in lead aVR, and discordant ST/T wave (*Table 1*, *Figure 1A*).[21] However, it worth noting that these criteria were introduced in 1941[24] on a dog model and extrapolated on humans afterwards. More recent studies utilizing endocardial mapping demonstrated that >30% of the patients meeting the conventional ECG criteria of LBBB did not have significant delays between the start of activation of the right and LV endocardium,[25,26] and therefore do not actually have complete LBBB.

In 2009 American Heart Association (AHA), American College of Cardiology Foundation (ACCF) and Heart Rhythm Society (HRS) proposed an amendment to the classical diagnostic criteria including a broad notched or slurred R wave in leads I, aVL, V5 and V6 (*Table 1*, *Figure 1B*).[22] This concept was strongly supported by the group of Strauss D., who reinforced the diagnostic value of the mid-QRS notches and provided their electrophysiological background using computer simulation of LBBB.[23] Moreover, in order to avoid the overdiagnosis of complete LBBB in patients with LV hypertrophy and left anterior fascicular block, who may have QRS slightly exceeding 120 ms, the same group suggested the higher threshold of QRS duration: ≥140 ms in men and ≥130 ms in women. A higher QRS cut-off for men was explained by the larger heart size, which takes longer time to depolarize both in normal and pathological conditions (*Table 1*, *Figure 1C*).[23]

The clinical value of these new criteria was investigated in several studies enroling patients undergoing CRT.[27–29] In a cardiac magnetic resonance (CMR) myocardial tagging study, patients meeting Strauss' criteria had a longer time delay between septal and lateral LV peak circumferential wall strain than those who satisfied only AHA/ACCF/HRS criteria (210 ± 137 ms vs. 122 ± 102 ms, $P = 0.045$).[27] They also predominantly demonstrated dyssynchronous LV contraction by two-dimensional echocardiography strain imaging (early termination of contraction in the septal wall and initial pre-stretch with late contraction of the opposing posterolateral wall).[28] The value of 'true'-LBBB using Strauss' criteria in improving the selection of potential CRT responders has not been fully established so far. Despite the fact that several studies demonstrated a higher event-free survival rate and better echocardiographic response in CRT patients with 'true'-LBBB morphology,[28–30] the authors failed to prove its independent association with outcomes after adjustment for aetiology (ischaemic/non-ischaemic) and QRS duration.[30]

Finally, in some patients LBBB was found to depend on heart rate ('rate-dependent LBBB'). During tachycardia this phenomenon occurs because of impulse falling in the relative refractory period of the bundle branch cells, also referred to as 'phase-3 block.' Spontaneous depolarization in phase 4 rendering the cells refractory to the next impulse is the most common explanation of the block occurring at a slower heart rate.[2]

Clinical significance and impact on prognosis and outcome

LBBB is associated with a poorer prognosis both in comparison to normal intraventricular conduction and RBBB.[31–34] Early studies reported a mean survival of less than 5 years after detection of LBBB.[35] More recent population-based longitudinal studies suggest that

Table 1 Existing electrocardiographic criteria to diagnose complete left bundle branch block in adults.

Criteria	de Luna[21]	AHA/ACC/HRS[22]	Strauss[23]
QRS duration (m/f, ms)	≥120/≥120	≥120/≥120	≥140/≥130
QRS notching or slurring	-	Broad notched/slurred R wave in leads I, aVL, V5, and V6	Mid-QRS notching/slurring in ≥2 of leads V1, V2, V5, V6, I, and aVL
QS or rS in leads V1 and V2	+	-	+
Delayed intrinsicoid deflection (>60 ms)	Present in leads V6 and I	Present in leads V5 and V6 absent in leads V1, V2, and V3	-
Usually discordant ST and T wave	+	+,a	-
QS pattern with a positive T wave in aVR	+	-	-
Q waves in leads I, V5, and V6	-	Absent	May be present in patients with concomitant anterior and/or apical infarct
ECG pattern V1, V2			
ECG pattern V5, V6			

+Criteria included as a criterion.
-Not mentioned criteria.
[a]Positive T wave in leads with upright QRS may be normal (positive concordance).

patients with LBBB have increased rates of cardiovascular mortality, sudden cardiac death (SCD), CAD, and HF (*Table 2*).[32,37] In the Framingham study half of cardiovascular deaths occurred in subjects with LBBB.[32] However, the issue of whether it is the LBBB itself or its combination with other cardiovascular disorders (i.e. CAD) that adversely affects mortality remains largely unsolved.

Longitudinal population-based studies have provided additional insights into the prognosis of asymptomatic patients with LBBB. In a large sample of 3983 subjects followed up for 29 years, LBBB was associated with increased cardiovascular morbidity and mortality, with SCD commonly being the first manifestation of cardiovascular disease in those with LBBB.[49] Cardiovascular risk factor free patients developing LBBB at a younger age (<45 years) had better prognosis compared with those who developed LBBB during or after their fifth decade and had associated risk factors.[49]

In a recent study conducted on the general population, prolonged QRS in a standard 12-lead ECG (≥110 ms with different QRS morphology including LBBB) was strongly associated with increased all-cause mortality, cardiac mortality, and sudden arrhythmic death in a large middle-aged cohort, while LBBB morphology separately predicted only sudden arrhythmic death.[42] In another cohort of patients with severe cardiac pathology (HF with LV ejection fraction (EF) ≤39%), LBBB as well as other interventricular conduction disorders (IVCD) including RBBB were equally strong independent predictors of mortality in all age groups.[47] Available evidence therefore suggests that LBBB can result from either intrinsic conduction system degeneration or an extrinsic insult from a variety of cardiovascular diseases, and the outcomes in these 2 distinct populations with LBBB could be different.[2]

The impact of the TAVR-induced LBBB on prognosis remains to be clarified as the results of available studies have so far been conflicting (*Table 2*).[50] In a multicentre Dutch registry, including patients with both Medtronic CoreValve and Edwards Sapien valves, all-cause mortality during long-term follow-up after TAVR was significantly higher in patients who developed LBBB than in patients with no LBBB (37.8% vs. 24.0%; $P = 0.002$).[16] There was some evidence suggesting that LBBB develops more frequently in patients with Medtronic CoreValve System, but the device type had no impact on the mortality of patients with TAVR-induced LBBB. Overall, iatrogenic LBBB was shown to be the strongest independent predictor of mortality at follow-up. These data confirm that conduction disturbances and, consequently, impaired ventricular performance, have a negative impact on outcome.

Conversely, a recent subanalysis of the PARTNER trial, in which patients with baseline conduction abnormalities and/or previous pacemaker implantation have been excluded, TAVR-induced LBBB correlated only with an increased rate of new pacemaker implantation during hospitalization and at 1-year follow-up, but had no

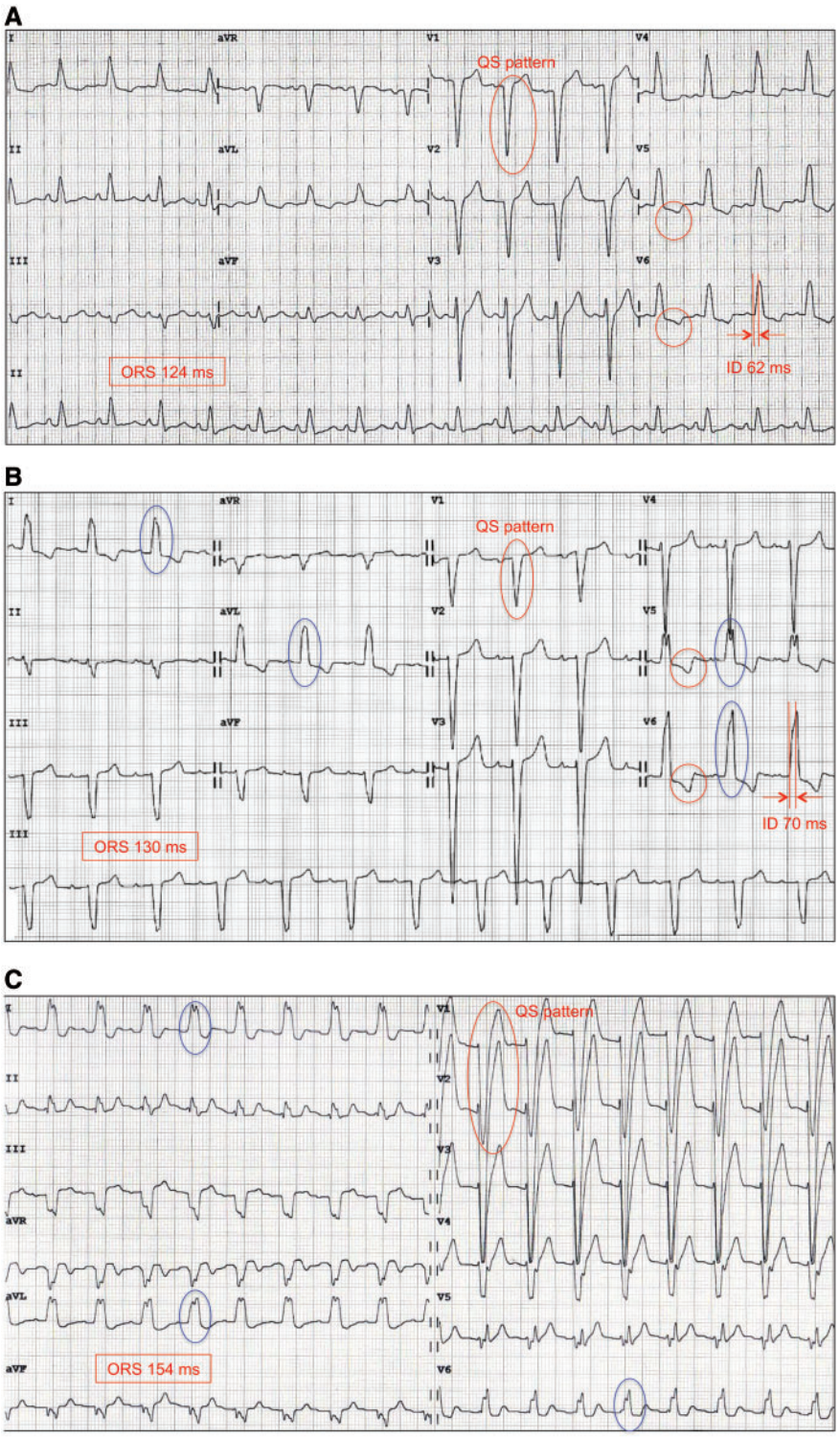

Figure 1 Examples of electrocardiograms showing specific features indicative of complete left bundle branch block compliant with different criteria. (*A*) Conventional electrocardiographic criteria proposed by Wilson (1941)[24] currently used in several CRT trials. (*B*) Criteria defined by the AHA/ACCF/HRS recommendations (2009) including a broad notched or slurred R wave in leads I, aVL, V5 or V6 (blue circles). (*C*) Strauss' criteria including QRS duration ≥140 ms in men and ≥130 ms in women, and mid-QRS notches in ≥ 2 of leads V1-2, V5-6, I, and aVL (blue circles). CRT, cardiac resynchronization therapy; ID, intrinsicoid deflection.

Table 2 Studies investigating the outcome of both patients with associated cardiac diseases and individuals with isolated left bundle branch block

Study	Patients (*n*)	Age, years	Male gender	Study population	Follow-up	Prevalence, *n*	Results
Rotman and Triebwasser 1975[36]	237 000	40 ± 7 for LBBB group	237 000 (100%)	U.S. Air Force	8.8 ± 4.8 years for LBBB group	125 (0.05%)	No increased cardiovascular morbidity and all-cause mortality for LBBB
Schneider *et al.* 1979[32]	5209	N/A	N/A	Framingham	18 years	55 (%)	Increased cardiovascular mortality for LBBB
Freedman *et al.* 1987[31]	15 609	54 ± 9	13 181 (84%)	CASS Study, Chronic CAD	4.9 ± 1.3 years	250 (1.6%)	LBBB was a strong independent predictor of all-cause mortality (survival rate 42 ± 3% vs. 74 ± 3% vs. 85 ± 3% for LBBB, RBBB and no bundle branch block, respectively, $P < 0.0001$)
Fahy *et al.* 1996[37]	110 000	51 ± 13 for LBBB group	82 (73.2%) for LBBB group	Screening	Mean: 9.5 years; median: 8.75 years	112 (0.1%)	Increased prevalence of cardiovascular disease at follow-up (21% for LBBB vs. 11% for no BBB; $P = 0.04$). Increased cardiac mortality for LBBB in association with CAD
Eriksson *et al.* 1998[7]	855	50	855 (100%)	Men born in 1913	30.5 ± 0.5 years	3 (0.4%) upon enrolment, 22 over follow-up	No differences in all-cause mortality for LBBB Increased mortality for LBBB in conjunction with CAD only
Hesse *et al.* 2001[33]	7073	66 ± 9 for LBBB group	5290 (74.8%)	Patients referred to nuclear exercise testing	6.7 ± 1.6 years	150 (2%)	Increased all-cause mortality for LBBB (24% vs. 11% in those with normal QRS, $P < 0.0001$). LBBB is a strong independent predictor of mortality (HR 1.5; 95% CI: 1.0 to 2.0; $P = 0.017$).
Brilakis *et al.* 2001[38]	894	75.7 ± 10.3 for LBBB group	546 (61.1%)	Acute MI	5.0 years	53 (5.9%)	Significantly higher long-term unadjusted mortality for LBBB (post-discharge survival at 1, 3, and 5 years was 78%, 56%, and 51% vs. 92%, 85%, and 76% in the group without BBB, $P < 0.0001$). Trend towards increased in-hospital mortality for LBBB (17.0% vs. 9.1% for patients with no BBB, $P = 0.11$). Lower pre-discharge LV EF (38 ± 16% for patients with bundle branch block vs. 50 ± 15%, $P < 0.0001$).
Baldasseroni *et al.* 2002[34]	5517	63 ± 12	3222 (76.5%)	Chronic HF of different aetiology	1 year	1391 (25.2%)	Increased 1-year mortality from any cause (HR 1.70; 95% CI, 1.41 to 2.05) and SCD (HR 1.58; 95% CI, 1.21 to 2.06)
Stenestrand *et al.* 2004[39]	88 026	77 ± 9 for LBBB group	56075 (63.7%)	Acute MI	1 year	8041 (9.1%)	Increased unadjusted 1-year mortality for LBBB (relative risk of death of 1.19 (95% CI, 1.14 to 1.24, $P < 0.001$)
Guerrero *et al.* 2005[40]	3053	69 ± 10 for LBBB group	2226 (72.9%)	Acute MI, emergency cardiac catheterization	30 days	48 (1.6%)	Increased in-hospital death for LBBB (14.6% vs. 7.4% for RBBB and 2.8% for no BBB, $P < 0.0001$). LBBB is an independent predictor of in-hospital death (OR 5.53, 95% CI 1.89 to 16.1, $P = 0.002$).

Continued

Table 2 *Continued*

Study	Patients (*n*)	Age, years	Male gender	Study population	Follow-up	Prevalence, *n*	Results
Wong *et al.* 2006[41]	17 073	68.5 (61–75) for LBBB group	11569 (67.8%)	Acute MI (HERO-2 trial)	30 days	300 (1.76%) at randomization + 25 (0.16%) within 60 min after commencement of fibrinolytic therapy	Increased 30-day mortality for new LBBB (adjusted ORs 2.97 (1.16–7.57) No significant prognostic impact on 30-day mortality for old LBBB (adjusted ORs 0.68 (0.48–0.99).
Aro *et al.* 2011[42]	10 899	44 ± 8.5	52%	Middle-aged Finnish general population	30 ± 11 years	33 (0.3%)	Prolonged QRS ≥110 ms (with different morphology) was a strong predictor of all-cause mortality (multivariate-adjusted relative risk [RR] 1.48, 95% CI 1.22–1.81, $P < 0.001$), cardiac mortality (RR 1.94, CI 1.44–2.63, $P < 0.001$), and sudden arrhythmic death (RR 2.14, CI 1.38–3.33, $P = 0.002$). LBBB morphology predicted only sudden arrhythmic death (RR 2.71, CI 1.20–6.11, $P = 0.04$).
Houthuizen *et al.* 2012[16]	679	81 (77–85)	319 (47%)	TAVR patients	449.5 (174–834) days	233 (34.3%)	TAVR-induced LBBB was an independent predictor of all-cause mortality (HR 1.54; CI 1.12–2.10).
Nazif *et al.* 2014[43]	1151	83.7 ± 7.3 for LBBB group	503 (43.7%)	TAVR patients without conduction disturbances or PPI at baseline (PARTNER trial)	1 year	121 (10.5%)	No increase in 1-year all-cause/cardiovascular mortality, hospitalization rate, stroke, myocardial infarction. Increased rate of pacemaker implantation during hospitalization (8.3 vs. 2.8%, $P = 0.005$) and 1 year-follow-up (4.7 vs. 1.5%, $P = 0.01$).
Urena *et al.* 2012[44]	202	80 ± 8	81 (40.1%)	TAVR patients without conduction disturbances or PPI at baseline	1 (0.5–2) year	61 (30.2%)	No differences in overall or cardiovascular mortality. Reduced LVEF at follow-up for LBBB (decrease of 4.75 ± 8.02%; 95% CI: 0.99 to 8.50; $P = 0.031$). Higher frequency of syncope and complete AVB requiring PPI for patients with new LBBB (16.0% vs. 0.7%, $P < 0.001$; and 20.0% vs. 0.7%, $P < 0.001$, respectively).
Franzoni *et al.* 2013[45]	238	79.4 ± 7.6	128 (53.8%)	TAVR patients without conduction disturbances or PPI at baseline	348.5 (0 to 1096) days	63 (26.5%)	No differences in overall, cardiovascular mortality or need for PPI for TAVR-induced LBBB.

Continued

Table 2 *Continued*

Study	Patients (*n*)	Age, years	Male gender	Study population	Follow-up	Prevalence, *n*	Results
Testa *et al.* 2013[46]	818	82 ± 5 for LBBB group	372 (45.6%)	TAVR patients without conduction disturbances or PPI at baseline	438 (174–798) days	224 (27.4%)	No differences in overall, cardiovascular mortality or hospitalization for heart failure for TAVR-induced LBBB. LBBB was associated with a higher short-term rate of pacemaker implantation (15% vs. 9.8%, P = 0.02).
Lund *et al.* 2014[47]	4233[a]	56 ± 9	3286 (78%)	Swedish Heart Failure	29 (12–53) months	847 (20%)	LBBB was a strong independent predictor of all-cause mortality in all ages (multivariable HR 1.29 (1.07–1.56, P = 0.009)*; 1.17 (1.06–1.30, P = 0.002)[γ], and 1.10 (0.99–1.22, P = 0.091)[ζ])
	6257[b]	73 ± 4	4524 (72%)	Registry, LV		1706 (27%)	
	4233[c]	85 ± 3	2089 (62%)	EF ≤ 39%		925 (28%)	
Witt *et al.* 2016[48]	1436	67 ± 13	780 (54%)	LBBB patients with LV EF 36%-50%	5 years	N/A	LBBB was associated with significantly worse mortality (HR: 1.17; 95% CI: 1.00–1.36), an LVEF drop ≤35% (HR: 1.34; 95% CI: 1.09–1.63), and the need for an ICD.

CAD, coronary artery disease; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LV, left ventricle/ventricular; MI, myocardial infarction; N/A, not available/applicable; PPI, permanent pacemaker implantation; RBBB, right bundle branch block; TAVR, transcatheter aortic valve replacement.
[a]Patients ≤65 years.
[b]Patients 66–80 years.
[c]Patients >80 years.

impact on 1-year all-cause mortality, cardiovascular mortality, rate of hospitalization, stroke or MI.[43] Similar results were reported by other studies.[44–46]

These conflicting results could be explained by differences in baseline patient characteristics, time point chosen for determination of LBBB onset (early vs. late, with the latter missing the transient LBBB cases), inclusion and/or exclusion criteria for individual studies (inclusion of patients with pacemakers in the LBBB group may confound the expected mortality due to decreased chances of bradyarrhythmic and SCD), lack of uniformity in diagnostic criteria used for LBBB, or lack of statistical power.[51]

Evidence is stronger regarding the effect of TAVR-induced LBBB on the LV performance reporting increase of LV EF after TAVR in patients with non-complicated post-operative period but decrease of LV EF in patients with induced LBBB.[43,44] It is worth noting that persistent LBBB after surgical aortic valve replacement was reported to occur in remarkably lower number of cases (early LBBB in 4% and persistent LBBB during follow-up in 1.7% of patients) than after TAVR.[52] Given the potential adverse effects of LBBB, the higher incidence of new LBBB in patients receiving TAVR should be weighted while addressing the management of patients with symptomatic severe aortic stenosis.[52]

Pathophysiological consequences of asynchronous electrical activation and LV remodelling

LBBB results in an altered pattern of LV activation and subsequent contraction. Due to block in the Purkinie system, the electric impulse is being transmitted through the myocardium but not through the specialized conduction tissue. This prolongs the time needed for the electric impulse to reach all LV segments and leads to mechanical dyssynchrony with the RV free wall and interventricular septum (IVS) contracting earlier than the lateral LV wall.[25,53]

Active forces generated by the RV and IVS at early systole become imbalanced because they are not opposed by the LV lateral regions. As a consequence, RV contraction applies force on the IVS through the attachment points, causing it to hinge leftwards and flatten, displacing blood towards the lateral wall.[54] Early septal contraction and inward motion terminates LV filling by closing the mitral valve, but does not lead to a relevant LV pressure rise, as the contracting myocardial volume is too small.[55] Prestretch of the lateral wall at pre-ejection phase due to IVS contraction and displacement of blood results in its powerful contraction. It enables LV ejection to start and causes a force imbalance in IVS which curves back into the RV.[54] Additionally, it leads to 'rebound' stretching of IVS during first part of the LV ejection despite the fact that septal myofiber stress still increases.[56] Most of the LV ejection work is done by the lateral regions which in long-term ultimately causes their hypertrophy.[55]

The reduced septal blood flow and relative hyperperfusion in the lateral wall are a common finding in LBBB patients.[57,58] Two possible mechanisms of such perfusion dysbalance include: (i) physiologically altered autoregulation in response to reduced workload of the septum and higher workload of the lateral wall, and (ii) the impairment of diastolic coronary blood flow caused by the abnormal septal post-

systolic motion leading to compression of the septal perforators ('phasic flow'), reduction in the length of true diastole, and microvascular dysfunction due to impaired septal endothelial function.[59–61]

In the long run, in an animal model, the redistribution of circumferential shortening, external myocardial work and blood flow was associated with unfavorable LV remodelling including LV dilatation, asymmetric hypertrophy and decreased pump function,[58] altered cellular Ca^{++} transport and a pro-arrhythmic state.[2] Subsequent deformation of the mitral valve apparatus with annular dilatation and dyssynchronous papillary muscle contraction lead to development and progression of functional mitral regurgitation[62,63] which begets more LV dilatation and thereby aggravates HF which is often resistant to conventional medical therapy.[64]

Use of computational heart and circulation models as well as recent advances in simulation studies have in many cases revolutionised our knowledge about the electromechanical mechanisms of failing hearts.[54,65–69] Advanced level models (e.g. CircAdapt) may realistically simulate cardiovascular system mechanics and haemodynamics thus allowing to adjust multiple parameters and differentiate underlying mechanisms associated with LBBB and subsequent cardiac remodelling.[54,65,66,69] Data derived from simulation studies may help in the interpretation of cardiovascular imaging findings (e.g. through provision of more specific diagnostic criteria)[67] therefore contributing to overall improvement of diagnostic and clinical management of patients with LBBB.

The role of cardiovascular imaging

Echocardiography

Echocardiography has long been considered the primary imaging modality for the assessment of the patients with LBBB. Typical echocardiographic patterns indicative of abnormal LV activation and remodelling in LBBB include:

1. Relatively thin IVS demonstrating minor rapid short leftward motion before or early during ejection termed 'septal beak' or 'septal flash' (SF),[70] which is followed by rightward paradoxical septal motion (*Figure 2A, B*). This abnormal motion is usually accompanied by another septal mechanical anomaly—IVS stretch during early systole, called 'septal systolic rebound stretch'.[54] According to the results of an animal model, SF may be caused by active contraction of IVS, whereas its amplitude is modulated by the changes in diastolic ventricular pressures.[71] A more recent study using computer stimulation, however, confirmed such behavior of IVS only when both the RV free wall and IVS were simultaneously activated before the LV lateral wall.[54] Simulations demonstrated that the main mechanism driving SF was the early contraction of the RV free wall which pulled the IVS leftward, whereas the IVS systolic rebound stretch depended on the forces generated by the late contraction of the LV lateral wall.[54]

Subsequently, SF does not seem to represent the same phenomenon as septal systolic rebound stretch. Care should therefore be taken to distinguish between abnormal early systolic motion of IVS as observed by M-mode (SF), and pre-ejection IVS shortening followed by systolic stretching (septal systolic rebound stretch) observed by strain echocardiography, as it may potentially influence patients' management.[54] Early septal contraction should also be taken into account when defining timing of septal activation for evaluation of the LV strain or dyssynchrony, as the analysis of the ejection phase only may be misleading because it excludes the early contraction of the IVS.[71]

The differential diagnosis of SF in LBBB may be challenging due to a number of other conditions affecting IVS motion, which should be taken into consideration: CAD (ischaemic dyskinesis/aneurism); other conduction system abnormalities (ventricular pacing, ventricular pre-excitation, ventricular premature contractions); post-cardiac surgery state; abnormal ventricular interactions (right ventricular pressure/volume overload, severe mitral stenosis); pericardial disease (large pericardial effusion, constrictive pericarditis, congenital absence of pericardium) or posterior compression (ascites, pregnancy, hiatal hernia) (*Figure 3*). Noteworthy, an abnormal IVS motion resulting solely from conduction disorder is commonly characterized by preserved (but delayed) septal thickening, which is normally decreased or not present in a case of ischaemia/injury.[72]

2. Short motion of the apex towards septum resulting from an early initial contraction of IVS and a subsequent lateral motion during ejection due to the late contraction of the lateral wall leading to a highly specific typical back-and-forth motion of the apex termed 'apical rocking'[55] (*Figure 2C*).

Both SF and apical rocking are also considered as important prognostic factors and markers of treatment success which can help in selection of candidates for CRT. Thus, it was demonstrated that patients presenting with apical rocking/SF before CRT had better outcomes and long-term survival characteristics.[73,74] Moreover, correction of apical rocking/SF by CRT was associated with significant reverse remodelling of the LV.[74,75]

Despite both apical rocking and SF being direct consequences of the LBBB-induced dyssynchrony,[74] there is a proportion of patients having only one of these signs. Thus, in a large cohort of CRT candidates either SF or apical rocking alone was seen in 8.4 and 8.6% of patients, respectively.[74] Authors noted that LV motion patterns are modulated by infarct scar[74] and that scar tissue in a part of septum or antero-septum affects the presence of apical rocking[63] and SF.[54] Another potential cause of the detection of only one sign may be the suboptimal accuracy of visual assessment of SF and apical rocking,[74] especially in patients with borderline dyssynchrony.[76] It has been suggested that a low-dose dobutamine test may be useful to un-mask or potentiate LV dyssynchrony.[77]

3. Hypertrophy of the LV lateral wall with its relatively late contraction during ejection phase (*Figure 4A*).

4. Shorter filling and ejection time intervals, and longer isovolumic time intervals due to delayed contraction of lateral wall causing late aortic valve opening (*Figure 4B*).

Novel echocardiographic techniques and indexes

1. Typical mechanical contraction pattern obtained by two-dimensional speckle-tracking echocardiography longitudinal strain includes a first IVS peak shortening within 70% of the ejection phase followed by a late lateral wall peak shortening after aortic valve closure[78] (*Figure 5A*). This pattern has an important prognostic value as its absence was associated with unfavourable long-term outcome after CRT and increased risk of death, LV assist device implantation or heart transplantation after adjustment for CAD and QRS width.[30]

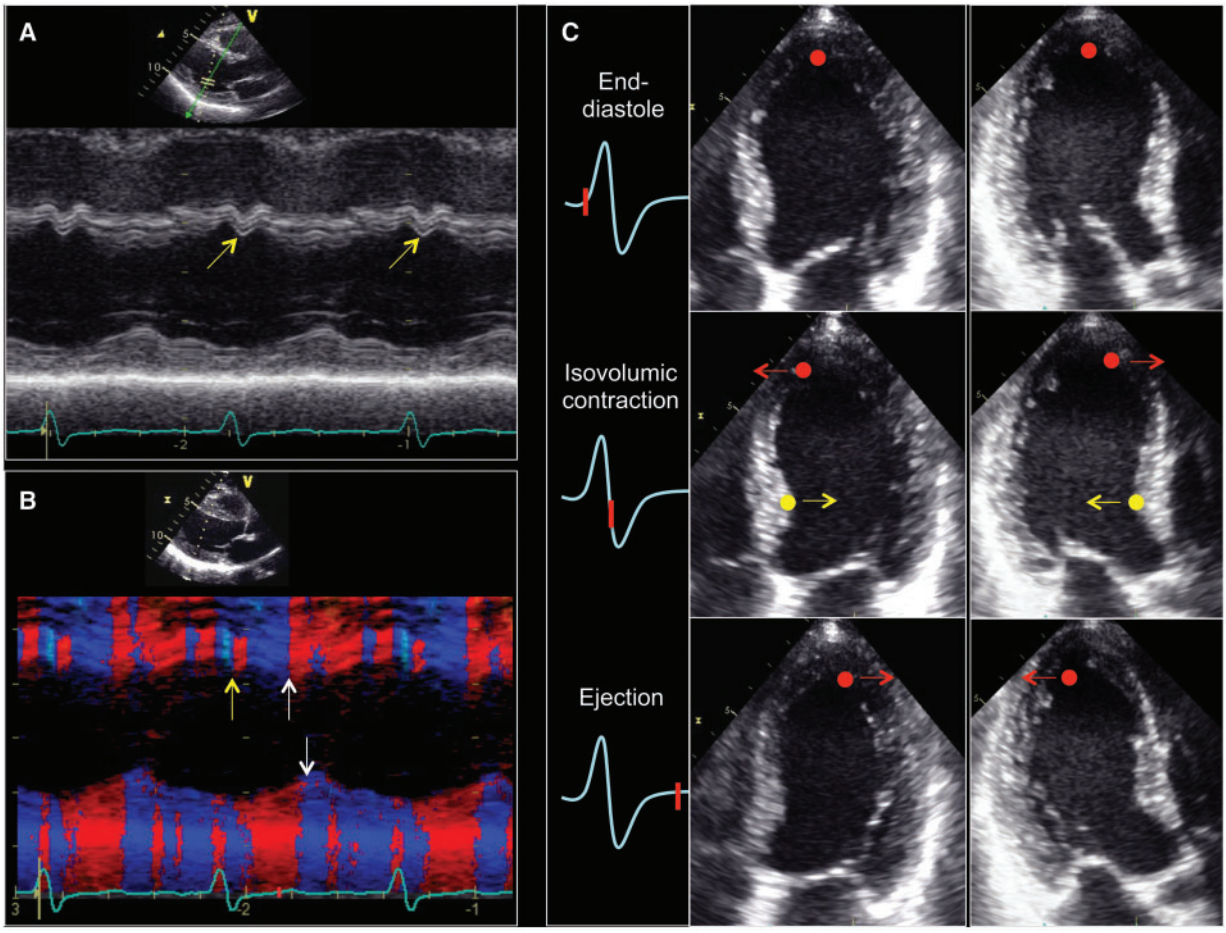

Figure 2 Typical echocardiographic patterns of abnormal left ventricular contraction termed 'septal beak' (or 'septal flash') and 'apical rocking' in patients with complete left bundle branch block. (*A*) M-mode tracing of the LV obtained from parasternal long-axis view demonstrating rapid short inward motion of the IVS before ejection (yellow arrows) followed by the stretching (outward motion) of the IVS with subsequent full contraction. (*B*) TDI M-mode tracing of the LV showing the changes in the direction of IVS movement (towards or away from the transducer) at different time intervals of cardiac cycle in a patient with LBBB, which can be easily tracked with the change of colour pattern. A short blue part and the next short red part during isovolumic contraction (yellow arrow) represent the early rapid movement of the IVS (septal flash); due to non-simultaneous electrical activation of the septum and lateral walls, they reach the peak of contraction at different time points (white arrows). (*C*) The sequence of mechanical events in patients with LBBB resulting in a typical septal-to-lateral apex motion pattern termed 'apical rocking'. An early electrical activation of the IVS causes its short contraction (yellow arrows) resulting in the medial apex moving (red arrows in the middle panels). Then, the delayed activation of the lateral wall pulls the apex laterally during the ejection phase while stretching the septum (red arrows in the bottom panels). IVS, interventricular septum; LBBB, left bundle branch block; LV, left ventricle; TDI, tissue Doppler imaging.

In a computer model, it has been shown that the double-peaked septal contraction (pattern 1) can change and become less typical due to co-existing impaired myocardial contractility. Pattern 1 can be transformed into pattern 2 (early systolic shortening followed by prominent systolic stretching) by reducing contractility of the IVS, and into pattern 3 (pseudonormal late-systolic shortening with less pronounced late systolic stretch) by reducing LV free wall or global LV myocardial contractility.[79] Only patterns 1 and 2 seem to be associated with LV reverse remodelling and better clinical outcomes after CRT.[79,80]

2. Newly developed speckle-tracking echocardiography parameters, such as start systolic index (the amplitude of peak segmental longitudinal strain during the first half of systole, normalized to the peak global longitudinal strain of the same image view multiplied by 100) and peak longitudinal displacement have been suggested for quantitative assessment of septal flash and apical rocking.[81] Authors showed that this automatic tool is comparably effective in identifying CRT responders as visual analysis by expert readers and significantly more effective than analysis performed by novice readers.[81]

3. Quantification of septal systolic rebound stretch obtained by speckle tracking echocardiography is another approach which has been shown to be a sensitive and practical diagnostic tool to assess the functional substrate amenable to CRT and to predict response.[82]

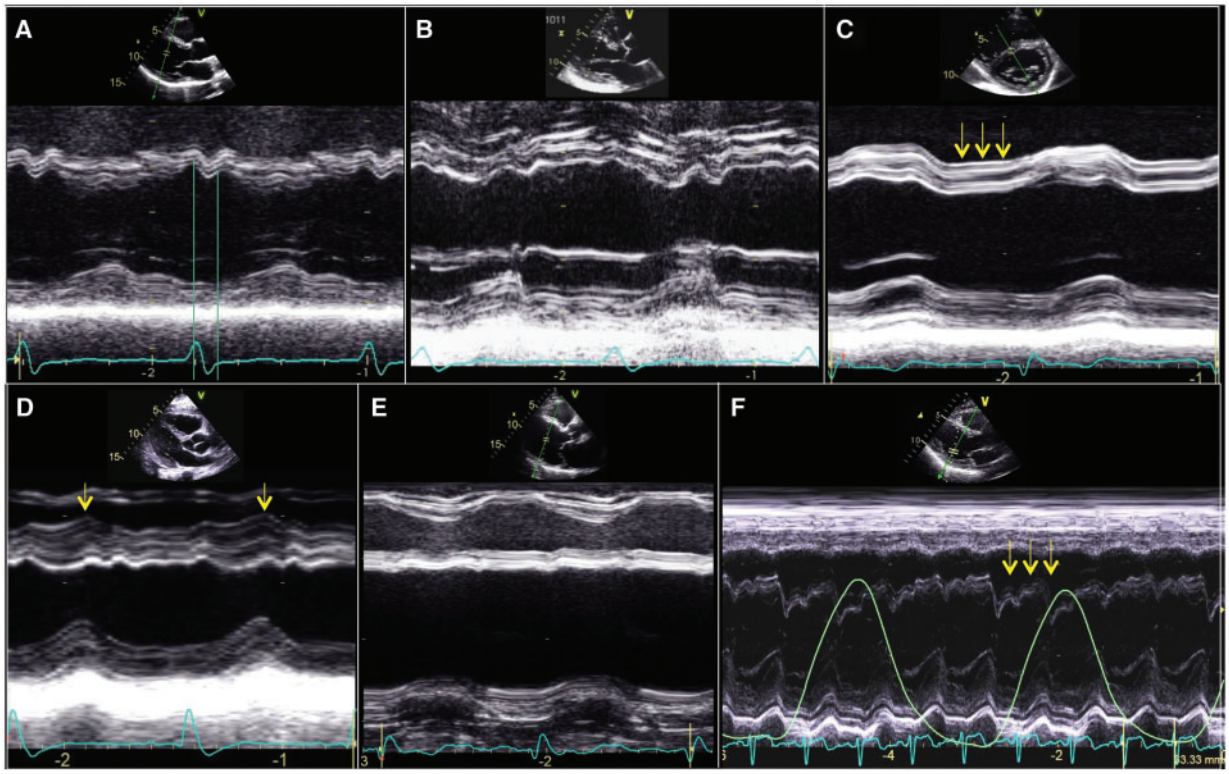

Figure 3 Comparison of the typical motion of the interventricular septum in a patient with left bundle branch block with other abnormal septal motion patterns obtained by M-mode echocardiography. (*A*) Septal flash in a patient with complete LBBB. Septal flash occurs early in systole during the QRS (green lines) before the opening of aortic valve. (*B*) Abnormal double-peaked septal motion in a patient with pacemaker. Septal contraction occurs later in systole, however before the contraction of lateral wall. (*C*) IVS motion pattern in a patient with volume overload of the right ventricle. Note flattening of the septum during diastole (arrows) and paradoxical movement of the septum in systole. (*D*) Abnormal IVS motion after open heart surgery. Contraction of the septum occurs towards the right ventricle with preserved septal thickening in systole (arrows). (*E*) Abnormal septal motion in a patient after anterior myocardial infarction. IVS is thin and hyperechogenic. Note absence of septal thickening during the cardiac cycle. (*F*) Septal bounce due to constriction and shift towards LV during inspiration (arrows) and towards RV during expiration in constrictive pericarditis. IVS, interventricular septum; LBBB, left bundle branch block; LV, left ventricle; RV, right ventricle.

4. Systolic stretch index is a recently developed quantitative parameter to provide an objective measurement of the apical rocking phenomenon.[66] It was obtained from the two-dimensional speckle-tracking radial strain analysis of the mid-LV short-axis view and defined as the sum of the posterior-lateral systolic prestretch at pre-ejection and septal systolic rebound stretch. A pre-implant systolic stretch index ≥9.7% was independently associated with more favorable clinical outcomes after CRT even in patients with intermediate QRS duration (120–149 ms) in whom CRT response is less certain by ECG criteria alone.[66]

5. LV workload quantification and analysis of energy loss and waste of myocardial work is a novel echocardiography-derived methodology, which may represent a mean to explore the haemodynamic impact of asynchronous electrical activation of myocardium in LBBB and potentially improve patients' stratification and management.[83] Using recently developed and validated non-invasive tool called LV pressure—strain loop area, researchers have been able to quantify regional myocardial work distribution and obtain information regarding metabolic demand (*Figure* 5B). Authors also demonstrated that contraction of the septum in patients with LBBB and chronic HF performs a net negative work (systolic lengthening), while after CRT the proportion of positive work (systolic shortening) increases dramatically.[84]

6. Evaluation of intraventricular fluid dynamics by echographic particle image velocimetry is another promising method potentially providing insights into the haemodynamic effects of altered electrical activation in LBBB patients and optimisation of patients' management. This technique allows tracking micro bubbles in the LV and analyse the overall haemodynamic forces associated with intraventricular blood motion, in particular identifying whether they are aligned along the base–apex direction, in compliance with the emptying–filling process, or they deviate by developing non-physiological transversal components[85] (*Figure 5C*). Authors showed that CRT responders present a longitudinal alignment of haemodynamic forces with a preferable base–apex orientation that is lost when the therapeutic support is discontinued. On the contrary, non-responders do not display

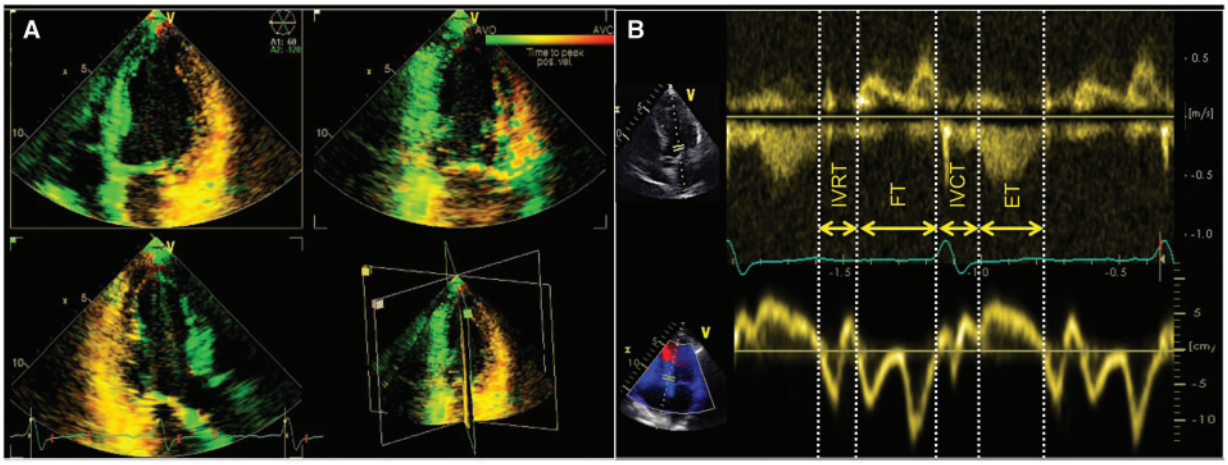

Figure 4 Typical electro-mechanical and haemodynamic changes in a patient with complete left bundle branch block. (*A*) The tissue synchronicity imaging uses the green-red color map to encode the time to the first positive myocardial velocity peak in a certain time window (red brackets on the ECG tracing). Three-plane LV data set demonstrates delayed contraction of the lateral and postero-lateral walls (yellow-orange) compared with the IVS (green). Both pulsed wave Doppler image with the control volume positioned between mitral and aortic flows (*A*) and pulse wave TDI at the basal segment of IVS (*B*) demonstrate relatively short filling and ejection time intervals and longer isovolumic time intervals. ECG, electrocardiography; IVS, interventricular septum; LV, left ventricle; TDI, tissue Doppler imaging.

longitudinal orientation and develop the transversal flow-mediated haemodynamic forces during either active or inactive synchronization therapy.[85]

Overall, the ability of echocardiography to detect the typical contraction 'signatures' of LBBB have significantly improved our understanding of the mechanical and haemodynamic consequences of abnormal electrical activation thus contributing to the selection of adequate treatment strategy. Furthermore, it had been shown that the presence of LBBB morphology on ECG is not always associated with 'typical' mechanical patterns. Risum *et al.*[30] reported that one third of LBBB patients selected for CRT did not have typical contraction pattern as indicated by speckle-tracking strain echocardiography. This mismatch between ECG and myocardial mechanics was independently associated with increased risk of adverse outcome.[30] Similar results were reported by other groups which assessed the prognostic value of apical rocking/SF in patients with LBBB undergoing CRT.[73,74] Conversely, apical rocking was observed in 26% and SF in 20% of CRT patients without typical LBBB morphology at ECG, most of whom responded to CRT.[74] Such findings clearly demonstrate that LV mechanics (assessed by echocardiography or other imaging modalities) may play a critical role in selecting patients to be referred to CRT independently on ECG morphology.

In addition to its role in recognition of contraction patterns listed above, echocardiography helps to obtain important information on LV volumes, EF, severity of mitral regurgitation, as well as a number of parameters to assess inter- and intraventricular dyssynchrony. However, the identification of the quantitative parameters that may provide an accurate LV mechanical dyssynchrony measurement remains a challenge. It's worth noting that differences in time-to-peak contraction between walls might be also caused by conditions other than LBBB, including the ischaemia/scar or unfavourable loading conditions.[86,87] Moreover, in clinical trials effectiveness of any dyssynchrony measurements was expressed through their ability to predict response to CRT, which, in its turn, may be confounded by other factors (e.g. location and extent of myocardial scar and position of LV lead).[88–90] The cut-off values (mostly derived from single centre studies), strengths and limitations of the main quantitative parameters of mechanical dyssynchrony proposed in current literature are summarized in *Table 3*.

Nuclear imaging

Single photon emission computed tomography (SPECT) and ^{18}F-fluorodeoxyglucose positron emission tomography (PET) have been used to characterize LV perfusion and metabolism mismatch in LBBB.[60,122] Typical myocardial perfusion pattern in LBBB patients reveals relative reduction in coronary flow within the septum and hyperperfusion of the lateral wall (*Figure 6*).[61] Moreover, a relative increase in global myocardial blood flow in the lateral wall both during rest and exercise was demonstrated in non-ischaemic LBBB patients compared with patients with normal ventricular conduction.[123] Data obtained using PET suggested that unlike non-dyssynchronous non-ischaemic subjects, LBBB patients had a higher myocardial glucose metabolism in the lateral wall compared with that in IVS.[124] Such increased metabolic load resulting from the dyssynchronous LV contraction may explain a higher demand on global myocardial perfusion in lateral LV segments.

In the semi-quantitative perfusion analysis, systolic thickness is assumed to be similar across the LV walls. LBBB patients, however, usually show reduced IVS and increased lateral systolic wall

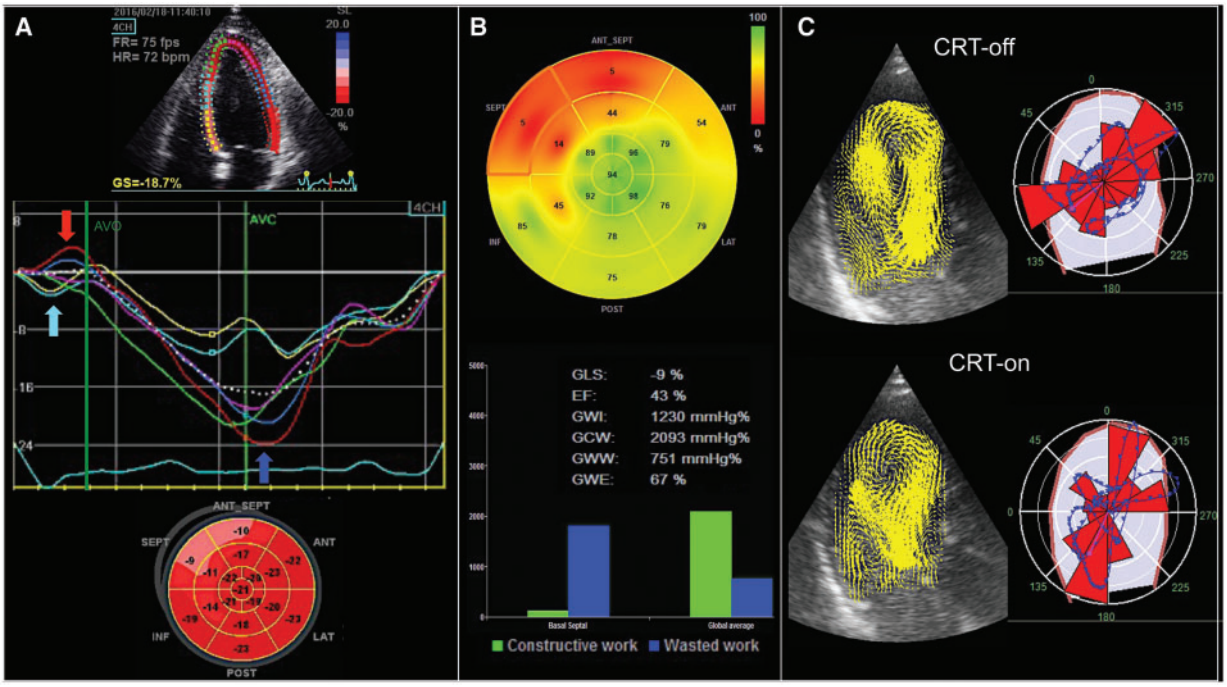

Figure 5 Assessment of myocardial mechanics and intraventricular flow dynamics using novel imaging techniques in patients with left bundle branch block. (*A*) Typical mechanical contraction pattern LV assessed by the 2DSTE longitudinal strain in a patient with LBBB. The following criteria are present (Risum *et al.* 2013): (i) Presence of a nadir of contraction of at least 1 basal or mid-ventricular segment of the septum (light-blue arrow) and early stretching of at least 1 basal or mid-ventricular segment of the opposite (postero-)lateral wall (red arrow) that ends during the LV ejection phase. (ii) The nadir of septal contraction occurs within 70% of the ejection phase (when there are 2 nadirs, only the first one is considered). (iii) The nadir of contraction of the (postero-)lateral wall occurs after aortic valve closure that defines the end of the LV ejection phase (blue arrow). The bull-eye view shows the decreased longitudinal strain in basal septal region. (*B*) Myocardial work and cardiac efficiency in a patient with left bundle branch block calculated from non-invasive LV pressure and 2DSTE longitudinal strain. Bull's-eye plot shows the segmental analysis of cardiac work efficiency. Diagram demonstrates the difference in constructive and wasted myocardial work performed by septal and lateral walls. Regional myocardial work is negative in septal and anteroseptal segments reflecting the systolic lengthening of the interventricular septum caused by the contraction of late activated lateral wall. It makes no contribution to the LV ejection and represents the waste of work. Global work efficiency is calculated as positive work divided by total work (Wpos/(Wneg + Wpos)). It is close to 100% in normally contracting segments and reduced when there is wasted work. (Courtesy of Dr Eigil Samset). (*C*) Analysis of flow force angle by echographic particle image velocimetry in a LBBB patient with CRT-off and CRT-on. Tracking of the intraventricular flow and polar histograms show the directional distribution of flow momentum. In LBBB the blood-induced intraventricular forces lose their normal longitudinal orientation and demonstrate more transversal one. While with active CRT a longitudinal alignment of haemodynamic forces within the LV is present. 2DSTE, two-dimensional speckle tracking echocardiography; AVC, aortic valve closure time; AVO, aortic valve opening time; CRT, cardiac resynchronization therapy; EF, ejection fraction; ET, left ventricular ejection time; FT, left ventricular filling time; GCW, global constructive work (total positive work from mitral valve closure to opening); GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index (total work from mitral valve closure to opening); GWW, global wasted work (total negative work from mitral valve closure to opening); IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LV, left ventricle/ventricular, Wneg, negative work; Wpos, positive work.

thickening. The aforementioned assumption together with the relatively low spatial resolution of the technique constitute the major limitations of nuclear imaging in LBBB settings since this so-called partial-volume effect may mimic perfusion heterogeneity. That is why SPECT/PET assessment of perfusion in LBBB patients should be interpreted with caution.[61,125]

Several nuclear imaging techniques permit also characterization of LV contraction and assessment of LV mechanical dyssynchrony with the phase analysis of gated myocardial perfusion SPECT being the most commonly used and extensively validated modality.[90] This method is based on determining the timing of wall thickening during a cardiac cycle and provides several indices of LV dyssynchrony (*Table 3*).

Cardiac magnetic resonance

CMR in LBBB patients has been predominantly used to assess LV mechanical dyssynchrony and predict response to CRT (*Table 3*). Measurements can be derived both from cine and tagged images and

Table 3 Cardiovascular imaging parameters proposed to assess mechanical left ventricular dyssynchrony in patients with left bundle branch block.

Parameter	Established cut-off value	Advantages	Limitations
Echocardiographic parameters			
Interventricular dyssynchrony			
Pulse-wave Doppler interventricular mechanical delay index[91]	≥40 ms	-Easy to obtain -Established predictive value in a large cohort of patients[92]	-Requires matching for R-R intervals when measurements are performed on separate recordings; -Applicable in regular heart rhythm only; -Requires high quality Doppler signal; -Prognostic value not confirmed in multicentre studies[93]
LV intraventricular dyssynchrony			
M-mode			
Septal-to-posterior wall motion delay[91,94]	≥130 ms	-Easy to obtain -High resolution -Predicted response to CRT and long-term outcomes in a small sample population[94]	-Not applicable in patients with akinesis of IVS or posterior wall; -Prognostic value not confirmed in larger studies[93,95,96]
TDI			
Maximum peak systolic velocity time delay between 4 opposing walls[97]	≥65 ms	-Predicted LV reverse remodelling and CRT response[97–99]	-Angle-dependent -Requires expertise in acquiring TDI data -Prognostic value not confirmed in larger studies[93,95,96]
Standard deviation of time to peak systolic velocity of 12 LV segments (Yu index)[100]	≥32 ms	-Related to a high likelihood of a favourable response to CRT[98,100]	
TDI-derived strain and strain rate imaging parameters (time difference of peak radial strain in the septum vs. the posterior wall)[101]	≥130 ms	-Enable identification of myocardial segments with active deformation (contraction) and passive motion (scar tissue). -Predicted immediate improvement in stroke volume with resynchronization therapy in a small studies[101]	-Did not accurately predict response to CRT during follow-up[98]
2DSTE strain			
Difference between peak radial strain of the anteroseptal and posterior segments[102]	≥130 ms	-Enables angle-independent multidirectional analysis of myocardial deformation; -Predicted LV reverse remodelling and CRT response at follow-up[102–104] -Additive predictive value when combined with TDI longitudinal velocity[104]	-Lack of standardization; -Lack of reproducibility; -Intervendor variability in the amplitude and timing of strain parameters[105]
The longitudinal strain delay index[a106]	≥25%	-Enables angle-independent multidirectional analysis of myocardial deformation; -Predicts CRT response at follow-up[106]	-Lack of standardization; -Lack of reproducibility; -Intervendor variability in the amplitude and timing of strain parameters[105]
3DSTE			
Maximal opposing wall delay[107]	59 ± 12 ms[b]	-Demonstrated effective LV resynchronization with significant improvement in LV systolic function soon after CRT[107]	-Lack of data and standardization; -Need of stable cardiac rhythm and cooperative patients; -Can be limited by poor window
Standard deviation in time-to-peak strain[107]	28 ± 11 ms[b]		
Systolic dyssynchrony index[c108]	≥10.4%	-Predicting improvement following CRT during 7+-3 months follow-up[108,109]; -High reproducibility	

Continued

Table 3 *Continued*

Parameter	Established cut-off value	Advantages	Limitations
CMR parameters			
Tagged CMR circumferential uniformity ratio estimate (CURE) index[110]	Ranges from 0 (dyssynchronous) to 1 (synchronous)	-High resolution; -Ability of tissue characterization (presence of scar); -Predicted clinical improvement at follow-up[110]; -Increased prognostic value in combination with tissue characterisation[111]	-Cost; -Limited availability; -Non-applicable in patients with intracardiac metallic devices, claustrophobia
Vector-velocity–encoded CMRdelay in regional time to peak myocardial velocities[112]	>80 ms (indicates extensive dyssynchrony)	- Excellent agreement between CMR and TDI for severity of LV dyssynchrony[112]	
Standard deviation of 16 segment time-to-maximum radial wall thickness (SDt-16)[113]	NA	-Independently predicted response to CRT and mortality[113,114]	
Systolic dyssynchrony index[c115]	>9.75%	-Predicted response to CRT[115]; -high reproducibility[115]	
Nuclear imaging (gated myocardial perfusion SPECT) parameters			
Phase standard deviation[116]	>24.4° in men and >22.2° in women[d]	-Predicts response to CRT in a small group[117,118]	-Radiation exposure -Low temporal resolution -Intervendor variability
Histogram bandwidth[116]	>62.2° in men and >49.8° in women[d]	-High repeatability and reproducibility[119.120] -Established reference values[116] -Ability to provide information on perfusion (scar and site of latest activation) -Ability to provide 3D representation of LV contraction	

3D, three-dimensional; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; IVMD, interventricular mechanical delay; IVS, interventricular septum; LV, left ventricle; LVPET, left ventricular pre-ejection time; RVPET, right ventricular pre-ejection time; SPECT, single-photon emission computed tomography; SPWMD, septal-to-posterior wall motion delay; TDI, tissue Doppler imaging.
[a]The strain delay index represents the sum of the wasted energy due to LV dyssynchrony across all (*n*) myocardial segments.[106]
[b]Values established in a group of healthy volunteers.[121]
[c]Systolic dyssynchrony index defined as standard deviation of the regional times to peak volume change normalized for the R-R duration, and expressed as a percentage of cardiac cycle duration.
[d]For Emory Cardiac Toolbox software package (ECTb; Emory University, Atlanta, GA).

based on the principles similar to those utilized in echocardiography, including radial, circumferential or longitudinal strain, timing of myocardial thickening and volume change.[115] Its ability to assess myocardial perfusion may potentially have an important added value in reducing the number of LBBB patients with false positive diagnosis of CAD made by both SPECT[126] and dobutamine stress echocardiography.[127,128] Additionally, superior image quality, provision of information on the location and extent of myocardial scar, and detailed cardiac anatomy including coronary veins constitute important potential advantages of CMR to select candidates for CRT.[115,110] However, its intrinsic limitations such as high cost, potential risk of nephrogenic systemic fibrosis and allergic reactions related to contrast agent, and contraindications in patients with metallic devices and claustrophobia make this imaging modality less frequently used in clinical routine (*Table 3*).

Diagnostic challenges posed by the LBBB on ECG interpretation, stress-testing and imaging

ECG detection of several important conditions including ST-segment elevation MI (STEMI), Q wave infarction, and LV hypertrophy, as well

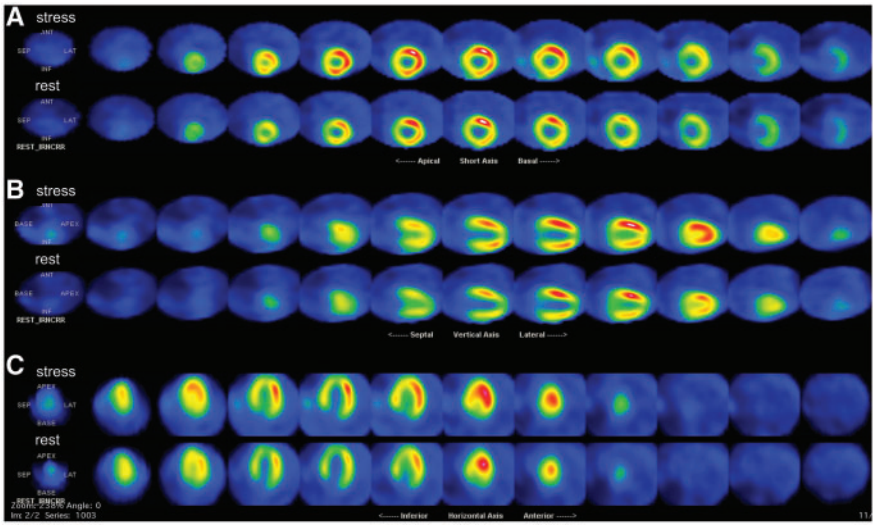

Figure 6 Perfusion defect associated with left bundle branch block on single photon emission computed tomography in a patient without significant lesions in left anterior descending artery. Short axis (*A*) and long axis (*B* and *C*) views show the defect located in septal and anterior region both at rest and stress.

as non-invasive testing for CAD could be affected by LBBB, which itself causes deviations in the QRS complex and ST-T segment similar to those induced by ischaemia or injury. While current guidelines recommend reperfusion therapy for patients with chest pain and new or presumably new LBBB,[129] it is often hard to confidently exclude STEMI equivalents in patients with 'old' LBBB, resulting in many inappropriate catheterization laboratory activations for primary percutaneous interventions.[130] Among criteria proposed for detecting acute MI by ECG in the presence of LBBB the Sgarbossa's criteria are the most widely used (*Table 4*).[131] Of the 3 criteria listed in *Table 4*, the highest score[5] is given to concordant ST-segment elevation ≥1 mm, because it was shown to have the greatest positive likelihood ratio for ongoing ischaemia. In contrast, discordant ST-segment elevation ≥5 mm is a relatively poor predictor and is assigned the lowest score.[2,131] In a meta-analysis of 10 studies a total score ≥3 yielded a sensitivity of 20% (95% CI 18–23%) and specificity of 98% (95% CI 97-99%) for the diagnosis of MI.[132]

Several attempts have been made to improve the diagnostic accuracy of the Sgarbossa score (*Table 4*). The Selvester ECG criterion for ST elevation in LBBB is based on standard STEMI thresholds plus 10% of the quantity S-wave amplitude minus the R-wave amplitude.[134] Smith proposed 25% of the absolute magnitude of the preceding S wave (as opposed to 5 mm in Sgarbossa's score) as the threshold for discordant ST elevation.[135] The rationale for emphasizing ST elevation during LBBB, whether concordant or discordant, is that the current of injury of a STEMI should produce new ST elevation in the recording leads facing the ongoing infarction.[130] More recently it was proposed to use QRS area (as opposed to amplitude) on the basis of its better correlation with ST level (Philips QRS area criteria).[134] Importantly, all criteria proposed so far, despite their high specificity, have relatively low sensitivity meaning that a significant number of patients with STEMI could be missed. This is the reason why in patients with LBBB of uncertain origin the decision making cannot be based on ECG criteria alone.[2] Positive point-of-care troponin test 1–2 h after symptom onset may be useful while considering whether to perform emergency angiography with a view to primary percutaneous coronary intervention.[129]

Accurate detection of regional wall motion abnormalities (WMA) constitutes another potential diagnostic challenge in patients with LBBB. Asynchronous activation of the IVS leading to the abnormal septal motion, which is aggravated by tachycardia, may mimic WMA and affect the results of both rest and stress echocardiography.[59] However the results of the studies evaluating the diagnostic accuracy of stress echocardiography in LBBB have been so far controversial. Some studies reported poor specificity (64%) and positive predictive value (40%)[136] while other researchers argue that in experienced hands it may reach sensitivity and specificity exceeding 90% and showed better performance than SPECT in diagnosis of CAD in the left coronary artery territory.[137] The addition of more advanced techniques such as measurement of regional myocardial deformation by speckle tracking echocardiography and assessment of myocardial perfusion by myocardial contrast echocardiography with vasodilators could be promising alternatives because, unlike standard echocardiography, they do not rely on regional wall thickening and endocardial displacement only.[2,59] Several studies demonstrated an excellent diagnostic accuracy of myocardial contrast echocardiography for CAD detection in patients with LBBB.[138,139]

However, the precise interpretation of myocardial perfusion pattern is also a diagnostic challenge in patients with LBBB due to the relative reduction of septal perfusion discussed above. This phenomenon might further exacerbate during exercise, as the lateral wall has to do more work, causing a more pronounced hyperemic response, and as the

Table 4 Existing criteria to diagnose acute myocardial infarction in patients with left bundle branch block.

Criteria	Description	Sensitivity	Specificity
Sgarbossa criteria[131]	(1) ST elevation ≥1 mm (100 μV) and concordant with QRS (score 5) (2) ST depression ≥1mm (100 μV) in leads V1–3 (score 3) (3) 3. ST elevation ≥5 mm (500 μV) and discordant with QRS (score 2)	20% (95% CI 18%-23%)[a132]	98% (95% CI 97–99%)[a132]
Selvester 10% RS criterion[133]	ST elevation which is 10% or more of |S|-|R| plus STEMI limits (ST elevation required for the given lead)	30.1%[b134]	93.2%[b134]
Smith 25% S-wave criterion[135]	ST elevation 25% or more of the S-wave amplitude	20.3%[b134]	94.9%[b134]
Philips QRS area criteria[134]	ST elevation ≥ 105% QRS area +100 μV	23.8%[134]	95.8%[134]

[a]For a total score ≥3.
[b]In combination with Sgarbossa criteria.

length of true diastole further shortens during exercise. This could potentially lead to the septal perfusion defects detected by nuclear imaging or myocardial contrast echocardiography being misinterpreted as significant coronary stenosis and thus increasing the rates of false-positive test results in the territory of left anterior descending artery.[122,123] Several methods have been used to overcome these problems including ECG-gated SPECT with image acquisition at end-diastole, which was found to be more accurate for identifying CAD in patients with LBBB.[140] Higgins *et al.*[122] suggested the following key findings that define true positives perfusion defects (ischaemia) in patients with LBBB: (i) reversible perfusion defects (especially at end-diastole), (ii) a concomitant apical defect, and (iii) systolic dysfunction matching the perfusion defect.

In the meta-analysis of 66 studies (with a total of 2203 patients) assessing the diagnostic accuracy of three main non-invasive techniques (exercise ECG, stress echocardiography and myocardial perfusion imaging) for diagnosis of CAD in patients with LBBB, exercise ECG and myocardial perfusion imaging had the highest sensitivity (83.4% and 82.1%, respectively), while stress echocardiography had the highest specificity (88.7%); diagnostic accuracy was highest for stress echocardiography (84.4%) and lowest for exercise ECG (66.4%).[141]

Stress CMR could be considered another promising technique to diagnose CAD and stratify the risk in LBBB patients, but lack of evidence-based data, limited availability and high cost currently precludes its usage in routine medical practice. A single study reported that, in patients with LBBB, comprehensive dobutamine stress CMR including cine, first-pass stress perfusion and late gadolinium enhancement imaging had greater diagnostic accuracy for detection of new WMA than dobutamine stress echocardiography.[127] In the setting of LBBB, the ability to assess the hypointensed regions of the IVS, visualized by imaging modalities assessing myocardial perfusion at rest that mimic 'true' perfusion defects, by using first-pass stress perfusion at 20 mkg/kg/min dose of dobutamine (when the maximum vasodilation of normal coronary arteries occurs leading to increase in myocardial blood flow) had important clinical value providing a viable non-invasive functional investigation for suspected CAD in LBBB patients as confirmed by invasive coronary angiography.[127]

It is also worth noting that most of the pathophysiological effects leading to false positive results of stress testing in LBBB patients are caused by increased cardiac inotropy and/or chronotropy, so vasodilator stress may be preferred to exercise or dobutamine in patients with LBBB.[59]

The main strengths and limitations of currently available non-invasive modalities for diagnosing CAD in patients with LBBB are summarized in *Table 5*.

Clinical management of patients with LBBB—current concepts and future perspectives

Currently no guidelines on clinical management of patients with LBBB are available except for those who already developed HF, severe LV systolic dysfunction and require CRT. In LBBB patients with preserved or mildly reduced LV EF the treatment strategy is usually determined by the concomitant cardiovascular pathology. In addition, there are no specific algorithms and early prognostic markers for selecting patients at higher risk of LV function deterioration and development of clinically significant HF.

CRT, first introduced in 1994, has dramatically changed the management of HF patients with LBBB, resulting in reverse myocardial remodelling, significant improvements in their clinical status and long-term survival.[50] Current guidelines give the class I indications for CRT implantation in LBBB patients with QRS duration ≥120 ms (level of evidence A for QRS >150 ms, and B for QRS 120-150 ms), chronic HF and LV EF ≤35%, who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment.[50] However, this therapy is still associated with a 30% failure rate, with an inadequate specificity of the CRT selection process being one of possible explanations. Recent advances in cardiovascular imaging modalities and a multimodality approach to select potential candidates to CRT is

Table 5 Main strengths and limitations of non-invasive techniques for detecting coronary artery disease in patients with left bundle branch block.

	Exercise ECG	Stress echocardiography	Nuclear imaging (SPECT, PET)	Stress CMR	Cardiac CT
Availability	++++	+++	++	++	++
Cost	+	++	+++	++++	+++
Safety	++++	++++	++ Ionizing radiations	+++ Contraindicated in patients with metallic implants and claustrophobia; Contrast potentially associated with nephrogenic systemic fibrosis in patients with GFR <30 ml/min; Allergic reaction to contrast	+ High ionizing radiations; Potentially nephrotoxic contrast; Allergic reaction to contrast
Imaging window dependence	–	Present	Absent	Absent	Absent
Ability to assess LV volumes/EF	Absent	Present	Present	Present	Present
Major limitations	Too low specificity and diagnostic accuracy for regular use	High interoperator variability Depends on acoustic window	Radiation exposure High rate of false positives in the septum	Costs Low availability More technically challenging Less validated	High radiation exposure Use is limited by patients with low probability of CAD High calcium may not correlate to significant stenosis Stable cardiac rhythm with a low heart rate for image acquisition

CMR, cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiography; EF, ejection fraction; GFR, glomerular filtration rate; LV, left ventricular; PET, positron emission tomography; SPECT, single photon emission computed tomography.

expected to provide a more accurate prediction of CRT response and outcomes.[30,108,142] In addition to intraventricular dyssynchrony, other factors including site of latest mechanical activation, extent and location of myocardial scar, LV lead positioning, and venous anatomy should be considered to predict CRT response.[90]

Data on the utility of novel approaches in identification of non-responders have so far been encouraging. Currently there is an increasing interest in the pathophysiological redistribution of coronary flow, myocardial perfusion and metabolism in LBBB patients as CRT is known to promote homogeneity in myocardial perfusion.[61] Analysis of LV contraction patterns, workload and energy loss[83] and assessment of intraventricular fluid dynamics[85] may also have potential in improvement of CRT candidates selection process in patients with LBBB.

To conclude, clinical and diagnostic notions about LBBB had evolved from just an ECG pattern to a critically important finding affecting diagnostic and clinical management of many patients and adversely influencing their outcomes. LBBB causes remarkable changes in LV mechanics, perfusion, metabolism and workload resulting in a pathologic cardiac remodelling. Recent advances in cardiovascular imaging techniques significantly improved assessment of patients with LBBB and provided insights into pathophysiological mechanisms of LV remodelling. More evidence is needed to identify early triggers of adverse outcomes in patients LBBB in order to improve risk stratification and treatment strategies before the development of severe LV dysfunction.

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