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Editorial

Impact of left bundle branch block (LBBB) in dilated cardiomyopathy (DCM) with intermediate left ventricular systolic dysfunction (LVSD)

Mohammed Majid Akhtar *, Perry Elliott

[a] Institute for Cardiovascular Science, University College London, London, UK
[b] Department of Inherited Cardiovascular Diseases, Bart's Heart Centre, St. Bartholomew's Hospital, London, UK

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Dilated cardiomyopathy (DCM) is the commonest cause of heart failure and cardiac transplantation worldwide [1]. Morbidity and mortality in DCM has improved considerably with optimal medical therapy (OMT), identification of affected individuals at earlier stages of the disease process, and by the use of implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT).

LBBB is a relatively common finding in patients with DCM, with registries reporting a prevalence of 25–30% [2–4]. LBBB results in dyssynchronous ventricular activation and impacts on myocardial efficiency. Although LBBB can itself contribute to the onset of LVSD, it is likely secondary to the underlying disease process in most cases.

The adverse impact of LBBB in DCM patients with EF ≤ 35% is well established with lower rates of EF-improvement over follow-up and increased mortality rates compared to those with a narrow QRS duration [2,4,5]. Less is known about the impact of LBBB in intermediate severities of LVSD.

The proportion of decompensated hospitalized heart failure (HF) patients with intermediate EF remains unchanged despite improvements in medical therapy, management of coronary disease and DCM diagnosis over the decades [6]. Published natural history data of DCM patients with LBBB and intermediate severities of EF is derived mostly from small retrospective single-centred cohorts. In a study of 206 DCM all-comers with varying severities of EF, LBBB was not associated with heart transplantation or mortality [7]. However, in an analysis of 1436 patients with LBBB and intermediate LVEF of 36–50%, the presence of LBBB was associated with increased risks of progressive LV dysfunction over follow-up, ICD implantation and increased mortality [8]. On multivariable modelling, LBBB remained an independent predictor of all-cause mortality but a considerable proportion of patients in this study had ischaemic or valvular disease and these findings may not be generalisable to a non-ischaemic DCM population.

The role of CRT in improving outcomes in patients with LBBB and EF ≤ 35% is unequivocal [9,10]. Importantly, LBBB morphology is a predictor of response to CRT [e11]. Limited data exists with respect to the beneficial impact of CRT in intermediate EF and data is predominantly obtained from small registries (Table 1). Some data are derived from randomized studies where patients were initially incorrectly classified to have an EF ≤ 35% but were subsequently correctly reclassified to have intermediate EF. These sub-studies of MADIT-CRT and PROSPECT have suggested that CRT, by improving ventricular synchrony, can be beneficial in patients with EF > 35% with associated reduction in LV dimensions, hospitalizations and mortality [e12, e13]. In another study of 15 patients with CRT and intermediate EF, CRT resulted in significant reductions in LV end-systolic and end-diastolic volumes, and improvements in EF and NYHA class [e14].

The REVERSE study demonstrated a beneficial effect of CRT in patients with EF ≤ 40% and QRS ≥ 120 ms (61.5% LBBB) with improved six-minute walk test distances and decreased LV end-diastolic volume, hospitalization rates and mortality. However, this study did not assess the impact of CRT (and dyssynchrony) in patients with EF > 40% and a considerable proportion of subjects had prior PCI or CABG [e15].

In this edition of the journal, Gentile et al. describe the impact of LBBB in a well-characterized group of 280 consecutive patients with intermediate LVEF from a specialist tertiary-referral cardiovascular centre [e16]. The cohort comprises a well-selected population of non-ischaemic DCM excluding phenocopies including alcohol, peripartum, sarcoid and tachycardia-induced DCM. Patients were on optimal medical therapy for at least 3 months prior to enrolment with 91% and 94% of the overall cohort on β-blockers and ACE inhibitors respectively. The prevalence of LBBB was 27% (n = 76) and patients were followed-up for a median of 151 months. Patients with LBBB had similar outcomes with respect to all-cause mortality and heart transplantation ($p = 0.52$) or sudden cardiac death and malignant ventricular arrhythmia ($p = 0.39$) to those without LBBB. In the subgroup of patients with LBBB at baseline evaluation, over a third (34%) developed severe LVSD over follow-up. Presence of moderate-severe mitral regurgitation, increased indexed left atrial end-systolic area and indexed LV end-diastolic volumes were identified as independent predictors of subsequent LV deterioration. Importantly, there was a trend towards increased all-cause mortality and heart transplantation ($p = 0.07$) in the LBBB cohort that develop progressive LVSD.

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* Corresponding author at: Barts Heart Centre, St. Bartholomew's Hospital, London EC1A 7BE, UK.
E-mail address: majid.akhtar@ucl.ac.uk (M.M. Akhtar).

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Table 1
Summary of trials analysing the impact of QRS duration in patients with DCM with different EF; as well as the role of CRT in these cohorts (Abbreviations: ACM: All-Cause Mortality; AS: Aortic Stenosis; CAD: Coronary Artery Disease; CI: Confidence Interval; CRT: Cardiac Resynchronization Therapy; CRTD: Cardiac Resynchronization Therapy – Defibrillator; CRTP: Cardiac Resynchronization Therapy – Pacemaker; DCM: Dilated Cardiomyopathy; EF: Ejection Fraction; FU: Follow-Up; HF: Heart Failure; HR: Hazard Ratio; ICD: Implantable Cardioverter-Defibrillator; ICM: Ischaemic Cardiomyopathy; IVCD: Intraventricular conduction delay; LBBB: Left Bundle Branch Block; LVEDV: Left ventricular end-diastolic volume; LVEDVi: Indexed LV End-Diastolic Volume; LVEF: Left Ventricular Ejection Fraction; LVESVi: Indexed LV End-Systolic Volume; LVSD: LV Systolic Dysfunction; MI: Myocardial Infarction; MR: Mitral Regurgitation; NYHA: New York Heart Association; OMT: Optimal Medical Therapy; QoL: Quality of Life; RBBB: Right Bundle Branch Block; VT: Ventricular Tachycardia; VF: Ventricular Fibrillation; 6MWT: Six-Minute Walk Test).

Trial	Inclusion criteria	Patient numbers	Outcome
Impact of LBBB in patients with intermediate LVSD			
Outcomes with LBBB and mildly to moderately reduced LV function [8]	Patients with LBBB and LVEF 36–50%. Exclusion: EF ≤ 35; or > 50%; RBBB, IVCD	1436 patients. Mean LVEF 44 ± 4%. Control group matched for age, sex and baseline EF but without IVCD. 35% of patients with LBBB had CAD; 7% previous MI and 5.4% had moderate + AS	LBBB is associated with increased mortality - HR 1.17 (1–1.36 CI); p = 0.04 LBBB is associated with a higher incidence of LVEF reduction to ≤35% - HR 1.34 (1.09–1.63 CI) LBBB patients have similar rates of HF admission (11% vs 13% control; p = 0.35) and similar incidence of VT/VF (15% vs 12% control; p = 0.1) compared to non-LBBB controls.
CRT in patients with intermediate LVSD			
The influence of LVEF on the effectiveness of CRT therapy: MADIT-CRT [e13, e17]	MADIT criteria with EF < 30%, Studied a subpopulation who had an EF ≥ 30% adjudicated by core lab compared to initially thought EF <30% by participating centre	1809 patients with CRT (696 patients with EF > 30% by corelab – 450 of these with LBBB) Response to CRT was an improvement in LVEDV Primary endpoint was Heart failure or death. Secondary endpoint was ACM.	Patients with EF > 30% had a 22.3% mean reduction in LVEDV with CRTD at 1 year. Reduced risk of HF hospitalization/death in EF > 30% with CRT - HR 0.56 (CI 0.39–0.82; p = 0.003).
CRT in patients with mildly impaired LV function [e18]	NYHA 3–4; QRS ≥ 120 ms; TTE LVEF ≤ 35% on pre-implant TTE. Sub-study with EF reclassification based on CMRI into those with EF > 35%.	157 Patients with CRT Group A (n = 130): CMR initial LVEF ≤ 35% vs Group B (n = 27): CMR initial LVEF reclassified to >35%	CRT resulted in an Improvement in NYHA class; QoL scores; 6MWT distance in both groups. Group A had a higher risk of ACM, hospitalization or major cardiovascular events.
CRT may benefit patients with LVEF > 35%: a PROSPECT trial substudy. [e12]	The Prospect trial was a prospective, multicentred study recruiting patients with LVEF ≤ 35%; QRS ≥ 130 ms; NYHA 3–4 on OMT This substudy assessed patients in whom corelab re-classified the initial EF to >35% versus EF < 35% with CRT implantation.	361 Patients in the substudy – 86 (24%) had LVEF reclassified to >35% by corelab.	In patients with LVEF > 35%, 63% improved in clinical composite score and 51% improved in LVESV. In patients with EF > 35% and NYHA 3–4, QRS > 130 ms – CRT appears to provide clinical and structural benefits.
Long-term impact of CRT in mild heart failure: 5-year results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. [e15, e19, e20]	Randomized, double-blind study on CRT in NYHA 1–2; QRS ≥ 120 ms and LVEF ≤ 40%.	419 CRT Patients (256 patients with LBBB) Randomized CRT to switch on or off - after randomized phase, all patients had CRT switched on.	6 min walk distance increased; mean LVESVi and LVEDVi decreased. Increase in mean LVEF with CRT-ON. Low rates of hospitalization and mortality with CRT. Effects persist over 5 years.
Effect of CRT in patients with moderate LVSD and wide QRS complex: a prospective study [e14]	15 patients NYHA 3; LVEF 36–44% and QRS > 120 ms on OMT compared to 30 age, sex, NYHA class and HF-aetiology matched patients with conventional CRT indications.	15 case patients (EF 36–44%) compared to 30 control patients (EF ≤ 35%).	Significant LV reverse remodeling by CRT in those with a wide QRS complex and moderate LVSD – significant reduction in LVEDV and LVESV and improvements in NYHA class and LVEF.
CRT in chronic heart failure with moderately reduced LVEF: Lessons from the Multicenter InSync Randomized Clinical Evaluation MIRACLE EF study. [e21]	Randomized, controlled, double-blind study with CRTP in NYHA 2–3, LBBB and LVEF 36–50%. Exclusion: Prior pacing or ICD.	44 patients (26 randomized). Patients Randomized 2:1 to CRTP-ON or CRTP-OFF. Minimum FU 24 months	Study prematurely stopped due to poor patient recruitment.
Biventricular pacing for atrioventricular block and systolic dysfunction – BLOCK HF [e22]	Patients with pacing Indications (AV block), NYHA 1–3; LVEF ≤ 50%. Primary outcome was time to ACM, urgent HF visit for intravenous diuretics or ≥15% increase in LVESVi	691 Patients (225 with LBBB) Randomized to CRT(P/D) vs RV pacing Mean FU 37 months	CRT resulted in significantly lower incidence of the primary outcome
CRT in patients with severe LVSD			
The effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure – CARE-HF [9]	Age ≥ 18, NYHA 3–4, on OMT, LVEF ≤ 35%; indexed LVEDD ≥ 30 mm, QRS ≥ 120 ms	813 Patients 38% DCM Randomized to OMT vs CRT + OMT	CRT reduces the composite of ACM or hospitalization vs OMT (39% vs 55%). CRT reduces mortality (20% vs 30%). CRT improves EF, NYHA class and QoL. CRT reduces LVESVi and area of MR jet.
CRT with or without an ICD in advanced chronic heart failure - COMPANION [e23]	NYHA 3–4, on OMT, QRS ≥ 120 ms; LVEF ≤ 35%, Sinus rhythm, Prior HF hospitalization in preceding 12 months Primary composite endpoint was time to all-cause mortality or hospitalization.	1520 patients Randomized 1:2:2 to OMT : CRTP : CRTD 70% in OMT group had LBBB (71% overall) 45% DCM	CRTP/D reduced rate of primary endpoint. CRTP/D both reduce risk of ACM compared to OMT. CRT has benefits in both DCM and ICM subgroups with respect to ACM/hospitalization.
CRT for mild-moderate heart failure (RAFT trial) [e24]	NYHA 2–3, LVEF ≤ 30%; QRS ≥ 120 ms or paced QRS > 200 ms;	1798 patients Randomized ICD vs CRTD. Mean FU 40 months.	CRTD compared to ICD alone reduced rates of composite of death or HF hospitalization.

This retrospective analysis comprises a well-defined cohort of DCM patients with over 90% of subjects on ACE inhibitors or ß-blockers and with good longitudinal follow-up duration to allow assessment of major events. However, limitations include the retrospective, single-centred data collation which may reflect selection bias from a specialist tertiary referral centre population. Importantly, a small proportion of patients were on mineralocorticoid antagonist (6%) or in NYHA class III–IV (3%) which may reflect in a lower event rate over follow-up in both the LBBB and non-LBBB groups. Although there wasn't any cross-over of patients between the LBBB and non-LBBB group at initial evaluation, 17% (n = 13) of the LBBB group developed progressive LVSD and had CRT implantation over follow-up which may have altered the natural history of these patients with LBBB for the primary study endpoints by impacting event rates, masking differences between groups.

Ultimately, a more refined diagnosis of DCM with characterization into inflammatory, genetic or infiltrative aetiologies is important to identify whether the adverse impact of LBBB for different EF is consistent across the spectrum of conditions or whether it is particularly relevant for one or more subcategories. Large-scale randomized data is necessary in patients with intermediate EF to test whether reversing LBBB, narrowing QRS duration, in this category of patients translates into improved outcomes. This study by Gentile et al. provides important insights into future research strategies by identification of a subgroup of 'high-risk' patients with intermediate EF that are at increased risk of deterioration over follow-up and consequently, that may benefit with earlier consideration for CRT implantation.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.12.036.

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