

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

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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 $EF \leq 35\%$ 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 $EF \leq 35\%$ 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 $EF \leq 35\%$ 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 \leq 40% and QRS \geq 120ms (61.5% LBBB) with improved six-minute walk test distances and decreased LV end-diastolic volume, hospitalisation 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-characterised 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.

This retrospective analysis comprises a well-defined cohort of DCM patients with over 90% of subjects on ACE inhibitors or β -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.

REFERENCES

1. Maron, B.J., et al., *Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention*. *Circulation*, 2006. **113**(14): p. 1807-16.
2. Aleksova, A., et al., *New-onset left bundle branch block independently predicts long-term mortality in patients with idiopathic dilated cardiomyopathy: data from the Trieste Heart Muscle Disease Registry*. *Europace*, 2014. **16**(10): p. 1450-9.
3. Grimm, W., et al., *How many patients with dilated cardiomyopathy may potentially benefit from cardiac resynchronization therapy?* *Pacing Clin Electrophysiol*, 2003. **26**(1 Pt 2): p. 155-7.
4. Lund, L.H., et al., *Prevalence, correlates, and prognostic significance of QRS prolongation in heart failure with reduced and preserved ejection fraction*. *Eur Heart J*, 2013. **34**(7): p. 529-39.
5. Sze, E., et al., *Impaired Recovery of Left Ventricular Function in Patients With Cardiomyopathy and Left Bundle Branch Block*. *J Am Coll Cardiol*, 2018. **71**(3): p. 306-317.
6. Steinberg, B.A., et al., *Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes*. *Circulation*, 2012. **126**(1): p. 65-75.
7. Karatolios, K., et al., *Long-term outcome and predictors of outcome in patients with non-ischemic dilated cardiomyopathy*. *Int J Cardiol*, 2016. **220**: p. 608-12.
8. Witt, C.M., et al., *Outcomes With Left Bundle Branch Block and Mildly to Moderately Reduced Left Ventricular Function*. *JACC Heart Fail*, 2016. **4**(11): p. 897-903.
9. Cleland, J.G., et al., *The effect of cardiac resynchronization on morbidity and mortality in heart failure*. *N Engl J Med*, 2005. **352**(15): p. 1539-49.
10. Ponikowski, P., et al., *2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC*. *Eur Heart J*, 2016. **37**(27): p. 2129-2200.