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Ejection fraction in left bundle branch block is disproportionately reduced in relation to amount of myocardial scar

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ABSTRACT

Introduction: The relationship between left ventricular (LV) ejection fraction (EF) and LV myocardial scar can identify potentially reversible causes of LV dysfunction. Left bundle branch block (LBBB) alters the electrical and mechanical activation of the LV. We hypothesized that the relationship between LVEF and scar extent is different in LBBB compared to controls.

Methods: We compared the relationship between LVEF and scar burden between patients with LBBB and scar (n = 83), and patients with chronic ischemic heart disease and scar but no electrocardiographic conduction abnormality (controls, n = 90), who had undergone cardiovascular magnetic resonance (CMR) imaging at one of three centers. LVEF (%) was measured in CMR cine images. Scar burden was quantified by CMR late gadolinium enhancement (LGE) and expressed as % of LV mass (%LVM). Maximum possible LVEF (LVEFmax) was defined as the function describing the hypotenuse in the LVEF versus myocardial scar extent scatter plot. Dysfunction index was defined as LVEFmax derived from the control cohort minus the measured LVEF.

Results: Compared to controls with scar, LBBB with scar had a lower LVEF (median [interquartile range] 27 [19–38] vs 36 [25–50] %, $p < 0.001$), smaller scar (4 [1–9] vs 11 [6–20] %LVM, $p < 0.001$), and greater dysfunction index (39 [30–52] vs 21 [12–35] % points, $p < 0.001$).

Conclusions: Among LBBB patients referred for CMR, LVEF is disproportionately reduced in relation to the amount of scar. Dyssynchrony in LBBB may thus impair compensation for loss of contractile myocardium.

Introduction

In left bundle branch block (LBBB), the extent to which reduction in left ventricular (LV) ejection fraction (EF) is caused by myocardial scar is both unexplored and of clinical interest. LBBB is a conduction disorder that may contribute to decreased LVEF and subsequent heart failure (HF) [1,2]. The presence of LBBB leads to an abnormal LV electrical and mechanical activation, which causes a dyssynchronous contraction of the LV [3,4], which is associated with poorer LV function [2,5].

Cardiovascular magnetic resonance (CMR) imaging enables excellent morphological and functional evaluation as well as tissue characterization of the myocardium [6,7]. Cardiovascular magnetic resonance imaging is currently the in vivo reference standard for assessing the presence and location of myocardial scarring [6,8], as well as for determining left ventricular (LV) volumes and left ventricular ejection fraction (LVEF). Furthermore, myocardial scar burden has also been found to be predictive of adverse outcomes after cardiac resynchronization therapy (CRT) in the presence of LBBB [7,9].

Following myocardial infarction or irreversible non-ischemic myocardial damage, focally fibrotic scar tissue gradually develops and replaces the area of necrotic myocardium. Scarred myocardium does not contract, and this leads to a reduction in systolic function [8]. Because

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myocardial scarring is irreversible, reduction in LVEF due to scarred myocardium is also likely to be irreversible. Besides myocardial scar, there are other causes of reduced LVEF that can potentially be reversible, e.g. myocardial stunning and hibernation [10]. Therefore, it is of interest to determine the proportion of LVEF reduction that can be attributed to myocardial scar. A previous study has investigated the relationship between LVEF and scar extent in consecutive patients with ischemic heart disease, without regard for presence of conduction abnormalities [11]. That study developed a left ventricular (LV) dysfunction index, which estimated the amount of reduction in LVEF that could not be explained solely by scar extent [11]. However, the relationship between LVEF and myocardial scar extent has not been studied in LBBB. It is thus unknown whether LBBB modifies the impact of scar burden on LVEF and whether it is reasonable to expect that CRT may remove such a negative synergistic effect of LBBB and scar burden. Therefore, the aim of the study was to compare the quantitative relationship between LVEF and myocardial scar extent in patients with normal conduction and LBBB using CMR. We hypothesized that in LBBB, LVEF is disproportionately reduced by small amounts of scar compared to a control group of patients with normal conduction and ischemic heart disease.

Material and methods

Study patients

This retrospective cross-sectional observational study was a substudy comparing two previously assembled consecutive cohorts, one with LBBB (n = 83) and one without (n = 90), both of whom had undergone CMR and standard 12-lead ECG. The LBBB patients were consecutively included from two centers: Duke University Medical Center, USA (2011–2015) and University of Pittsburgh Medical Center, USA (2009–2015). The normal conduction control cohort was included from Skåne University Hospital, Lund (2004–2009). All patients were included following approval by the local human subjects research ethics committee or investigational review board, and following written informed consent or retrospective waiver of individual informed consent as part of the ethics approval.

LBBB cohort

The LBBB cohort consisted of consecutive patients (n = 83) referred for a CMR scan for any reason who had presence of scar confirmed by CMR (regardless of clinical indication) and who were identified by comparing clinical electrocardiogram (ECG) and CMR databases. Inclusion criteria were: 1) Available CMR including late gadolinium enhancement (LGE) and cine images of acceptable quality, 2) ECG recordings of acceptable quality within 30 days of CMR scan date, and 3) presence of LBBB by manual interpretation of ECG in accordance with previously published strict LBBB criteria [12]. The exclusion criteria were: 1) Patients with congenital heart defects, 2) Presence of amyloidosis with cardiac involvement as diagnosed by CMR, 3) Prior cardiac or thoracic surgery, and 4) Arrhythmia on ECG determined to preclude analysis of representative QRS complexes.

Indications for CMR were diverse and included, among others: post-infarction assessment of viability; heart failure evaluation; dyspnea evaluation; inconclusive prior non-invasive testing; suspected hemochromatosis; assessment of left ventricular hypertrophy; assessment of non-ischemic cardiomyopathy; assessment of aorta; assessment of pericardium; prior cardiac arrest; suspected cardiac thrombus; constrictive/restrictive disease; suspected myocarditis and arrhythmia or palpitations. Patients frequently had multiple reasons for testing.

Normal conduction cohort

The normal conduction cohort was derived from a previous study on the relationship between scar and LVEF, which included n = 149 consecutive ischemic heart disease patients who were referred for CMR [11]. Inclusion and exclusion criteria for the original n = 149 cohort have been previously described [11]. In brief, patients who underwent CMR-LGE at Skåne University Hospital, Lund, between 2000 and 2004 were retrospectively screened for inclusion. In order to be included, clinical CMR reports needed to contain quantitative LVEF, LVM, and manually delineated quantification of LGE scar size as well as diagnosis of ischemic heart disease. For inclusion in the present study, we added a requirement of available ECG with QRS duration <120 ms and frontal plane QRS electrical axis between −30 and 90°. Application of these criteria identified n = 90 patients comprising the normal conduction control cohort.

ECG analysis

All patients included in the LBBB cohort fulfilled the strict LBBB criteria proposed by Strauss et al. [12]. In summary, these criteria are as follows: (1) QRS duration ≥140 ms in men and ≥130 ms for women; (2) rS/QS configuration in V1 and V2; and (3) presence of mid-QRS notching/slurring in two or more of leads I, aVL, V1, V2, V5 and V6. All ECGs in the LBBB and normal conduction cohort were reviewed manually by an experienced observer (BW).

CMR imaging

In order to meet the target sample size for the LBBB cohort, clinical CMR databases had to be screened from two centers spanning long periods of time. Therefore, specific LGE and Cine imaging sequences and imaging parameters varied. However, scar was quantified using LGE images and LVEF was measured in cine images that were determined by an experienced observer (BW) to be of adequate quality. Imaging was performed using ECG gating and a phased-array cardiac receiver coil at all centers. Both 1.5 T scanners (Avanto, Magnetom Espree, or Magnetom Vision, Siemens, Erlangen, Germany or Intera CV, Philips, Best, the Netherlands) and a 3.0 T scanner (Verio, Siemens, Erlangen, Germany) were used. Cine imaging was performed with a SSFP sequence, and short axis stacks were evaluated to measure LVEF. Typically, in plane resolution was 1.6 × 1.8 mm^2, slice thickness was 6–8 mm with 0–4 mm interslice gap. For all cine images, temporal resolution was below 45 ms. For evaluation of scar presence, LGE images were acquired 10–15 min following administration of 0.15–0.20 mmol/kg of a gadolinium-based contrast agent (Gadoversetamide; Mallinckrodt Inc., St. Louis, MO, USA or gadoteridol, Bracco Diagnostics, Monroe Township, NJ, USA). Pulse sequences for LGE imaging included 2D and 3D segmented inversion recovery gradient-echo pulse sequences [13], a 2D phase-sensitive inversion recovery (PSIR) sequence, or a 2D single-shot inversion recovery sequence. For LGE images, typical imaging parameters were: in plane resolution 1.4–1.8 mm^2, slice thickness 6–8 mm and 0–4 mm inter-slice gap. Inversion delay was typically between 250 and 350 ms, with signal intensity of healthy myocardium nulled. The images acquired from each subject included long-axis images (2-, 3-, and 4-chamber views) and full short-axis stacks of cine and LGE images spanning from the base to the apex of the LV. The number of slices in each stack varied accordingly between subjects due to variations in heart size, but there were typically about 8–12 slices available for analysis.

Quantification of ejection fraction

Calculated LVEF and LVM were obtained, when available, from clinical CMR reports after confirmation that cine images were of sufficient quality. When not available in clinical CMR reports, LVEF and LVM were measured retrospectively by delineation of cine images. Images were analyzed using the freely available image analysis software Segment (version 2.0 R4755, Medviso AB, Lund, Sweden) [14]. To determine LVEF, short-axis cine stacks were semi-automatically analyzed by