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The definition of left bundle branch block influences the response to cardiac resynchronization therapy

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ABSTRACT

Background: CRT has been proven to achieve most benefit in patients with left bundle branch block morphology (LBBB). However, ECG criteria to define LBBB significantly differ from each other.
Objective of the study was to evaluate the impact of different ECG criteria for LBBB definition on survival, hospitalization for heart failure and reverse remodelling in patients who received cardiac resynchronization therapy (CRT).
Methods and results: Three-hundred-sixteen consecutive patients were included in the analysis. Six different classifications were assessed in baseline ECGs of patients who received a CRT device: a QRS duration of ≥150 ms and LBBB according to AHA/ACC/HRS, ESC 2006, ESC 2009, ESC 2013 and the classification proposed by Strauss and colleagues. In univariate analysis, the ESC 2009 and 2013 and the Strauss classifications were significantly associated with a reduction in cumulative probability for heart failure (HF) and mortality (HR 0.60, 95% CI 0.42–0.86, HR 0.61, 95% CI 0.43–0.87 and HR 0.57, 95% CI 0.40–0.80, respectively). In multivariate analysis, the association with the combined endpoint was confirmed only for ESC 2009 and 2013 classifications and for Strauss. Moreover, the cumulative probability of all-cause death and HF hospitalizations was higher in patients who were negative for all the 5 LBBB classifications.
Conclusions: This study shows that the strength of the association of LBBB to outcome in CRT depends on the ECG classifications used to define LBBB, the simplest criteria (ESC 2009 and 2013) providing the best association with clinical endpoints in CRT.

1. Introduction

Cardiac resynchronization therapy (CRT) improves symptoms, quality of life, and survival in patients with reduced left ventricular (LV) ejection fraction, heart failure symptoms, and prolonged QRS duration. The randomized clinical trials that lead to the initial widespread adoption of CRT used only QRS duration of >120 ms as entry criteria [1–4]. Ever since, multiple sub-analyses of large randomized trials showed QRS morphology to be associated to the measured benefit by CRT [5]. Where the benefit in patients presenting left bundle branch block (LBBB) on baseline ECG was shown to be very robust [6,7], in non-LBBB patients the benefit is still controversial [6,7]. Moreover, the specific criteria used to classify LBBB are not indicated in clinical practice guidelines [7,8].

Currently, there are multiple ECG criteria for LBBB proposed by scientific organizations [6,9–11] and research groups [12]. Moreover, the European Society of Cardiology (ESC) has changed criteria for LBBB a few times over the last decade [6,10,11]. While initially these criteria were used to classify the conduction abnormality per se, the more recent ones implicitly assume that LBBB represents the most important substrate for CRT. The lack of uniformity of LBBB criteria and uncertainty about the differences in association with outcomes to CRT can contribute to the still remaining group of patients experiencing no benefit from CRT.

Therefore, we aimed to study in a population of patients implanted with a CRT: 1) the consistency of a CRT patient to be classified as having LBBB, and 2) the association of different LBBB criteria with both reverse remodelling and hospitalization for HF and all-cause death.

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2. Methods

2.1. Study population

All consecutive patients who received a CRT at two different European centres (Cardiocentro Ticino, Lugano, Switzerland and Maastricht University Medical Center, Maastricht, The Netherlands) since 2006 to 2016 were retrospectively analysed for the inclusion in the study. Patients were indicated to CRT according to European guidelines indications available at time of CRT implantation. All patients underwent implantation of a CRT system, with or without implantable cardioverter-defibrillator capabilities based upon clinical decision and patient decision. Exclusion criteria were unavailable or poor quality baseline ECG, baseline right ventricular pacing, incomplete follow up data and biventricular pacing inadequate after implantation (≤95%). The study protocol was approved by the locally appointed ethics committee and complied with the Declaration of Helsinki. Written informed consent has been obtained from all the subjects (or their legally authorized representative).

2.2. ECG acquisition and analysis

Standard supine 12 lead ECGs (filter range, 0.15 to 100 Hz; AC filter, 60 Hz, 25 mm/s speed, 1 mm/mV) were obtained at baseline and before discharge. In a blinded manner, one experienced reader interpreted QRS morphology based on morphological features of the five different ECG criteria. LBBB definitions used were the ones recommended by the AHA/ACC/HRS [9], the ones suggested by the ESC in 2006 [10] and 2009 [11] textbooks and the 2013 ESC guidelines [6], and finally the ECG definition proposed by Strauss et al. [12]; the criteria are summarized in Table 1. Notching in the QRS complex and slurring were defined according to Almer et al. [13] Notching was defined as a sudden change, within a slope (waveform), in direction ≥ 90°; slurring was defined as sudden change in the slope of a waveform with a change in direction 0°–90°. QRS duration was always automatically measured by using ECG machine of two different vendors (Schiller CARDIOVIT CS-200 Excellence, Doral, FL, USA and ELI 350, Mortara Instrument, Inc., Milwaukee, WI, USA). In order to qualify for LBBB according to a specific definition, the ECG should comply with all required criteria for that definition.

2.3. Echocardiographic measurements

Echocardiographic evaluation was performed at baseline and at 6 months after device implantation. Images were acquired in the left lateral decubitus position with a commercially available system (GE Healthcare, Horten, Norway) with a 3.5-MHz transducer at a depth of 16 cm in conventional parasternal and apical views. LV end-systolic volume (LVESV) and end-diastolic volume (LVEDV) were measured at the apical 2- and 4-chamber views; LV Ejection Fraction (LVEF) was calculated with the use of the biplane Simpson method. Reverse remodelling was defined as a reduction of LVESV of at least 15% assessed at 6 months after CRT implantation compared to baseline.

2.4. Follow up

Clinical follow-up of patients consisted of physical examination, ECG and echocardiogram performed at least every 6 months. Follow-up of the device was performed at 1 and 3 months after CRT implantation and every 6 months thereafter. Data on hospitalization for acute heart failure were systematically collected. The diagnosis of heart failure required signs and symptoms consistent with congestive heart failure that was responsive to intravenous decongestive therapy.

2.5. Statistical analysis

Continuous data are presented as median and 25th–75th percentiles (IQR) and categorical data as counts and percentages. They were compared between groups dichotomic with the Mann Whitney *U* test and the Fisher exact test, respectively. Each patient's ECG was classified as LBBB or not according to the five classification methods described above. Therefore, each patient could have from 0 to 5 LBBB criteria satisfied. Comparisons according to the number of LBBB positive classification per patient used the Kruskal–Wallis test for continuous variables and the Fisher exact test for categorical variables. The test for trend was also applied. Significance was set at 0.003 for pairwise post-hoc comparisons.

The association of LBBB and reverse remodelling measured as a reduction of 15% of the LVESV at 6 months was assessed with a logistic model. Odds ratios (OR) and 95% confidence intervals (95%CI) were computed. Median follow-up (IQR) was computed with the inverse Kaplan Meier method. Event rates per 100 person year and 95%CI were computed.

Event-free survival was estimated by Kaplan-Meier method and compared with the logrank test. Hazard ratios (HR) and 95%CI were calculated with a Cox model. The proportional hazard assumption was satisfied in all cases. Endpoints for these analyses were hospitalization for heart failure, death and the combined endpoint. For both modeling procedures, both univariable and multivariable models with adjustment for a priori selected clinical confounders were fitted. We computed the Harrell's c concordance statistic for all Cox models including in turn each LBBB classification (the higher the Harrell's c, the better model discrimination); we informally compared classifications by ranking the Harrell's c.

Statistical analyses were conducted using the Stata 15.1 software (Stata Corporation, College Station, TX, USA). A 2-sided p-value < 0.05 was considered statistically significant.

3. Results

Since January 2006 to December 2016, 498 patients received a CRT at the two participating institutions. Of them, 45 patients were excluded because of poor quality of baseline ECG, 25 patients for biventricular pacing <95% despite reprogramming, 15 patients because of baseline paced QRS without intrinsic rhythm and 97 patients were excluded due to incomplete follow up data. Three-hundred sixteen patients were finally included in the analysis (Lugano n: 156; Maastricht n: 160). Demographic characteristics of the study cohort are summarized in Table 2. The frequency of LBBB strongly depended on the ECG classification used, the proportion of patients meeting LBBB definitions ranging from 29% (AHA) to 61% (Strauss). One-hundred ninety-eight patients (63%) had a LBBB according to at least one definition; of these, 33% were positive for all five ECG classifications. As illustrated in the Table included in the Supplemental material, overlap among the LBBB classifications is present.

3.1. QRS morphology and reverse remodelling

One-hundred seventy-six patients (55%) out of the 316 patients had a ≥15% reduction of baseline LVESV at 6-month follow up. The proportion of patients with reverse remodelling varied according to different LBBB definitions and QRS duration (Fig. 1 - Supplemental material). Among all considered LBBB definitions, the ESC definitions showed the strongest association with reverse remodelling. When adjusted for confounding factors (age, gender, renal impairment, anti-remodelling therapy), the association with reverse remodelling was significant only for ESC 2009 and ESC 2013 definitions (OR 8.8, 95% CI 1.3–56.5, p 0.01 and OR 8.7, 95% CI 1.4–56.4, p 0.01, respectively).

3.2. QRS morphology and heart failure hospitalization

During a median follow up time of 55 months (IQR 25–79 months), 104 patients (33%) were admitted to the hospital for acute heart failure after CRT implantation. The cumulative probability of hospitalization for

Table 1
ECG criteria to define Left bundle branch block.

	AHA/ACC/HRS (2009)	ESC 2006	ESC 2009	ESC 2013	Strauss (2011)
QRS duration	≥120 ms	≥120 ms	≥120 ms	≥120 ms	M: ≥140 ms, F: ≥130 ms
QS or rS pattern	–	V1	V1, V2	V1	V1, V2
QS pattern	–	aVR	–	–	–
Positive T-wave/QRS concordance	Yes	V1 and aVR	–	–	–
Delayed ID-time (≥60 ms)	V5, V6	I and V6	–	–	–
Discordant T-waves	Usually	Usually	–	–	–
Notch/slurred R-wave	I, aVL, V5,V6	–	I, aVL, V5, V6	I, aVL, V5, V6	I, aVL, V1, V2, V5, V6
Negative T-wave in leads with upright QRS	Yes	–	I, aVL, V5, V6	–	–
Absent Q-wave	I, V5, V6	–	I, aVL, V5, V6	V5, V6	–

ID: intrinsicoid deflection.

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