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Large variability in clinical judgement and definitions of left bundle branch block to identify candidates for cardiac resynchronisation therapy

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ABSTRACT

Background: Left bundle branch block (LBBB) morphology is associated with improved outcome of cardiac resynchronisation therapy (CRT) and is an important criterion for patient selection. There are, however, multiple definitions for LBBB. Moreover, applying these definitions seems subjective. We investigated the inter- and intraobserver agreement in the determination of LBBB using available definitions, and clinicians' judgement of LBBB.
Methods: Observers were provided with 12-lead ECGs of 100 randomly selected CRT patients. Four observers judged the ECGs based on different LBBB-definitions (ESC, AHA/ACC/HRS, MADIT, and Strauss). Additionally, four implanting cardiologists scored the same 100 ECGs based on their clinical judgement. Observer agreement was summarized through the proportion of agreement (P) and kappa coefficient (k).
Results: Relative intra-observer agreement using different LBBB definitions, and within clinical judgement was moderate (range k 0.47–0.74 and k = 0.76 (0.14), respectively). The inter-observer agreement between observers using LBBB definitions as well as between clinical observers was minimal to weak (range k 0.19–0.44 and k = 0.35 (0.20), respectively). The probability of classifying an ECG as LBBB by available definitions varied considerably (range 0.20–0.76). The agreement between different definitions of LBBB ranged from good (P = 0.95 (0.07)) to weak (P = 0.40 (0.22)). Furthermore, correlation between the different LBBB definitions and clinical judgement was poor (range phi 0.30–0.55).
Conclusion: Significant variation in the probability of classifying LBBB is present in using different definitions and clinical judgement. Considerable intra- and inter-observer variability adds to this variation. Interdefinition agreement varies significantly and correlation of clinical judgement with LBBB classification by definitions is modest at best.

1. Introduction

Cardiac resynchronisation therapy (CRT) is an established treatment for heart failure patients with concomitant ventricular conduction disturbances on the 12 lead ECG [1,2]. Studies have shown that the presence of left bundle branch block (LBBB) is one of the best predictors of response to CRT [3–6]. Therefore, current guidelines use LBBB QRS morphology next to QRS duration as a tool for patient selection for CRT [2]. Currently, patients with LBBB QRS morphology have a class I recommendation for CRT, whereas patients with non-LBBB QRS morphology have a class IIa or IIb recommendation depending on QRS duration.

The use of the LBBB morphology in clinical practice is, however, not straightforward. LBBB morphology has been defined differently by the European and American cardiology societies [1,7], landmark trials (REVERSE and MADIT-CRT) [4,6] and by experts [8]. In addition, applying these different definitions requires careful evaluation of the ECG. Therefore, implanting cardiologists' judgement of the presence of LBBB may not be in concordance with these definitions. Even when the LBBB definitions would be used in clinical practice, they are extensive (many criteria) and sensitive to different interpretations, which may result in significant variation in patient selection for CRT.

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Table 1
Left bundle branch block definitions.

Definitions	Criteria
ESC [1]/REVERSE [4]	• QRS ≥120 ms • QS or rS in V1 • Broad (frequently notched/slurred) R in I, aVL, V5 or V6 • Absent Q in V5 and V6
AHA/ACC/HRS [7]	• QRS ≥120 ms • Notch-, slurred R in I, aVL, V5 and V6 • Occasional RS pattern in V5–6 • Absent q in I, V5–V6 and aVL • R peak time >60 ms in V5 and V6 • Normal R peak time in V1–V3 • No negative concordance • Usually discordant ST-T segments
MADIT [6]	• QRS ≥130 ms • QS or rS in V1 • Broad (frequently notch-/slurred) R in I, aVL, V5 or V6 • Absent q in V5 and V6
Strauss [8]	• QRS ≥130 ms in women, ≥140 ms in men • QS or rS in V1 and V2 • Mid QRS notching/slurring in ≥2 congruent leads V1, V2, V5, V6, I or aVL

In this study we aim to investigate (1) the agreement in identification of LBBB by clinical judgement of implanting cardiologists; (2) the agreement in identification of LBBB using available LBBB definitions; (3) the agreement between available LBBB definitions and (4) the correlation between LBBB identification with use of definitions and of clinical judgement by implanting cardiologists.

2. Methods

From a large cohort of over 500 consecutive patients implanted with a CRT device in the University Medical Centre Utrecht, 100 baseline 12-lead ECGs were randomly selected. The ECGs were recorded at 25 mm/s paper speed and displayed in a 2 × 6 lead fashion. Four expert cardiologists involved in patient selection for CRT in daily clinical practice (JL, AA, AM, KV) classified the presence of LBBB on the ECG according to their clinical judgement. The ECGs were provided as printed 12-lead ECGs. For the classification of LBBB according to the different LBBB definitions, four independent, trained observers judged the ECGs according to four currently used LBBB definitions (Table 1). As can be seen in Table 1, REVERSE-trial and ESC definition contain the same morphological features. Therefore the REVERSE-trial LBBB definition was not included as a separate definition. The evaluation of the four different LBBB definitions was performed on digital ECGs (using up to 400% zoom to judge the individual LBBB criteria). QRS duration was determined by the automated ECG algorithm.

2.1. Statistical analysis

Intra-observer agreement for all five ways to determine LBBB was investigated using repeated independent observations from two observers; both for definitions and clinical judgement. Inter-observer agreement was defined between pairs of observers. Intra-observer and inter-observer agreement levels were quantified in two ways: through the probability to agree and through the kappa coefficient. While the first measure accounts for disagreement on the classification of the ECGs themselves (absolute agreement), the kappa coefficient also accounts for disagreement on the probability to be classified as LBBB with the different definitions (including interobserver variability). Kappa coefficients therefore mix two sources of disagreements (relative agreement). The effect of predictors (type of criterion and QRS duration larger than 150 ms for clinical classification) on the intra- and interobserver agreement levels and the probability of LBBB were analyzed using a multilevel approach [9]. Random effects relative to the patients were introduced in the models to capture the dependency between the multiple measurements made on each patient (different pairs of observers using the same definition or the same observers using different definitions). Large values of the variance of the random effects indicate heterogeneous agreement levels, while small values indicate homogeneous agreement levels. A Bayesian approach with vague priors was used to estimate the parameters in the model. A predictor is said to be significant if the 95% equal-tailed posterior credibility interval relative to the predictor does not contain the value 0. Posterior marginal distributions were obtained by averaging over the random effects and are summarized using posterior mean (posterior standard deviation). Data analysis was conducted using R (version 3.2.5 for Windows) and JAGS statistical packages.

3. Results

Mean QRS duration of the patients was 160 ± 24 ms. Baseline characteristics reflect a typical CRT population. Three patients had a QRS duration shorter than 120 ms, and were implanted with a CRT device for an ablate-and-pace indication.

3.1. Intra-observer agreement in LBBB classification

Overall absolute intraobserver agreement between LBBB definitions is strong (P range 0.87–0.95), however relative agreement (kappa), corrected for probability of the presence of LBBB, is only moderate (k range 0.47–0.74). Intraobserver (absolute and relative) agreement was lower with AHA/ACC/HRS definition than with ESC, MADIT and Strauss definitions (Table 2). Within the AHA/ACC/HRS definition, the agreement level on the detection of notched and slurred R criterion was lower (P = 0.81 (0.09)) than on other criteria. Agreement on morphological criteria of other LBBB definitions did not significantly differ.

Absolute Intra-observer agreement on clinical judgement was good (P = 0.93 (0.05)), but only moderate relative agreement was found (k = 0.76 (0.14)) (Table 2).

Absolute and relative agreement did not differ for patients with QRS duration below and above 150 ms (P = 0.96 (0.09) and P = 0.88 (0.16), respectively).

3.2. Inter-observer agreement in LBBB classification

Absolute inter-observer agreement was good for all LBBB definitions (P range 0.81–0.88), however relative agreement (kappa) was minimal to weak (range k 0.19–0.44) (Table 2). Agreement level in AHA/ACC/HRS definition was reduced by variability in scoring notching/slurring of the R-wave in leads I, aVL, V5 and V6, the absence of a Q-wave in leads I, V5, V6 and aVL and R-peak time criteria (P = 0.73 (0.06), P = 0.75 (0.07) and P = 0.71 (0.07), respectively).

The same trend was visible for clinical judgement of LBBB. Whereas there was good absolute agreement of clinical judgement (P = 0.81 (0.81)), relative agreement is weak (k = 0.35 (0.20)) (Table 2).

QRS duration did not influence inter-observer variability (P = 0.73 (0.34) and P = 0.82 (0.19), for QRS duration below and above 150 ms respectively) for clinical judgement.

3.3. General variation in observation of LBBB

There was a considerable difference in the probability of classification as LBBB between the four available definitions and clinical judgement, ranging between 0.20 (0.27) for AHA/ACC/HRS definition and 0.76 (0.29) for ESC definition (Fig. 1). The error bars in Fig. 1 indicate large variability in scoring LBBB between the four observers, even when using the same definition. The probability of being classified as LBBB with clinical judgement was higher in patients with QRS duration

Table 2
Intra- and interobserver agreement in LBBB classification.

Criterion	Prevalence	Intra-observer agreement (P)	Kappa (K)	Inter-observer agreement (P)	Kappa (K)
ESC	0.75 ± 0.29	0.94 ± 0.05	0.67 ± 0.22	0.85 ± 0.08	0.27 ± 0.25
AHA/ACC/HRS	0.20 ± 0.27	0.87 ± 0.08	0.47 ± 0.28	0.81 ± 0.09	0.19 ± 0.25
MADIT	0.71 ± 0.31	0.95 ± 0.04	0.74 ± 0.19	0.88 ± 0.07	0.44 ± 0.22
Strauss	0.65 ± 0.32	0.92 ± 0.06	0.65 ± 0.22	0.85 ± 0.08	0.40 ± 0.22
Clinical judgement	0.50 ± 0.35	0.93 ± 0.05	0.76 ± 0.14	0.81 ± 0.08	0.35 ± 0.20

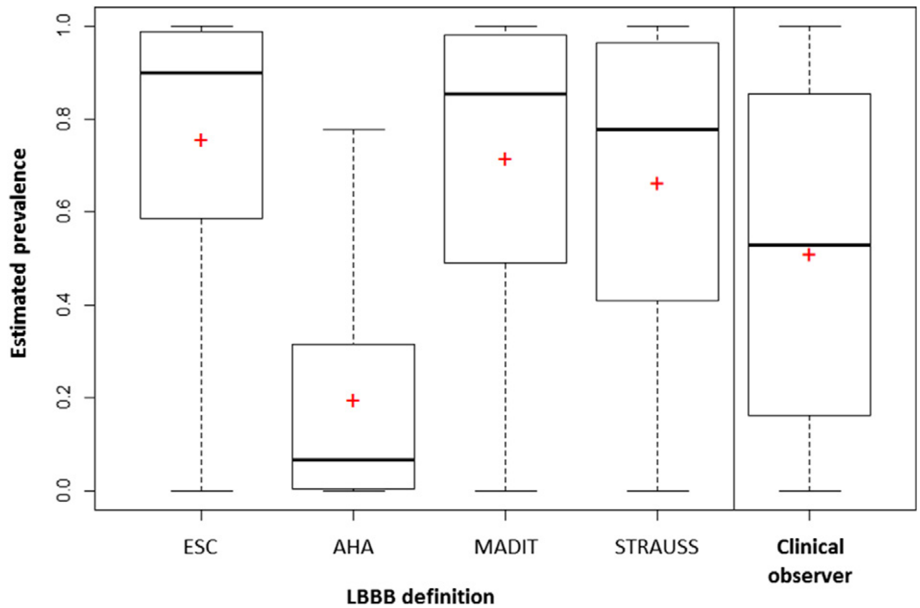

Fig. 1. Prevalence of LBBB according to available definitions and clinical judgement. Summary of the estimated prevalence of LBBB according to four definitions each used by 4 observers and clinical judgement made by 4 clinicians. Data are presented as mean (cross), median (bar), 25–75 percentiles (box) and minimum and maximum (dotted line). AHA = American Heart Association, American College of Cardiology and Heart Rhythm Society conjoint definition of LBBB [18], CLI = clinical judgement, ESC = European Society of Cardiology [1], MADIT = Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) [6], Strauss = LBBB definition according to Strauss et al. [8].

above 150 ms than in patients with a QRS duration <150 ms, 0.68 (0.36) versus 0.26 (0.34) respectively.

3.4. Inter-definition agreement in LBBB classification

Highest inter-definition agreement was observed between ESC and MADIT definitions (P = 0.95 (0.07)), whereas lowest agreement was seen between the AHA/ACC/HRS and the ESC, MADIT and Strauss criteria (P = 0.40, (0.22), P = 0.44, (0.23), and P = 0.50 (0.23) respectively).

3.5. Correspondence of clinical judgement with available definitions

As shown in Fig. 2, the clinical judgement of the presence of LBBB correlated only modestly (phi coefficient range 0.10–0.68) to LBBB according to the available definitions of LBBB. Clinical judgement correlated best with Strauss definition (mean phi = 0.52 (0.10)) and worst with AHA/ACC/HRS definition (mean phi = 0.30 (0.10)).

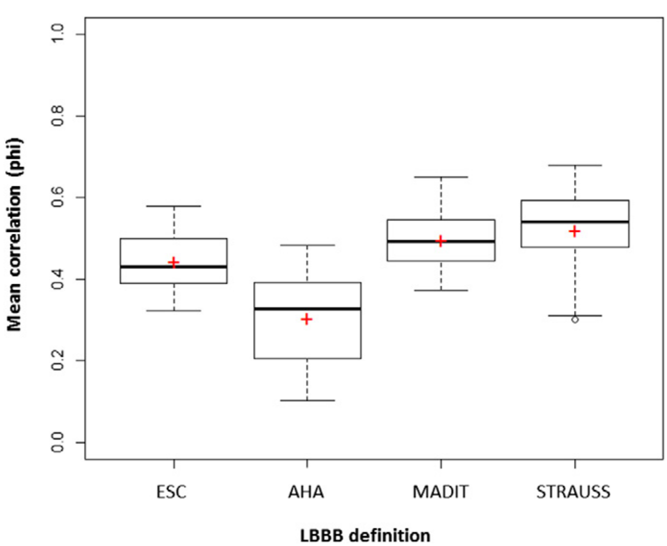

Fig. 2. Correlation of clinical LBBB classification with classification according to available LBBB definitions. Summary of the correlation (phi coefficient) between LBBB according to clinical judgement and the four LBBB definitions. Data are presented as mean (cross), median (bar), 25–75 percentiles (box) and minimum and maximum (dotted line). Symbols and abbreviations are explained in the legends to Fig. 1.

4. Discussion

The present study shows that LBBB classification by clinical judgement as well as classification by use of definitions of LBBB shows significant interobserver, and to lesser extent intra-observer variability. Variability seems to depend on the complexity of the definition of LBBB. The probability of classifying an ECG as LBBB by clinical judgement and available definitions varied considerably. Furthermore the correlation between clinical judgement and the LBBB definitions was poor. These results are important in the light of LBBB being an important selection criterion for CRT. The lack of a standardized and well defined classification of LBBB may hamper consistent selection of patients. Moreover study results that have established the role of LBBB in patient selection for CRT, may not be reproducible in daily practice.

4.1. Classification according to clinical judgement of LBBB

Clinical judgement of LBBB seems reproducible as it showed good intra-observer agreement. Although still close to 1 in 10 ECGs will be classified differently by the same observer. However, inter-observer agreement is only 0.81, which implies that implanting cardiologists will disagree on 1 in 5 ECGs. This large inter-observer variability exists despite the fact that the observers in this study are experienced and have been dealing with this issue extensively in research and clinical settings. Although QRS duration influences the likelihood for a patient to be classified as LBBB, no evidence of an influence of QRS duration on the intra- and interobserver agreement was found. Meaning that the subjectivity in LBBB classification depends predominantly on morphological features. The 50 ± 0.35% prevalence of LBBB by clinical classification adds to the low kappa-value (0.35 ± 0.20) which translates to the poor correlation with LBBB definitions.

The poor correlation of clinical judgement with LBBB classification according to the definitions implies that the abundance of research showing the relation of LBBB to improved outcomes in CRT may not be applicable to LBBB based on clinical judgement.

Since all observers were from Europe, a larger correlation of the clinical judgement with the ESC definition was expected that with the other definitions. However, the correlation was the highest with the MADIT and the Strauss LBBB definitions, the two least complex definitions. These definitions also incorporate a larger QRS duration criterion, which could reflect that clinical judgement is sensitive to wider QRS duration, as was shown in this study.

4.2. Classification using different LBBB definitions

There is great variability in classification of LBBB according to different definitions with AHA/ACC/HRS definitions classifying every other ECG different from ESC, MADIT and Strauss definitions. This obviously leads to great differences in implantation practice. However even using Strauss and ESC or MADIT definitions will lead to a different classification in 1 out of 5 ECGs.

The probability of observing LBBB according to the definitions investigated in this study correlates well to findings in earlier studies [4,6,10]. The REVERSE-trial subanalyses reported 60% patients to show LBBB, whereas 70% of MADIT-CRT patients had LBBB on their baseline 12-lead ECG. The REVERSE definition differs from the MADIT definition by the inclusion of a shorter QRS duration, which would make it less specific. The difference can also be explained by the difference in populations, with a larger mean QRS duration in the MADIT-trial (158 ms) as compared to the REVERSE-trial (151 ms). Studies incorporating the Strauss LBBB definition report approximately 40% of patients classified as LBBB [11]. Interestingly, a recent study investigated the effect of the application of Strauss (strict) LBBB definition on CRT patients that were included for 'less' strict criteria, according to the AHA/ACC/HRS definition in the CRT MORE registry. In this subanalysis only 39% of patients classified as LBBB by AHA/ACC/HRS definition, were classified as LBBB by Strauss definition [12]. According to the current analyses however AHA/ACC/HRS LBBB definition is far more specific than the definition Strauss and colleagues used. This once more shows the complex nature of the morphological features the definitions are composed of. The standard deviations shown in Fig. 2 confirm these issues, even within our own group.

Intra-observer variability in LBBB classification using different LBBB definitions is generally good, leading to less than 1 in 10 ECGs classified differently by the same observer. Inter-observer variability however is a little higher, with 1 in every 5 to 6 ECGs being classified differently by different observers. The lower kappa values in comparison to the probabilities reflect the respective prevalences of LBBB by different definitions. Therefore the percentage of patients (0.20 ± 0.27) classified as LBBB by AHA/ACC/HRS definition leads to relatively large difference in probability (0.87 ± 0.08) and kappa (0.47 ± 0.28) values. The small difference in absolute probability between LBBB definitions therefore increases with taking into account the prevalence of LBBB by the different definitions. Moreover variability seems to depend on the complexity of the definition. As the AHA/ACC/HRS definition entails judgement of the presence of 8 separate morphological features, this is by far the most complex definition. Easily misinterpreted morphological criteria as 'notching or slurring' seem to contribute to the higher intra- and interobserver variability. This becomes even more clear when reviewing previous studies' summary of 12-lead ECG characteristics of LBBB. Gold et al. [4] in the REVERSE-trial subanalyses, Zareba et al. [6] in the MADIT-CRT-trial subanalyses, and Birnie et al. [3] in the RAFT-trial subanalyses, all refer to the WHO classification [7] also used by the AHA/ACC/HRS guidelines. The summary of these characteristics in the respective papers however differ significantly from the original WHO criteria that are referred to. Furthermore in the determination of the presence of LBBB (according to the aforementioned definitions) these trials all had a (trained) core-laboratory at their disposal. The results in the current analyses clearly show that this is not a good representation of clinical practice as this reduces inter-observer variability apart from inter-definition and intra-observer variability present in every day clinical practice. Furthermore interpretation of morphological criteria might also depend on the format and filtering of the ECG. When a digital ECG is used, zooming in on the QRS-complex may reveal (or seem to reveal) distinct criteria. When using a printed ECG however, this is not possible. This has also been shown for the interpretation of QRS duration [13].

A possible solution to the observed variability in using LBBB definitions could be the use of automated detection algorithms. Xia et al. [14] have shown this to be a feasible effort, with good correlation to manual observation of LBBB by the Strauss definition (using 4 different observers).

4.3. Limitations

This study did not include outcomes to CRT. Therefore this analysis cannot show the implications for patient benefit from CRT. Although this would further establish the importance of reaching consensus on the definition of LBBB, this was not the primary aim of the current analyses. A recent analysis by Caputo et al. [15] however showed that the definition of LBBB indeed influences the association to CRT. Moreover they show profound differences in patient populations (size) deemed LBBB and non-LBBB by various LBBB definitions. This study stresses the need for standardization of the definition of LBBB, or replacement by alternative marker, which are not so sensitive to interpretation as LBBB.

A limitation in the selection of ECGs in this study, was that all ECGs were from patients actually implanted with a CRT device. This may have caused selection bias in the probability of scoring LBBB. It is unlikely that this affected the variability in the classification of LBBB. However, as observers using clinical judgement were different from observers using LBBB definitions for classification, inter-observer variability could have influenced the relationship between clinical judgement and LBBB definitions.

4.4. Clinical relevance

The observed variability in LBBB classification might in part be an explanation for the high variations in patient selection for CRT and abiding existence of non-response in every day practice [16,17]. The present results also indicate that combining studies on outcome of CRT using different LBBB definitions may produce unreliable indications about the value of LBBB as selection criterion [1]. Finally, while results from subanalyses of the MADIT and REVERSE trials have led to the introduction of LBBB as a selection criterion in all CRT guidelines, this study shows considerable difficulties in the application in daily clinical practice.

5. Conclusions

Classification of the presence of LBBB on the ECG is not straightforward at all. There is considerable difference in identification of LBBB by experienced cardiologists' clinical judgement, as well as by observers using the available LBBB definitions. Furthermore, clinical judgement of LBBB correlates poorly with all of these LBBB definitions. These data indicate that great variability in LBBB classification is bound to be present between the landmark trails confirming the association between LBBB and positive response to CRT, as well as in current CRT practice.

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Conflict of interest

None of the authors involved report any conflicts of interests in the production of the present manuscript.

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