



Aortic valve implantation-induced conduction block as a framework towards a uniform electrocardiographic definition of left bundle branch block

S. Calle · M. Coeman · A. Demolder · T. Philipsen · P. Kayaert · M. De Buyzere · F. Timmermans · J. De Pooter

Accepted: 17 March 2021 / Published online: 30 April 2021
 © The Author(s) 2021

Abstract

Introduction New-onset left bundle branch block (LBBB) following transcatheter or surgical aortic valve replacement (LBBB_{AVI}) implies a proximal pathogenesis of LBBB. This study compares electrocardiographic characteristics and concordance with LBBB definitions between LBBB_{AVI} and non-procedure-induced LBBB controls (LBBB_{control}).

Methods All LBBB_{AVI} patients at Ghent University Hospital between 2013 and 2019 were enrolled in the study. LBBB_{AVI} patients were matched for age, sex, ischaemic heart disease and ejection fraction to LBBB_{control} patients in a 1:2 ratio. For inclusion, a non-strict LBBB definition was used (QRS duration ≥ 120 ms, QS or rS in V1, absence of Q waves in V5-6). Electrocardiograms were digitally analysed and classified according to three LBBB definitions: European Society of Cardiology (ESC), Strauss and American Heart Association (AHA).

Results A total of 177 patients (59 LBBB_{AVI} and 118 LBBB_{control}) were enrolled in the study. LBBB_{AVI} patients had more lateral QRS notching/slurring (100% vs 85%, $p=0.001$), included a higher percentage with a QRS duration ≥ 130 ms (98% vs 86%, $p=0.007$) and had a less leftward oriented QRS axis (-15° vs -30° ,

$p=0.013$) compared to the LBBB_{control} group. ESC and Strauss criteria were fulfilled in 100% and 95% of LBBB_{AVI} patients, respectively, but only 18% met the AHA criteria. In LBBB_{control} patients, concordance with LBBB definitions was lower than in the LBBB_{AVI} group: ESC 85% ($p=0.001$), Strauss 68% ($p<0.001$) and AHA 7% ($p=0.035$). No differences in electrocardiographic characterisation or concordance with LBBB definitions were observed between LBBB_{AVI} and LBBB_{control} patients with lateral QRS notching/slurring.

Conclusion Non-uniformity exists among current LBBB definitions concerning the detection of proximal LBBB. LBBB_{AVI} may provide a framework for more consensus on defining proximal LBBB.

Keywords Left bundle branch block · Transcatheter aortic valve replacement · Surgical aortic valve replacement · QRS notching

Supplementary Information The online version of this article (<https://doi.org/10.1007/s12471-021-01565-8>) contains supplementary material, which is available to authorized users.

S. Calle (✉) · M. Coeman · A. Demolder · P. Kayaert · M. De Buyzere · F. Timmermans · J. De Pooter
 Department of Cardiology, University Hospital Ghent, Ghent, Belgium
simon.calle@ugent.be

T. Philipsen
 Department of Cardiac Surgery, University Hospital Ghent, Ghent, Belgium

What's new?

- Lateral QRS notching/slurring is an essential criterion for diagnosing proximal left bundle branch block (LBBB).
- The use of different LBBB definitions results in discordance when scoring LBBB.
- Aortic valve implantation (AVI)-induced LBBB showed the highest concordance with the 2013 European Society of Cardiology and Strauss definitions.
- AVI-induced LBBB provides a framework for uniform criteria for true proximal LBBB.



Table 1 Clinical, echo- and electrocardiographic characteristics of aortic valve implantation (AVI)-induced left bundle branch block (LBBB_{AVI}) and matched control LBBB (LBBB_{control}) patients

	LBBB _{AVI} (n= 59)	LBBB _{control} (n= 118)	p-value
<i>Clinical characteristics</i>			
Median age (years)	82 (75;85)	81 (75;84)	Matched
Male	25 (42)	50 (42)	Matched
BMI (kg/m ²)	26 ± 4.5	26 ± 4.1	0.592
BSA (m ²)	1.80 ± 0.207	1.80 ± 0.207	0.920
Coronary artery disease	23 (39)	46 (39)	Matched
Acute coronary syndrome	6 (10)	12 (10)	Matched
<i>Echocardiographic measurements</i>			
End-diastolic diameter (mm)	47 ± 6.0	48 ± 7.7	0.506
Left ventricular mass/BSA (g/m ²)	102 ± 28.9	103 ± 36.4	0.562
Left ventricular systolic function			Matched
	Normal (≥ 55%)	41 (70)	82 (70)
	Mildly reduced (45–54%)	9 (15)	18 (15)
	Moderately reduced (30–44%)	7 (12)	14 (12)
	Severely reduced (<30%)	2 (3)	4 (3)
<i>ECG measurements</i>			
PR interval (ms)	191 (168;208)	174 (158;204)	0.072
QRS duration (ms)	148 (140;160)	145 (136;154)	0.074
Frontal QRS axis (°)	-15 (-37;11)	-30 (-45;-3)	0.013
R wave peak time (lead I) (µV)	58 (50;70)	62 (56;72)	0.065
Notching/slurring lateral leads	59 (100)	100 (85)	0.001
Notching/slurring inferior leads	49 (83)	83 (70)	0.067
Notching/slurring V1-2	12 (20)	6 (5)	0.002
Values are mean ± standard deviation, median (first quartile; third quartile) or number (%)			
BMI body mass index, BSA body surface area			

Introduction

Left bundle branch block (LBBB) in humans was first recorded electrocardiographically in 1914 [1]. Multiple criteria for LBBB have been proposed since, based on experimental canine studies [1, 2], human case studies [3], electrophysiological data [4] and observations in cardiac resynchronisation therapy (CRT) responders [1, 5–7]. However, the electrocardiographic pattern of LBBB has not been fully clarified and various LBBB definitions are currently used [1, 8–10], resulting in significant discordance when scoring LBBB in clinical practice [7, 11].

Although conduction block may theoretically occur at any level in the His-Purkinje network, growing evidence suggests that only proximal left bundle branch (LBB) lesions cause ‘true’ LBBB [12] and that only ‘true’ LBBB is considered a strong predictor of CRT response in heart failure patients [6, 13]. Notching or slurring of the QRS complex during LBBB has been linked to a proximal origin of the LBB conduction block and might be considered a key feature of proximal LBBB [14, 15]. A limitation of current LBBB definitions is that they are not exclusively based on electrocardiographic observations in patients with proximal LBBB, which may contribute to the heterogeneity in LBBB definitions.

New-onset LBBB after transcatheter (TAVR) or surgical aortic valve replacement (SAVR) implies a proximal pathogenesis of LBBB and may provide a ‘framework’ towards uniform criteria for proximal LBBB. In this study, we compare the electrocardiographic characteristics and LBBB definitions in aortic valve implantation (AVI)-induced LBBB to a non-procedure-induced LBBB control group.

Methods

Study populations

Enrolled in the study were all patients with AVI-induced LBBB (LBBB_{AVI}), including both patients with TAVR- and SAVR-induced LBBB, at Ghent University Hospital between January 2013 and June 2019. All patients with a primary TAVR and SAVR procedure and without pre-existing LBBB were screened. Exclusion criteria were pre-procedural ventricular pacing and peri-procedural permanent pacemaker implant. Presence of acute LBBB was scored within 24 h following TAVR/SAVR.

A control group of LBBB patients (LBBB_{control}) consisted of randomly selected LBBB patients at Ghent University Hospital. LBBB_{control} patients were matched for age, sex, left ventricular ejection fraction (LVEF),

Table 2 Agreement with various left bundle branch block (LBBB) definitions among aortic valve implantation (AVI)-induced LBBB (LBBB_{AVI}) and matched control LBBB patients (LBBB_{control})

	LBBB _{AVI} (n= 59)	LBBB _{control} (n= 118)	p-value
<i>LBBB definition features</i>			
QRS duration ≥ 120 ms	59 (100)	118 (100)	NP
QRS duration ≥ 130 ms	58 (98)	101 (86)	0.007
QRS duration ≥ 130 ms in females and ≥ 140 ms in males	56 (95)	95 (81)	0.012
QS or rS in V1	59 (100)	118 (100)	NP
Absence of Q waves in V5-6	59 (100)	118 (100)	NP
Absence of Q waves in V5-6 and I	57 (97)	111 (94)	0.720
Absence of Q waves in V5-6, I and aVL	50 (85)	92 (78)	0.286
Presence of Q waves in aVL	9 (15)	26 (22)	0.286
R wave peak time > 60 ms in V5-6	16 (27)	20 (17)	0.113
R wave peak time > 60 ms in V6 only	30 (51)	60 (51)	1.000
Notching/slurring in V5-6, I or aVL	59 (100)	100 (85)	0.001
Notching/slurring in V5-6, I and aVL	32 (54)	37 (31)	0.003
Notching/slurring in ≥ 2 leads (I, aVL, V1-2, V5-6)	59 (100)	93 (79)	<0.001
<i>LBBB definitions</i>			
ESC 2013 definition	59 (100)	100 (85)	0.001
Strauss definition	56 (95)	80 (68)	<0.001
AHA 2009 definition	10 (17)	8 (7)	0.035
<i>AHA 2009 definition variations</i>			
Absence of Q waves in V5-V6-I and R wave peak time > 60 ms in V5-6	10 (17)	8 (7)	0.035
Absence of Q waves in V5-V6-I-aVL and R wave peak time > 60 ms in V5-6	10 (17)	8 (7)	0.035
Absence of Q waves in V5-V6-I and no R wave peak time criterion	31 (53)	37 (31)	0.006
Absence of Q waves in V5-V6-I-aVL and no R wave peak time criterion	28 (48)	35 (30)	0.020
Values are number (%)			
AHA American Heart Association, ESC European Society of Cardiology, NP not possible			

history of coronary artery disease (CAD) and acute coronary syndrome to the LBBB_{AVI} group in a 2:1 ratio. In both the AVI and control groups, LBBB was defined according to broad conventional criteria (QRS duration (QRSD) ≥ 120 ms, QS or rS in lead V1 and absence of Q waves in leads V5 and V6) [16]. The study was approved by the ethics committee of Ghent University Hospital.

Electrocardiographic analysis and LBBB definitions

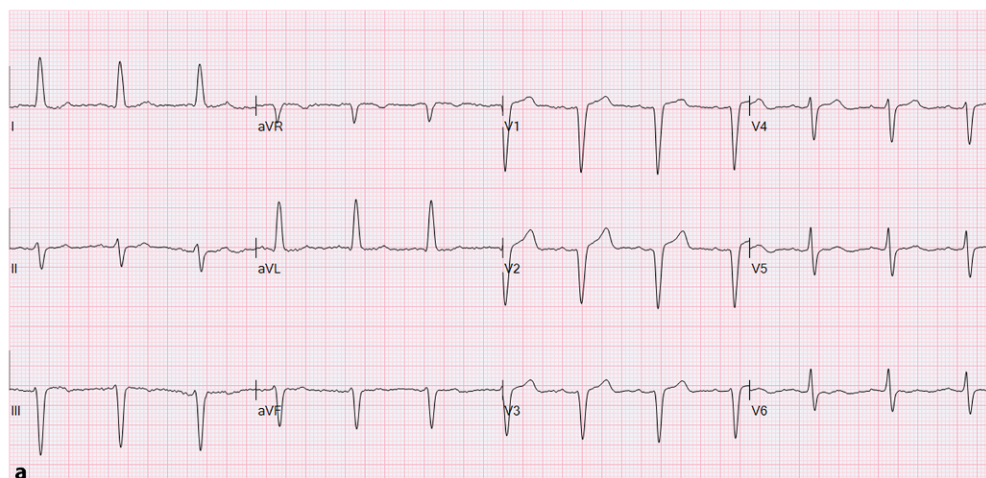
Electrocardiograms (ECGs) were recorded at a sweep speed of 25 mm/s and a calibration of 10 mm/mV, and digitally stored in the MUSE ECG database (GE Healthcare, Chicago, IL, USA). All ECGs were independently reviewed by two investigators and classified according to three currently used LBBB definitions: European Society of Cardiology 2013 (ESC 2013) [9], Strauss et al. [1] and American Heart Association 2009 (AHA 2009) [10] (see Electronic Supplementary Material, Fig. S1). Continuous electrocardiographic characteristics (QRSD, QRS axis, R wave peak time (RWPT)) were digitally analysed by the Marquette 12SL algorithm (GE Healthcare) [17]. RWPT was defined according to the Minnesota Code [18].

Validation of proposed criteria for proximal LBBB

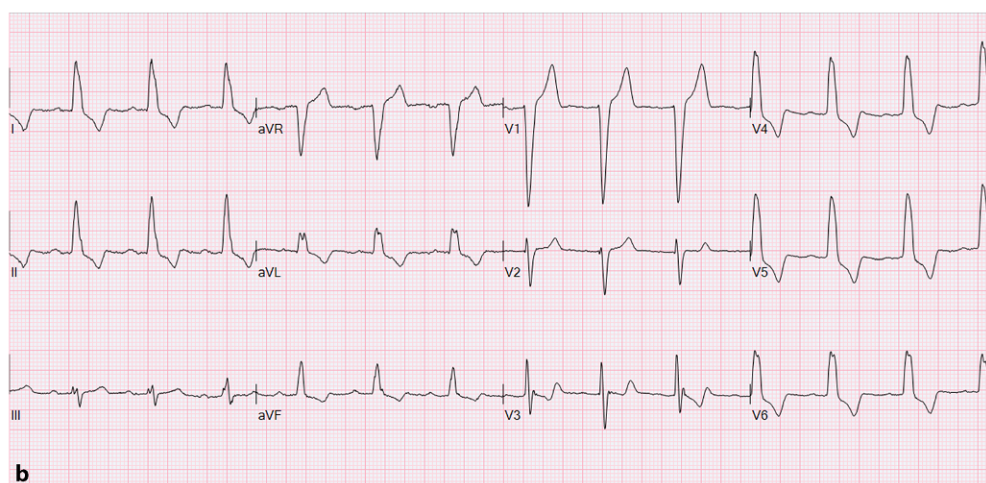
Based on our observations in LBBB_{AVI}, we adapted currently used LBBB criteria and propose a revised definition of LBBB. The revised definition was validated in consecutive LBBB patients (broad criteria) who underwent implantation of a CRT device at Ghent University Hospital according to current guidelines (LVEF ≤ 35%) [9] and who were categorised as CRT super-responders (LBBB_{CRT}) based on improvement in LVEF to > 45% after at least 6 months of CRT therapy at a prospective echocardiographic examination between October 2018 and August 2020. All pre-implant ECGs were reviewed by an investigator blinded to the revised LBBB criteria.

Statistical analysis

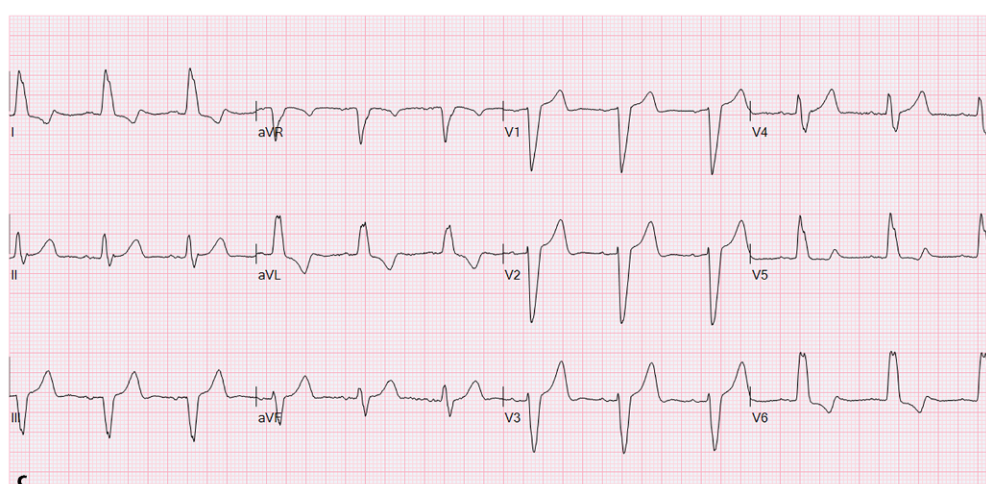
Categorical variables are expressed as absolute number (percentage). Continuous variables are expressed as mean (± standard deviation) in the case of Gaussian distribution or median (1st quartile; 3rd quartile) if data are non-Gaussian distributed. Normality was tested using the Shapiro-Wilk test. To compare means/medians of two variables, Student's *t*-test and the Mann-Whitney U test were used. Comparison of categorical variables among groups was performed by

LBBB_{control} fulfilling none of the ESC 2013, Strauss and AHA 2009 definitions

QRS duration: 130 ms
 Frontal QRS axis= -42°
 QS in V1
 Absent Q waves in V5-6
 R wave peak time <60 ms in V5-6 and normal in V1
 No QRS notching/slurring in I, aVL, V5 and V6

LBBB_{AVI} fulfilling ESC 2013 and Strauss definition

QRS duration: 136 ms
 Frontal QRS axis= 29°
 rS in V1
 Absent Q waves in V5-6
 R wave peak time <60 ms in V5-6 and normal in V1
 QRS notching in aVL and V6
 QRS slurring in I

LBBB_{AVI} fulfilling ESC 2013, Strauss and AHA 2009 definition

QRS duration: 154 ms
 Frontal QRS axis= -9°
 rS in V1
 Absent Q waves in V5-6
 R wave peak time >60 ms in V5-6 and normal in V1
 QRS notching in I, aVL, V5 and V6

Fig. 1 **a** Electrocardiogram of an 85-year-old control patient with non-procedure-induced left bundle branch block (LBBB_{control}) fulfilling none of the European Society of Cardiology (ESC) 2013, Strauss and American Heart Association (AHA) 2009 definitions. **b** Electrocardiogram of a 72-year-old

patient with left bundle branch block following aortic valve implantation (LBBB_{AVI}) fulfilling the ESC 2013 and Strauss definitions. **c** Electrocardiogram of a 86-year-old LBBB_{AVI} patient fulfilling the ESC 2013, Strauss and AHA 2009 definitions

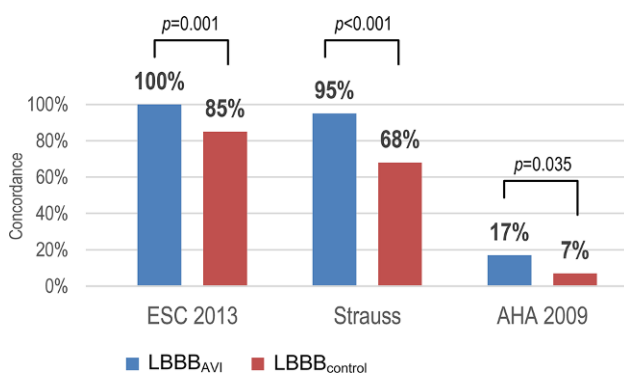


Fig. 2 Classification according to currently used left bundle branch block (LBBB) definitions among aortic valve implantation-induced LBBB (*LBBB_{AVI}*) patients and a non-procedure-induced LBBB control group (*LBBB_{control}*)

Fisher's exact test and chi-square test. Linear regression analysis was used to assess the effects of clinical, echo- and electrocardiographic parameters on QRSD. Statistical significance was set at a two-tailed probability level of <0.05 . All statistical analyses were performed using SPSS software (version 26.0, IBM, Armonk, NY, USA).

Results

Characteristics of patients with new-onset *LBBB_{AVI}*

A total of 59 *LBBB_{AVI}* patients (34 TAVR and 25 SAVR patients, median age 82 years, 42% male) were enrolled in the study. The characteristics of the TAVR and SAVR patients are shown in the Electronic Supplementary Material (Table S1). All patients had severe aortic valve stenosis with an aortic valve area $<1.0\text{ cm}^2$ as the indication for TAVR/SAVR. Pre-procedural conduction disease (left anterior/posterior hemiblock or intraventricular conduction delay) was observed in 8 (15%) patients. All patients developed LBBB immediately during implantation or within 24 h post-procedure. Except for age, no significant differences were observed between TAVR and SAVR patients.

With the occurrence of *LBBB_{AVI}*, QRSD increased from 94 (86;100) ms to 148 (140;160) ms ($p<0.001$) (Tab. 1). An LBBB QRSD of ≥ 130 ms was observed in 98% of patients and, with regard to the Strauss definition, 95% of patients met the sex-specific QRSD cut-off (Tab. 2). Notably, 100% of females had a QRSD ≥ 130 ms and 88% of males had a QRSD ≥ 140 ms. QRSD in *LBBB_{AVI}* males was longer than in females (154 [145;162] ms vs 145 [138;153] ms, $p=0.006$). No other electrocardiographic differences were observed between the sexes. In a multivariate linear regression model including age, height, weight, sex, CAD and end-diastolic diameter, only male sex was independently associated with increased QRSD ($\beta=11.49$; $p=0.039$). The baseline frontal QRS axis shifted from $9 (-15;45)^\circ$ to $-15 (-37;11)^\circ$ post-AVI ($p=0.001$). In

72% of *LBBB_{AVI}* patients with a normal QRS axis (90°), a leftward shift was observed.

Electrocardiographic analysis of *LBBB_{AVI}* and *LBBB_{control}*

The 59 *LBBB_{AVI}* patients were matched to 118 *LBBB_{control}* patients. The characteristics of *LBBB_{AVI}* and *LBBB_{control}* patients are shown in Tab. 1. Representative ECGs are shown in Fig. 1. No clinical or echocardiographic differences were observed between the two groups.

All *LBBB_{AVI}* patients presented with QRS notching/slurring in the lateral leads (I, aVL, V5 or V6), whereas this was present in only 85% (100) of the *LBBB_{control}* group ($p=0.001$). Inferior (lead II, III or aVF) and septal (lead V1 or V2) QRS notching/slurring was also more prevalent in the *LBBB_{AVI}* group (83% vs 70%, $p=0.067$ and 20% vs 5%, $p=0.002$, respectively).

Overall, QRSD was not significantly different between the two groups, neither was RWPT. However, patients with LBBB QRSD ≥ 130 ms (98% vs 86%, $p=0.007$) and patients meeting the Strauss sex-specific QRSD cut-off (95% vs 81%, $p=0.012$) were more frequently observed in the *LBBB_{AVI}* group.

Classification according to current LBBB definitions

Of all *LBBB_{AVI}* patients, 100% met the ESC 2013 and 95% the Strauss LBBB definition, whereas only 17% of patients met the AHA 2009 definition (Tab. 2, Fig. 2). Low concordance with the AHA definition is explained by the low prevalence of QRS notching/slurring combined in all four lateral leads (54%, Tab. 2). Interestingly, except for one patient, all *LBBB_{AVI}* patients had QRS notching in at least two lateral leads (I, aVL, V5 or V6). Furthermore, only 27% of patients had an RWPT >60 ms in both leads V5 and V6, contributing to the low agreement with the AHA 2009 definition. When the analysis was restricted to the first three AHA 2009 criteria only, 48–53% of *LBBB_{AVI}* patients fulfilled the AHA 2009 definition. The presence of a Q wave in lead aVL minimally reduced adherence to the AHA 2009 definition (Tab. 2).

In the *LBBB_{control}* group, concordance with the different definitions was significantly lower than in the *LBBB_{AVI}* group: ESC 2013 85% ($p=0.001$) and Strauss 68% ($p<0.001$) (Tab. 2, Fig. 2). The lower agreement with the different LBBB definitions is explained by: (1) lower prevalence of lateral notching/slurring (85% vs 100%, $p=0.001$) and (2) the higher number of patients with a shorter QRSD (QRSD ≥ 130 ms, 86% vs 98%, $p=0.007$) in the *LBBB_{control}* group. Only 7% of patients fulfilled the AHA 2009 definition ($p=0.035$, compared to *LBBB_{AVI}*). As in the *LBBB_{AVI}* group, low concordance with the AHA 2009 criteria is caused by a low combined prevalence of QRS notching/slurring in all four lateral leads (31%) and most patients not meeting the RWPT criterion (83%).

Table 3 Baseline clinical, echo- and electrocardiographic characteristics of cardiac resynchronisation therapy (CRT) super-responders with left bundle branch block (LBBB) before CRT implantation

	LBBB _{CRT} (n= 33)	p-value compared to LBBB _{AVI}
<i>Clinical characteristics</i>		
Median age (years)	61 (48;71)	
Male	17 (52)	
Coronary artery disease	6 (18)	
Acute coronary syndrome	1 (3)	
<i>Echocardiographic measurements</i>		
End-diastolic diameter (mm)	61 ± 7.7	
End-systolic diameter (mm)	52 ± 9.1	
End-diastolic volume (ml)	185 ± 48.0	
End-systolic volume (ml)	135 ± 37.0	
Left ventricular ejection fraction (%)	27 ± 5.9	
<i>ECG measurements</i>		
PR interval (ms)	180 (156;194)	0.103
QRS duration (ms)	160 (155;173)	<0.001
Frontal QRS axis (°)	-12 (-38;6)	0.937
<i>LBBB definition features</i>		
QRS duration ≥ 120 ms	33 (100)	NP
QRS duration ≥ 130 ms	32 (97)	0.149
QRS duration ≥ 130 ms in females and ≥ 140 ms in males	31 (94)	0.369
QS or rS in V1	33 (100)	NP
Absence of Q waves in V5-6	33 (100)	NP
Notching/slurring in V5-6, I or aVL	33 (100)	NP
Notching/slurring in V5-6, I and aVL	25 (76)	0.047
Notching/slurring in ≥ 2 leads (I, aVL, V1-2, V5-6)	32 (97)	0.359
<i>LBBB definitions</i>		
ESC 2013 definition	33 (100)	NP
Strauss definition	32 (97)	1.000
AHA 2009 definition	11 (33)	0.119
AHA 2009 definition without R wave peak time criterion	23 (70)	0.127

Values are mean ± standard deviation, median (first quartile; third quartile) or number (%)
 AHA American Heart Association, ESC European Society of Cardiology, NP not possible

Subanalysis of LBBB_{AVI} versus LBBB_{control} with presence of lateral QRS notching

Comparison of LBBB_{AVI} patients and LBBB_{control} patients with lateral QRS notching/slurring is shown in the Electronic Supplementary Material (Table S2).

No differences in frontal QRS axis, nor in QRSD and number of patients with QRSD ≥ 130 ms were observed between the LBBB_{AVI} group and the LBBB_{control} group with lateral notching. Furthermore, concordance with the different LBBB definitions was comparable between LBBB_{AVI} patients and LBBB_{control} patients with lateral notching, but not when comparing LBBB_{AVI} versus LBBB_{control} without lateral notching.

Extrapolation of LBBB_{AVI} features to LBBB_{CRT}

Clinical, echo- and electrocardiographic characteristics of the 33 CRT responders (median age 61 (48;71) years, 52% male) are summarised in Tab. 3.

During a median follow-up of 53 (20;77) months, as per definition, LVEF increased from 27 ± 5.9% to 54 ± 7.5% ($p < 0.001$). Except for an increased QRSD (160 [155;173] ms vs 148 [140;160] ms, $p < 0.001$) and a higher prevalence of QRS notching/slurring in all four lateral leads (76% vs 54%, $p = 0.047$) in the LBBB_{CRT} group, no differences in electrocardiographic features or agreement with the LBBB definitions were observed between LBBB_{AVI} and LBBB_{CRT}.

Discussion

Main findings

This study assesses and reviews electrocardiographic features of LBBB in a population with proximal LBBB, i.e. patients with AVI-induced LBBB. As all LBBB_{AVI} patients had lateral QRS notching/slurring, QRS notching/slurring in the lateral leads is fundamental in the diagnosis of proximal LBBB. The LBBB_{AVI} group

Advertisement placed here.



Houten 2021

Advertisement placed here.



Houten 2021

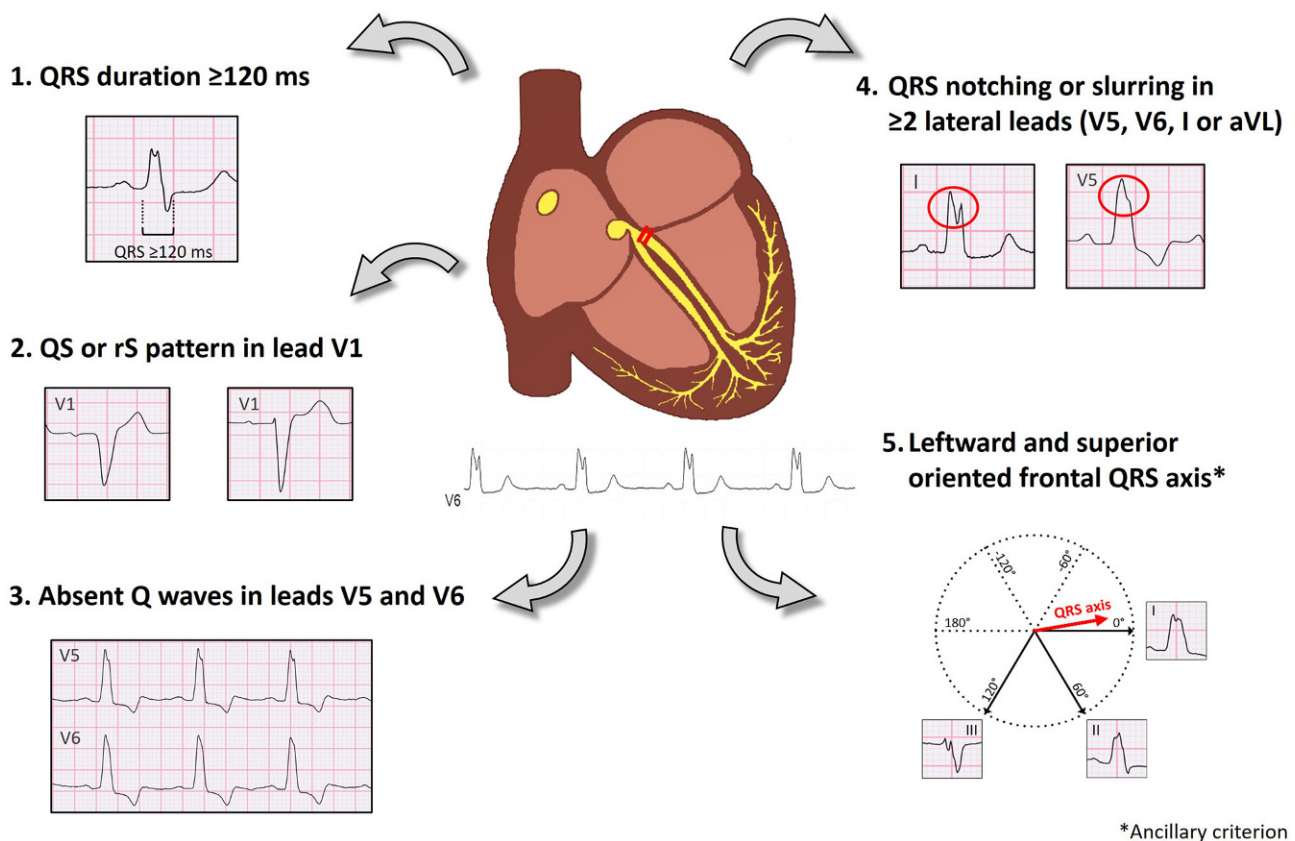


Fig. 3 Proposed criteria for proximal left bundle branch block

showed high concordance with ESC 2013 and Strauss definitions, but low agreement with the AHA 2009 definition. Our observations in LBBB_{AVI} were compared to matched LBBB patients from a general population, showing a higher number of patients with QRSD ≥ 130 ms, a higher prevalence of lateral QRS notching/slurring and a higher concordance with LBBB definitions in the LBBB_{AVI} group.

Obstacles in defining LBBB

Current controversy in defining LBBB is primarily related to the difficulty in identifying patients with ‘true’ electrocardiographic LBBB. As studies over the past century have included patients with various types of conduction delay (proximal vs distal, focal vs diffuse), this obviously resulted in heterogeneous LBBB electrocardiographic patterns and criteria. Furthermore, most current LBBB definitions are derived from the same 1985 consensus criteria [19], but with different adaptations and interpretations (Electronic Supplementary Material, Fig. S1).

True LBBB and proximal LBBB: two of a kind?

Although the importance of QRS notching/slurring was acknowledged even in early LBBB definitions [1, 20, 21], CRT was fundamental to the understanding of the relationship between electro-mechanical

dyssynchrony in LBBB and a subset of LBBB electrocardiographic patterns with lateral QRS notching/slurring (‘true’ LBBB) [1, 13]. Patients without ‘true’ LBBB morphology were shown to demonstrate less electromechanical dyssynchrony [22], and absence of QRS notching/slurring resulted in less clinical and echocardiographic improvement than in true LBBB patients [6]. Experimental animal studies [14], His bundle pacing [23] and recent mapping studies [15] were able to link these ‘true’ LBBB electrocardiographic patterns with QRS notching to a proximal block in the LBB.

In our procedure-induced LBBB population, QRS notching/slurring was the most distinctive electrocardiographic characteristic of proximal LBBB. Our findings are in line with observational TAVR studies [24, 25] and a recent mapping study by Upadhyay et al., showing that QRS notching had the highest sensitivity and best negative predictive value to diagnose proximal LBBB [15]. Moreover, most proximal LBBBs were correctable by His bundle pacing in their study, indicating that in these patients no distal conduction disease was present. In contrast, LBBB patients without lateral notching demonstrated an intact proximal left conduction system and their LBBB was not correctable by His bundle pacing [15]. These findings suggest that an LBBB pattern without notching/slurring most likely reflects ‘distal block’ [1].

The question remains whether the presence of lateral QRS notching/slurring in a non-AVI-induced LBBB population also corresponds to proximal conduction disease of the left bundle. However, as uniformity was observed among LBBB_{AVI} patients and LBBB_{control} patients with lateral notching, these findings suggest pathophysiological similarities between the two groups and corroborate the evidence of a proximal block in all LBBB patients when notching/slurring is present.

Proposed criteria for proximal LBBB

AVI-induced LBBB implies an unequivocal proximal block and is therefore well suited for defining proximal LBBB. Based on our findings in LBBB_{AVI}, we selected and adapted currently used criteria (Fig. 3).

QRS duration ≥ 120 ms

A minority of LBBB_{AVI} patients might present with a QRS duration < 130 ms. Of interest is that female LBBB_{AVI} patients had a shorter QRSD than male LBBB_{AVI} patients. This is in line with the findings of previous work by our group, showing that female patients show proximal LBBB morphology at shorter QRSD [26].

QS or rS in lead V1 and absent Q waves in leads V5-6

At inclusion, all our patients had a QS or rS in lead V1 and absent Q waves in leads V5-6. We observed a small Q wave in leads I and aVL in 15% of proximal LBBB patients and therefore recommend against an 'absent Q wave' criterion in leads I and aVL.

QRS notching or slurring in ≥ 2 lateral leads

Patients with proximal LBBB always presented QRS notching/slurring in at least two lateral leads. Only half of the LBBB_{AVI} patients had QRS notching/slurring in all four lateral leads, indicating that AHA 2009 requirements may lead to significant underdiagnosis of LBBB [7, 11, 27]. Whether the variable degree of QRS notching/slurring relates to suboptimal detection and/or differences in underlying electro-anatomical myocardial substrate remains unclear [28].

Leftward and superior oriented frontal QRS axis

Our observations in LBBB_{AVI} support those of previous studies [25, 29], which showed that the onset of LBBB causes a variable degree of QRS axis shift in a leftward and superior direction in most patients. A more leftward oriented QRS axis may support the diagnosis of proximal LBBB, but we recommend against absolute cut-off values because of the large range.

Advantages of the revised LBBB definition

The ESC 2013 and Strauss definitions identify most LBBB_{AVI} patients. However, 5–14% of our proximal LBBB patients did not reach the computer-simula-

tion-based Strauss QRSD thresholds of 130 and 140 ms for females and males, respectively. As such, QRS prolongation with a lower limit of 120 ms is preferable to define proximal LBBB. Although the ESC 2013 definition provides excellent sensitivity (100% of LBBB_{AVI} patients fulfilling the definition), the specificity might still be improved by adding the requirement of QRS notching/slurring in at least two lateral leads and the ancillary criterion of a leftward and superior oriented frontal QRS axis: 98% of LBBB_{AVI} patients had QRS notching/slurring in at least two lateral leads and 85% of patients had a QRS axis $\leq 30^\circ$. As AVI-induced LBBB patients and CRT super-responders both represent a 'true' LBBB electromechanical substrate within the large spectrum of left ventricular dysfunction, excellent compliance (97%) with the proposed criteria among CRT super-responders corroborates our revised LBBB definition.

Limitations

A potential drawback in LBBB_{AVI} patients for studying the characteristics and definition of LBBB may relate to the age and co-morbidity in this particular population. Studying LBBB in a population with an unaffected myocardial substrate could overcome these issues. However, the almost identical observations in LBBB_{AVI}, matched LBBB_{control} with lateral notching and LBBB_{CRT} patients argue against important myocardial substrate differences between these populations. In acute LBBB, as in LBBB_{AVI}, electrical remodelling might affect electrocardiographic characteristics and alter LBBB features over time. However, this mainly involves changes in repolarisation features rather than changes in QRS features [30].

Conclusion

In patients with proximal procedure-induced LBBB, the presence of QRS notching/slurring in the lateral leads seems a sine qua non for proximal LBBB. Non-uniformity exists among current recommendations for the diagnosis of proximal LBBB, with the ESC 2013 and Strauss definitions providing a higher sensitivity than the AHA 2009 definition. The LBBB_{AVI} population may therefore provide a framework for uniform criteria for assessing proximal LBBB.

Conflict of interest S. Calle, M. Coeman, A. Demolder, T. Philipsen, P. Kayaert, M. De Buyzere, F. Timmermans and J. De Pooter declare that they have no competing interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material



is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Strauss DG, Selvester RH, Wagner GS. Defining left bundle branch block in the era of cardiac resynchronization therapy. *Am J Cardiol*. 2011;107:927–34.
2. Rodriguez MI, Sodi-Pallares D. The mechanism of complete and incomplete bundle branch block. *Am Heart J*. 1952;44:715–46.
3. Grant RP, Dodge HT. Mechanisms of QRS complex prolongation in man—left ventricular conduction disturbances. *Am J Med*. 1956;20:834–52.
4. Vassallo JA, Cassidy DM, Marchlinski FE, et al. Endocardial activation of left bundle branch block. *Circulation*. 1984;69:914–23.
5. Mascioli G, Padeletti L, Sassone B, et al. Electrocardiographic criteria of true left bundle branch block: a simple sign to predict a better clinical and instrumental response to CRT. *Pacing Clin Electrophysiol*. 2012;35:927–34.
6. Tian Y, Zhang P, Li X, et al. True complete left bundle branch block morphology strongly predicts good response to cardiac resynchronization therapy. *Europace*. 2013;15:1499–506.
7. Caputo ML, van Stipdonk A, Illner A, et al. The definition of left bundle branch block influences the response to cardiac resynchronization therapy. *Int J Cardiol*. 2018;269:165–9.
8. Zareba W, Klein H, Cygankiewicz I, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT). *Circulation*. 2011;123:1061–72.
9. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Europace*. 2013;15:1070–118.
10. Surawicz B, Childers R, Deal BJ, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram. Part III: intraventricular conduction disturbances. *Circulation*. 2009;119:e235–e40.
11. van Stipdonk AMW, Vanbelle S, ter Horst IAH, et al. Large variability in clinical judgement and definitions of left bundle branch block to identify candidates for cardiac resynchronization therapy. *Int J Cardiol*. 2019;286:61–5.
12. Nguyen UC, Verzaal NJ, van Nieuwenhoven FA, Vernoooy K, Prinzen FW. Pathobiology of cardiac dyssynchrony and resynchronization therapy. *Europace*. 2018;20:1898–909.
13. Calle S, Delens C, Kamoen V, De Pooter J, Timmermans F. Septal flash: at the heart of cardiac dyssynchrony. *Trends Cardiovasc Med*. 2020;30:115–22.
14. Liu L, Tockman B, Girouard S, et al. Left ventricular resynchronization therapy in a canine model of left bundle branch block. *Am J Physiol Heart Circ Physiol*. 2002;282:H2238–H44.
15. Upadhyay GA, Cherian T, Shatz DY, et al. Intracardiac delineation of septal conduction in left bundle-branch block patterns. *Circulation*. 2019;139:1876–88.
16. Surkova E, Badano LP, Bellu R, et al. Left bundle branch block: from cardiac mechanics to clinical and diagnostic challenges. *Europace*. 2017;19:1251–71.
17. De Pooter J, El Haddad M, Stroobandt R, De Buyzere M, Timmermans F. Accuracy of computer-calculated and manual QRS duration assessments: clinical implications to select candidates for cardiac resynchronization therapy. *Int J Cardiol*. 2017;236:276–82.
18. Prineas RJ, Crow RS, Zhang Z. The Minnesota code manual of electrocardiographic findings: standards and procedures for measurement and classification. London: Springer; 2010.
19. Willems JL, Robles de Medina EO, Bernard R, et al. Criteria for intraventricular conduction disturbances and pre-excitation. World Health Organization/International Society and Federation for Cardiology Task Force Ad Hoc. *J Am Coll Cardiol*. 1985;5:1261–75.
20. Scott RC. Left bundle branch block—a clinical assessment. *I. Am Heart J*. 1965;70:535–66.
21. The Criteria Committee of the New York Heart Association. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. Boston: Little, Brown and Co; 1964.
22. Corteville B, De Pooter J, De Backer T, El Haddad M, Stroobandt R, Timmermans F. The electrocardiographic characteristics of septal flash in patients with left bundle branch block. *Europace*. 2017;19:103–9.
23. Huang W, Su L, Wu S, et al. Long-term outcomes of His bundle pacing in patients with heart failure with left bundle branch block. *Heart*. 2019;105:137–43.
24. Sundh F, Simlund J, Harrison JK, et al. Incidence of strict versus nonstrict left bundle branch block after transcatheter aortic valve replacement. *Am Heart J*. 2015;169:438–44.
25. Alqarawi W, Sadek MM, Golian M, et al. A new electrocardiographic definition of left bundle branch block (LBBB) in patients after transcatheter aortic valve replacement (TAVR). *J Electrocardiol*. 2020;63:167–72.
26. De Pooter J, Kamoen V, El Haddad M, et al. Gender differences in electro-mechanical characteristics of left bundle branch block: potential implications for selection and response of cardiac resynchronization therapy. *Int J Cardiol*. 2018;257:84–91.
27. van Stipdonk AMW, Hoogland R, Ter Horst I, et al. Evaluating electrocardiography-based identification of cardiac resynchronization therapy responders beyond current left bundle branch block definitions. *JACC Clin Electrophysiol*. 2020;6:193–203.
28. Nguyen UC, Potse M, Regoli F, et al. An in-silico analysis of the effect of heart position and orientation on the ECG morphology and vectorcardiogram parameters in patients with heart failure and intraventricular conduction defects. *J Electrocardiol*. 2015;48:617–25.
29. Chou TC. *Electrocardiology in clinical practice*. Philadelphia: Saunders; 2008.
30. Engels EB, Poels TT, Houthuizen P, et al. Electrical remodeling in patients with iatrogenic left bundle branch block. *Europace*. 2016;18:iv44–iv52.